NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Erenumab for preventing migraine [ID1188]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Erenumab for preventing migraine [ID1188]

The final scope and final matrix are available on the NICE website

Contents:

1. **Pre-Meeting Briefing**

2. **Company submission** from Novartis Pharmaceuticals (UK) Ltd

3. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification

4. **Patient group, professional group and NHS organisation submission** from:
   - Migraine Trust
   - OUCH UK
   - Association of British Neurologists – prepared by clinical expert, Nicola Giffin
   - British Association for the Study of Headache
   - Primary Care Neurology Society
   - National Hospital for Neurology and Neurosurgery

5. **Expert personal perspectives** from:
   - Sarah Broderick – patient expert, nominated by Migraine Trust
   - Wendy Thomas – patient expert, nominated by Migraine Trust

6. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews Ltd

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

8. **Evidence Review Group report – erratum**

9. **Evidence Review Group report – addendum**

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

NICE National Institute for Health and Care Excellence

Erenumab for preventing migraine

ID1188

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

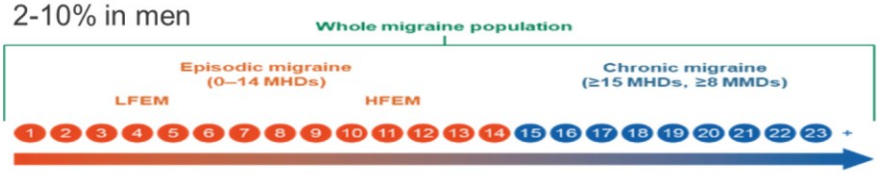
The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

NICE

2

Migraine

- Headache disorder with recurring attacks usually lasting 4-72 hours
- Often accompanied by nausea, vomiting, sensitivity to light/sound
- Factors triggering attacks can include stress, change in sleep pattern, overtiredness, menstruation, caffeine/alcohol consumption
- ~190,000 migraine attacks every day; 5-25% prevalence in women; 2-10% in men



- Episodic migraine = headaches on <15 days per month
- Chronic migraine = headaches on ≥15 days per month, of which at least 8 headache days have features of migraine
- High-frequency episodic migraine (HFEM) = 8-14 monthly headache days

3

Source: NICE scope; Company submission: section B.1.2.1 (page 18)

Erenumab (Aimovig, Novartis)

Marketing authorisation (received July 2018)	For the prophylaxis of migraine in adults who have at least 4 migraine days per month when initiating treatment
Mechanism of action	Monoclonal antibody calcitonin gene-related peptide receptor antagonist (inhibiting the transmission of signals that cause severe pain)
Administration	Subcutaneous injection
Dose	70 mg or 140 mg every 4 weeks (recommended dose 70 mg but some patients may benefit from 140 mg)
Discontinuation	Regular evaluation recommended. Consider stopping treatment if no response after 3 months
List price	£386.50 per dose (70 mg pre-filled pen for self-injection) Patient access scheme agreed (simple discount)
Average cost of treatment (list price)	Non-responders: £1,159.50 Responders: £35,171.50 (based on modelled 7 year median duration)

NICE 4

Source: Company submission: section B.1.2 (pages 13-14); Summary of Product Characteristics

Patient and clinical view: need for treatment

- Can lead to social isolation, depression, loneliness, poor quality of life; prevent normal activities and family life → hard to manage → it is fluctuating, disabling & unpredictable
- Treatment aims to reduce frequency, duration, severity of migraine (by ≥50% in episodic; ≥30% in chronic and HFEM), improve quality of life, reduce acute medicine use
- Current options include beta-blockers, tricyclic antidepressants, anti-convulsants:
  - can be ineffective (re-purposed drugs used to treat other conditions)
  - side effects can be debilitating (e.g. drowsiness, mood disturbance, cognitive dysfunction, weight gain) → can't be tolerated by many people
  - contraindicated for people with multiple conditions and pregnant women
- Botulinum toxin type A ('Botox') is resource intensive and not available everywhere
- Regular use of acute pain-relief risks medication-overuse headaches
- Variation in care; specialist services for chronic refractory migraine limited; many patients not getting appropriate treatment
- Unmet need for effective, well-tolerated preventive treatments, particularly for refractory chronic migraine

NICE HFEM, High Frequency Episodic Migraine 5

Source: Migraine Trust patient organisation submission; professional organisation submissions from Association of British Neurologists, British Association for the Study of Headache, Primary Care Neurology Society; clinical and patient expert submissions

Patient and clinical view: erenumab

- First migraine-specific preventive treatment targeted at underlying biology
- Can reduce frequency and severity of migraine; has rapid onset; reduces acute medicine use; clinically meaningful benefits and improved quality of life anticipated, especially in HFEM and chronic migraine, and for people who cannot tolerate current treatments
- Potential for reducing days affected by migraine, enhancing productivity, reducing absenteeism
- Well tolerated; fewer side-effects than current oral treatments
- Easy self-injectable treatment: empowers patients; improves compliance
- Reduced follow-up and monitoring for side effects, reduced burden on health services
- Likely to be used for refractory chronic migraine
  - starting and stopping criteria needed to appropriately target use
  - greater investment in specialist headache services may be needed
  - high anticipated demand if recommended
- Potential disadvantages: pain at injection site, allergic reaction, needle phobia
- Concern it will not be widely available given variable access to specialist clinics

NICE HFEM, High Frequency Episodic Migraine 6

Source: Migraine Trust patient organisation submission; professional organisation submissions from Association of British Neurologists, British Association for the Study of Headache, Primary Care Neurology Society; clinical and patient expert submissions

Decision problem: NICE scope

Population	People with migraine
Intervention	Erenumab
Comparators	Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least 3 prior pharmacological prophylaxis therapies
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 • Adverse effects of treatment • Health-related quality of life
Subgroups	• People with chronic or episodic migraine • Number of previous prophylactic treatments • Frequency of episodic migraine

NICE 7

Source: NICE scope

Company decision problem & ERG critique

Population	Adults with migraine with ≥4 migraine days per month **for whom ≥3 prior prophylactic treatments have failed** • optimised use appropriate to NHS context where low cost oral prophylactics available 1st line • targeted for patients with unmet need and lack of treatment options **ERG comment**: does not fully reflect scope or marketing authorisation, but likely to reflect expected use in NHS
Intervention	Erenumab 70 mg/140 mg (140 mg considered may be appropriate for patients with ≥3 prior failed treatments)
Comparators	• Best supportive care • Botox (for chronic migraine population only) **ERG comment**: appropriate for subgroup
Outcomes	As per NICE scope. Outcomes used in model: • change from baseline in mean monthly migraine days (MMDs) • proportion of patients with ≥50% reduction in mean MMDs from baseline **ERG comment**: Patients may consider reductions <50% clinically meaningful Unclear whether treatment would be stopped if <50% reduction in practice
Subgroups	As per NICE scope

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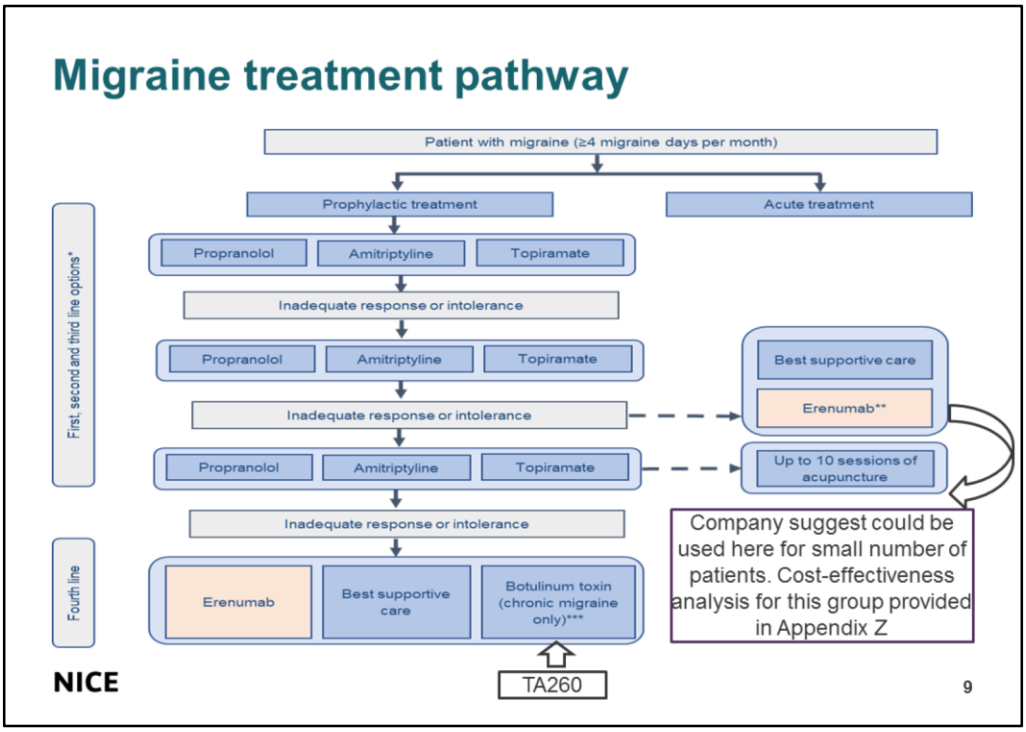
8

Source: Company submission: section B.1.1 (pages 9-12); ERG report: section 3 (pages 28-31)



Source: Company submission: section B.1.2.2 (pages 20-22); Company clarification response question A.14 (page 19)

*If treatment at its maximum tolerated dose in the first-line is ineffective or poorly tolerated, the other two treatment classes may be considered for second-line. The same applies in moving from second-line to third-line treatment.

**There may be clinical desire to use erenumab at an earlier point in the treatment pathway: in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions (a minority of patients, who would otherwise have BSC).

***Botulinum toxin recommended for chronic migraine only. TA260: Should be stopped if disease does not respond (<30% reduction in monthly headache days) after 2 treatment cycles or if migraine has become episodic for 3 consecutive months.

Pathway based on NICE CG150 'Management of headaches in over 12s'; British Association for the Study of Headache guidelines for the diagnosis and management of migraine, tension-type, cluster and medication-overuse headaches; NICE TA260 'Botulinum toxin type A

for the prevention of headaches in adults with chronic migraine'; expert opinion.

Propanolol = beta blocker; Amitriptyline = tricyclic antidepressant; Topiramate = anti-convulsant

Key trials

	Study 295 n=667	STRIVE n=955	ARISE n=577	LIBERTY n=246
Design	Multicentre, randomised, double-blind, placebo-controlled			
	Phase II	Phase III	Phase III	Phase IIIb
Population				Adults (18-65 years)
Migraine type	Chronic	Episodic	Episodic	Episodic
Prior treatments	≤3	≤2	≤2	2-4
Dose	70 mg; 140 mg	70 mg; 140 mg	70 mg	140 mg
Duration of blinded phase	3 months	6 months	3 months	3 months
Primary outcome	Change in MMD from baseline to last month	Change in MMD from baseline to last 3 months	Change in MMD from baseline to last month	≥50% reduction in MMD from baseline to last month
Placebo considered to represent best supportive care, defined by continued treatment with acute medication. Patients in placebo arms of trials had acute treatments aligned with UK clinical guideline recommendations.				

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MMD, Monthly migraine days

10

Source: Company submission: section B.2.2 (pages 29-30); B.2.3.1 (pages 33-36); Company clarification response question A.6 (pages 11-12)

Chronic migraine = ≥15 headache days per month, of which ≥8 days were migraine days, in each of the 3 months prior to screening

Episodic migraine = ≥4 and <15 migraine days per month with <15 headache days per month, with history of migraine for ≥12 months

See section B.2.3.1 (pages 40-42) for specific definitions of qualifying migraine headaches. Note that for all trials, if the patient took an acute migraine-specific drug on a calendar day, then it was counted as a migraine day regardless of the duration and pain features/associated symptoms.

Results (ITT population): MMD reduction

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295 (chronic)	n=281	n=188	n=187
Mean change from baseline	-4.2	-6.6	-6.6
Difference (95% CI)		-2.5 (-3.5, -1.4) p=<0.0001	-2.5 (-3.5, -1.4) p=<0.0001
STRIVE (episodic)	n=316	n=312	n=318
Mean change from baseline	-1.8	-3.2	-3.7
Difference (95% CI)		-1.4 (-1.9, -0.9) p=<0.001	-1.9 (-2.3, -1.4) p=<0.001
ARISE (episodic)	n=288	n=282	N/A
Mean change from baseline	-1.8	-2.9	N/A
Difference (95% CI)		-1.0 (-1.6, -0.5) p=<0.001	
LIBERTY (episodic)	n=124	N/A	n=119
Mean change from baseline	-0.2	N/A	-1.8
Difference (95% CI)			-1.6 (-2.7, -0.5) p=0.004

NICE ITT, Intention-to-treat; MMD, Monthly migraine days; CI, Confidence interval 11

Source: Company submission: section B.2.5.1 (pages 58, 61, 63, 65)

Results (ITT population): 50% responder

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295 (chronic)	n=281	n=188	n=187
Proportion of patients % (n) Odds ratio (95% CI)	23.5% (66)	39.9% (75) 2.2 (1.5, 3.3) p=<0.001	41.2% (77) 2.3 (1.6, 3.5) p=<0.001
STRIVE (episodic)	n=316	n=312	n=318
Proportion of patients % (n) Odds ratio (95% CI)	26.6% (84)	43.3% (135) 2.1 (1.5, 3.0) p=<0.001	50.0% (159) 2.8 (2.0, 3.9) p=<0.001
ARISE (episodic)	n=288	n=282	N/A
Proportion of patients % (n) Odds ratio (95% CI)	29.5% (85)	39.7% (112) 1.6 (1.1, 2.3) p=0.010	N/A
LIBERTY (episodic)	n=124	N/A	n=119
Proportion of patients % (n) Odds ratio (95% CI)	13.7% (17)	N/A	30.3% (36) 2.7 (1.4, 5.2) p=0.002

NICE ITT, Intention-to-treat; MMD, Monthly migraine days; CI, Confidence interval 12

Source: Company submission: section B.2.5.1 (pages 59, 61, 64, 66)

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Results (≥3 prior subgroup): MMD reduction

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295 (chronic)	n=[redacted]	n=[redacted]	n=[redacted]
Mean change from baseline Difference (95% CI)	[redacted]	[redacted] -2.5 (-4.3, -0.8) p=0.005	[redacted] -4.1 (-5.8, -2.3) p<0.001
STRIVE (episodic)	n=[redacted]	n=[redacted]	n=[redacted]
Mean change from baseline Difference (95% CI)	[redacted]	[redacted]	[redacted]
ARISE (episodic)	n=[redacted]	n=[redacted]	N/A
Mean change from baseline Difference (95% CI)	[redacted]	[redacted]	N/A
LIBERTY (episodic)	n=[redacted]	N/A	n=[redacted]
Mean change from baseline Difference (95% CI)	[redacted]	N/A	[redacted]

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MMD, Monthly migraine days; CI, Confidence interval

13

Source: Company submission: section B.2.6.1 (pages 82-85)

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Results (≥3 prior subgroup): 50% responder

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295 (chronic)	n=[redacted]	n=[redacted]	n=[redacted]
Proportion of patients % (n) Odds ratio vs. placebo (95% CI)	15.3% (15)	34.8% (23) 3.0 (1.4, 6.3) p=0.004	38.5% (25) 3.5 (1.6, 7.4) p=0.001)
STRIVE (episodic)	n=[redacted]	n=[redacted]	n=[redacted]
Proportion of patients % (n) Odds ratio vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
ARISE (episodic)	n=[redacted]	n=[redacted]	N/A
Proportion of patients % (n) Odds ratio vs. placebo (95% CI)	[redacted]	[redacted]	
LIBERTY (episodic)	n=[redacted]	N/A	n=[redacted]
Proportion of patients % (n) Odds ratio vs. placebo (95% CI)	[redacted]		[redacted]

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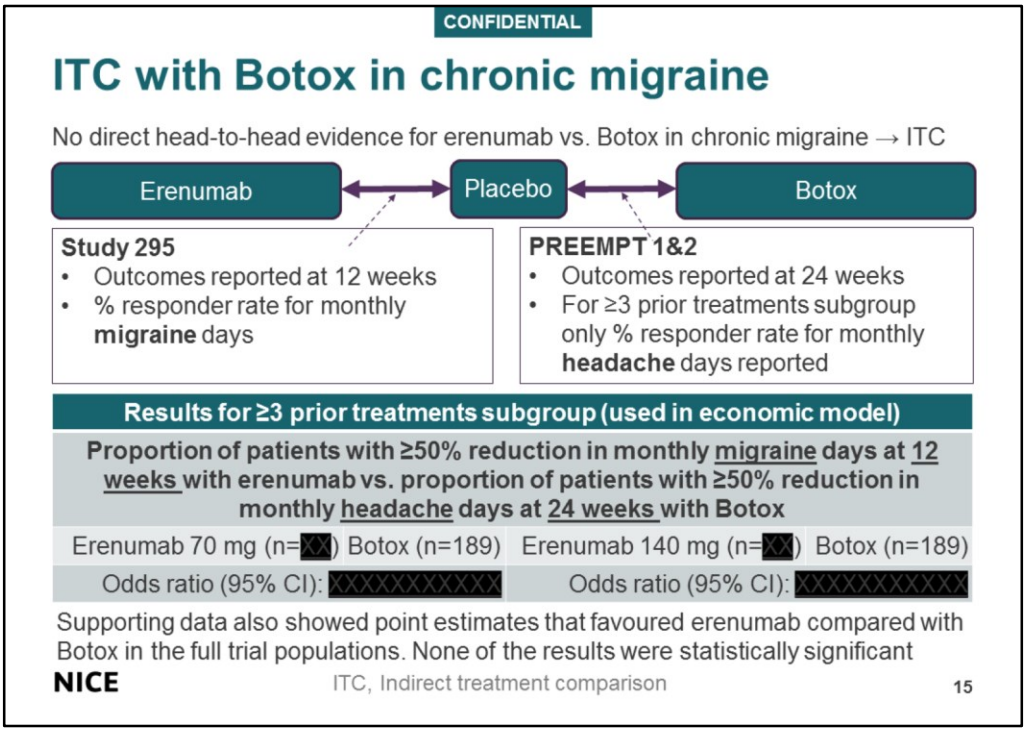
MMD, Monthly migraine days; CI, Confidence interval

14

Source: Company submission: section B.2.6.1 (pages 82-84, 86-87)



Source: Company submission: section B.2.8.1 (pages 95-97); section B.2.8.2 (pages 98-99)

Company consider it appropriate to compare reduction in monthly migraine days with reduction in monthly headache days because the response assessment for Botox is based on monthly headache days whereas the response assessment for erenumab is expected to be monthly migraine days in line with the clinical trials.

Indirect treatment comparison: limitations

- Company: 'best available analysis' of erenumab vs Botox in people with ≥3 prior failed treatments, but notes limitations
- Patients in Study 295 and PREEMPT not stratified by prior treatments so randomisation broken – patient characteristics may be imbalanced between arms
- Baseline characteristics not available for the PREEMPT subgroup so could not be compared to Study 295 subgroup (although baseline characteristics for full trial populations were similar)
- Outcomes reported at different time points (company considers likely to represent conservative estimate for erenumab vs. Botox because results were better for Botox vs. placebo after 24 weeks than 12 weeks in full population)
- Comparing full trial populations overcomes some uncertainties but not relevant to decision problem

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16

Source: Company submission: section B.2.8.3 (pages 99-100)

Quality of life (MSQ v2.1 results)

- Migraine-Specific Quality of Life Questionnaire; self-administered
- 3 sub-domain scores measuring the extent to which migraine limits daily activities and affects related emotions: Role-function restrictive; role-function preventative; emotional-function
- Chronic migraine (full trial population)
  - Study 295: scores improved from baseline in erenumab patients (both doses) across all 3 domains compared with placebo
- Episodic migraine (full trial populations)
  - STRIVE: erenumab patients had greater improvement in scores across all 3 domains compared with placebo at nearly all assessment timepoints. Earlier improvement and sustained higher scores shown in 140 mg dose compared with 70 mg dose.
  - ARISE: erenumab patients had greater improvement in scores across all 3 domains at week 12 compared with placebo.
  - LIBERTY: MSQ not collected. Minimal differences observed in EQ-5D-5L but EQ-5D-5L not considered to adequately reflect health-related quality of life in migraine.
- MSQ results mapped to EQ-5D and used in economic model

NICE 17

Source: Company submission: section B.2.5.2 (pages 66-68, 70-71, 74-75, 77)

Adverse events (full trial populations)

Trial	Treatment-emergent adverse events	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295	Adverse events	39.0%	43.7%	46.8%
	Serious adverse events	2.5%	3.2%	1.1%
	Events leading to discontinuation	0.7%	0.0%	1.1%
STRIVE	Adverse events	63.0%	57.3%	55.5%
	Serious adverse events	2.2%	2.5%	1.9%
	Events leading to discontinuation	2.5%	2.2%	2.2%
ARISE	Adverse events	54.7%	48.1%	N/A
	Serious adverse events	1.7%	1.1%	N/A
	Events leading to discontinuation	0.3%	1.8%	N/A
LIBERTY	Adverse events	54.0%	N/A	54.7%
	Serious adverse events	0.8%	N/A	1.7%
	Events leading to discontinuation	0.8%	N/A	0.0%

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18

Source: Company submission: section B.2.9.2 (pages 103-105)

Adverse event data from the full trial populations are used in the economic model. Adverse event data for the subgroup of patients with ≥3 prior failed treatments can be found in the company's clarification response question A.9 (page 14).

ERG critique: clinical effectiveness

Trials

- Placebo considered representative of best supportive care
- Males, non-white populations and older people under-represented
- No evidence for people with ≥15 headache days per month of which 4 – 7 are migraines (not covered by either chronic or episodic definition)
- 3/4 studies had double-blind phases of just 12 weeks which may be inadequate given primary outcome is mean monthly migraine days
- Subgroup relatively small (~20% of studied population) and is post-hoc analysis

Results

- Better outcomes for erenumab (both doses) compared with placebo
- No statistically significant results for 70 mg dose in ≥3 prior failed treatments subgroup
- Lack of long-term data (beyond 24 weeks) on comparative effectiveness

Indirect treatment comparison

- No concerns about methods or results
- No evidence that difference in outcome timepoints would be likely to favour Botox

NICE 19

Source: ERG report: section 1.3 (page 12); section 3.1 (page 28); section 4.2.1 (page 42); section 4.6 (pages 66-67)

Cost-effectiveness

Economic model

NICE Reference case	Company's model		
Type	• Decision tree (assessment period) • Markov (post-assessment period)		
Population	Adults with ≥3 prior failed treatments • Whole population (66% chronic; 34% episodic) • Chronic migraine population • Episodic migraine population		
Intervention	• Erenumab 70 mg and 140 mg 'blended dose' (50%; 50%) • Erenumab 140 mg		
Comparators	• Episodic migraine: Best supportive care • Chronic migraine: Botox and best supportive care		
Time horizon	10 years	**Cycle length**	12 weeks
Measure of health effects	QALYs	**Discounting of utilities and costs**	3.5%
Perspective	NHS/PSS		

NICE QALYs, Quality-adjusted life years; PSS, Personal Social Services 21

Source: Company submission: section B.3.2 (pages 124-137); Company clarification response question A.8 (pages 12-13)

The model structure enables the tracking of both change in monthly migraine days and the proportion of responders to treatment, which are both considered important outcomes.

Assumed proportions of people with chronic and episodic migraine in the whole population based on UK market research and literature.

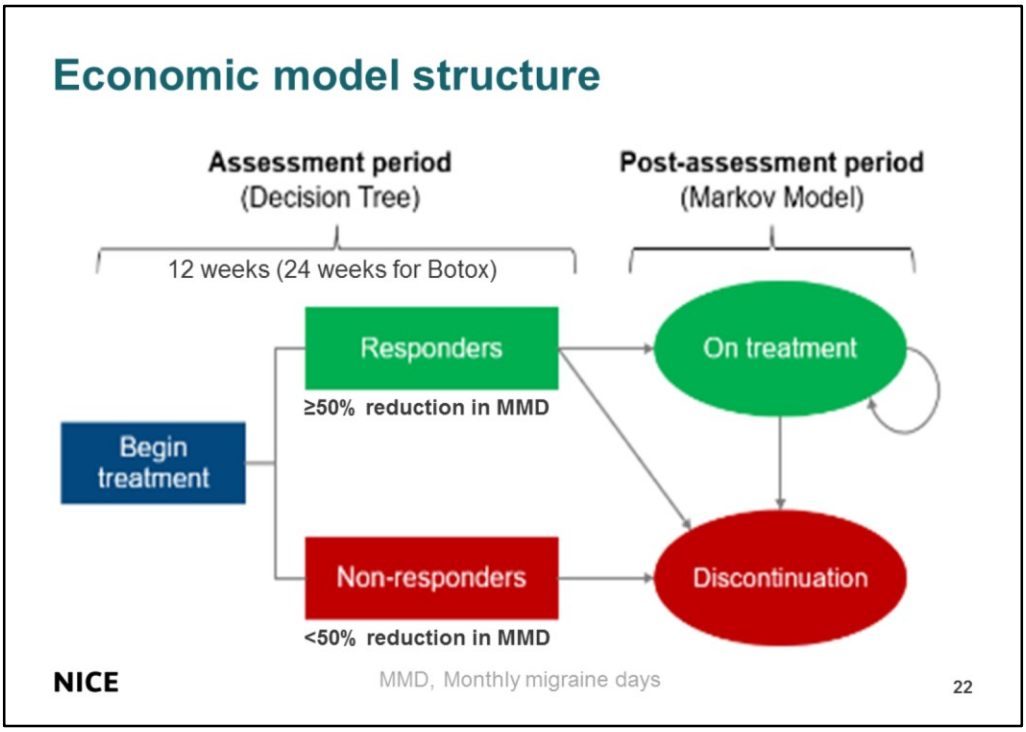
Base case is the whole population because this is consistent with the marketing authorisation and NICE scope, and because migraine is a spectrum disorder with patients distributed across a continuum of migraine frequencies, it can difficult to distinguish between chronic and episodic migraine in practice.

Company considers 140 mg dose may be appropriate for patients with ≥3 prior failed treatments because:

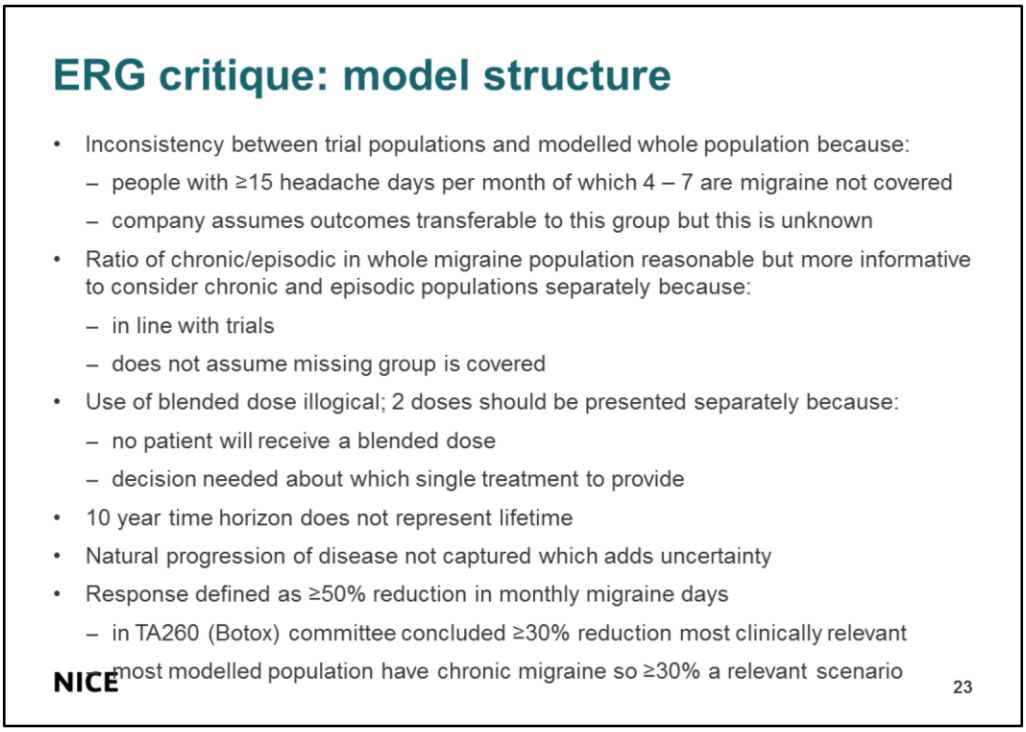
- Better outcomes for 140 mg compared with 70 mg in subgroup of patients for whom ≥3 prior treatments had failed
- Feedback from 6 expert UK neurologists who indicated they may initiate the 140 mg dose in these patients

Company presents a 'blended dose' and 140 mg dose analysis in its

base case, because given the lack of long-term experience with erenumab, some clinicians may wish to start the 70 mg dose initially, but as clinical experience increases a higher proportion of patients may start treatment with the 140 mg dose.



Source: Company submission: section B.3.2.2 (page 128)



Source: ERG report: section 5.2.2 (pages 75-76); section 5.2.3 (page 77); section 5.2.4 (page 78); section 5.2.5 (page 78); Company's clarification response question B8. (page 32)

Natural progression of disease: ERG notes that people with migraine can have stable/persistent migraine, clinical remission, partial remission or progression. Based on the AMPP study (US), after 1 year the proportions would be 84% persistence, 10% clinical remission, 3% partial remission and 3% progression. Accordingly, people can go from low frequency episodic migraine, to chronic migraine (potentially via high frequency episodic migraine) and vice versa. During clarification the company provided scenarios to reflect progression and remission which showed lower ICERs. The ERG considers justification for not modelling disease progression is reasonable but notes that the impact of this and direction of any potential bias is not known.

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Clinical parameters: outcomes

- **Treatment- and response-dependent MMD frequency distributions assigned to each health state**
- Distributions of patients across MMD frequencies taken from trial data (Study 295 and ITC for chronic migraine; pooled results from STRIVE, ARISE and LIBERTY for episodic) and weighted (66% chronic; 34% episodic)
- Statistical distribution (normal) fitted to model predicted proportions of patients with each MMD frequency in each health state
- Erenumab distributions applied for Botox (because no access to patient data)
- Probability of response (≥50% reduction) then applied to the MMD frequency distributions
- Response defined as ≥50% because it is trial outcome, most patients consider it important and whole migraine population being considered

MMD distributions predicted by model

Probability of response		
	Chronic	Episodic
Erenumab 70 mg	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Botox	[redacted]	N/A

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MMD, Monthly migraine days

24

Source: Company submission: section B.3.3.2; B.3.3.3 (pages 140-143)

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Clinical parameters: long-term efficacy

- **Treatment effect assumed to be maintained over time**
- Improved monthly migraine days at 12 weeks maintained until end of time horizon while still on treatment
- Supported by data from ongoing open label extension study of phase II trial in episodic migraine and of Study 295 in chronic migraine
- Literature review of long-term progression of patients having prophylactic treatments identified 10 studies of either erenumab, Botox, beta-blockers or topiramate which showed efficacy maintained for a year or more and associated with sustained improvements in quality of life

Episodic (phase II trial)	Week 64
383 patients having erenumab 70 mg for median duration of ~20 months	
Mean MMD change from baseline	-5.0 (SD 4.2)
≥50% responder rate	65%
Associated with sustained quality of life benefit	

Chronic (Study 295)	Week 24	Week 52
549 patients having erenumab 70 mg, 140 mg or 70 mg followed by 140 mg		
Mean MMD change from baseline	-8.36 (-8.92, -7.80)	-9.29 (-9.96, -8.62)

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MMD, Monthly migraine days

25

Source: Company submission: section B.3.3.4 (pages 143-144)

Clinical parameters: stopping treatment

Stopping because of adverse events in 12 week assessment period (24 weeks for Botox)

- Patients revert to baseline MMDs
- Rate derived from trials for erenumab and Diener et al. (2014) for Botox

Stopping because of non-response

- Patients maintain MMDs at 12 weeks for remaining time horizon
- Assumed a different propensity to respond to treatment also means a different disease status when coming off treatment (those who respond would have experienced better natural improvement compared with non-responders)

Stopping because of other reasons (in post-assessment period)

- Patients revert to baseline MMDs
- Constant per cycle risk of 2.38% applied (based on long-term discontinuation observed for patients having erenumab 70 mg in ongoing open label extension of phase II study)

Positive discontinuation scenario to reflect that treatment may not continue indefinitely

- Responders re-evaluated after 64.5 weeks (enter 12 week assessment period)
- 20% assumed to stop treatment and maintain improvement in MMDs (remaining patients resume treatment and re-enter re-evaluation period every 76.5 weeks thereafter)

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MMD, Monthly migraine days

26

Source: Company submission: section B.3.2.2 (page 129); section B.3.3 (pages 137-146); Company clarification response question A.15 (page 20); question B.10 (pages 39-40)

ERG critique: clinical parameters

Long-term efficacy

- Supporting data from open label extension studies (a phase II trial in episodic migraine and Study 295 in chronic), suggests reasonable to assume treatment effect maintained but no data on maintenance of comparative effectiveness
- Without evidence of long-term effectiveness beyond the open label extension studies it is uncertain whether the treatment effect wanes over time
- Company provided scenario during clarification whereby costs and utilities for erenumab and Botox were linearly reduced over the 10 years until they became those associated with BSC non-responders; ERG adopts this scenario and also models effect waning over 5 years

Stopping treatment

- Patients maintaining MMDs at 12 weeks when stopping because of non-response (compared with patients reverting to baseline MMDs after stopping for other reasons)
  - Company's rationale inconsistent with modelling; non-responders have [redacted] (i.e [redacted]) MMD frequency than baseline in chronic migraine, and frequencies are [redacted] in episodic
  - ERG therefore assumed all those stopping treatment after assessment would revert to a 12 week non-responder MMD frequency
- ERG adopts positive discontinuation scenario but notes there is no evidence that positive discontinuers do not incur cost and maintain benefit of treatment

27

MMD, monthly migraine days

Source: ERG report: section 5.2.2 (pages 75-76); section 5.2.6 (pages 80-82); Company's clarification response question B.9d. (pages 37-39)

Note: TA260 stopping rule that Botox should be stopped in people whose condition has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.

Health state utilities: methods

- **MSQ v2.1 results mapped to EQ-5D-3L to generate utility values for each MMD frequency, which informed utility values for each health state based on that population's MMD frequency distribution**
- EQ-5D-5L collected in LIBERTY but not considered sensitive to changes in quality of life impact on migraine because data not collected during migraine
- MSQ questionnaire has 4 week recall period so considered appropriate
- MSQ results from ITT populations of Study 295, STRIVE and ARISE mapped to EQ-5D-3L using Gillard et al. (2012) algorithm
- Separate algorithms for mapping to chronic/episodic migraine; applied at individual patient level based on number of migraine/headache days at baseline
- Statistical models fitted to combined trial data to predict utilities associated with each MMD frequency
- No treatment effect assumed
- No adverse event disutility applied (mostly non-severe; comparable across arms)
- Botox values the same as erenumab (same MMD distribution assumed)

NICE [illegible], Migraine-specific quality of life questionnaire; ITT, Intention-to-treat; MMD monthly migraine days 28

Source: Company submission: section B.3.4.1 (pages 146-147, 150); Company clarification response question B.14b (page 52)

Company did not map results from the ≥3 prior failed treatment subgroup because this would limit the number of patients in the analysis. Furthermore, it considered that ≥3 prior failed treatments would have a greater disutility and would therefore only have the potential to increase the cost-effectiveness of erenumab in the results.

Health state utilities: values used in model

	Baseline and discontinuation (adverse event or long-term)	Responder at 12 weeks	Non-responder discontinuation	On treatment post-assessment
Whole population				
Erenumab 70 mg	0.577	0.743	0.601	0.741
Erenumab 140 mg	0.577	0.762	0.603	0.761
Placebo	0.577	0.746	0.592	0.741
Chronic migraine				
Erenumab 70 mg	0.466	0.735	0.491	0.735
Erenumab 140 mg	0.466	0.752	0.512	0.752
Placebo	0.466	0.731	0.495	0.731
Episodic migraine				
Erenumab 70 mg	0.688	0.769	0.695	0.760
Erenumab 140 mg	0.688	0.784	0.686	0.779
Placebo	0.688	0.770	0.685	0.756

NICE

29

Source: Company submission: section B.3.4.5 (page 152)

Resource use and costs

- **Resource use frequency and associated cost estimated for each MMD frequency; management costs for each health state a weighted average of costs per MMD frequency based on that population's MMD frequency distribution**
- Frequency of healthcare professional resource use sourced from National Health and Wellness Survey 2017: patients' perspective on burden according to frequency of headache (assumed to approximate migraine)
- Frequency of medication usage sourced from Study 295, STRIVE, ARISE and LIBERTY; linear regression used to predict number of migraine days with/without medication
- Treatment acquisition: no vial sharing assumed for erenumab and Botox
- Treatment administration:
  - Erenumab: one-off initiation cost for self-administration training
  - Botox: per cycle cost for trained specialist
- No best supportive care costs because acute medicines given alongside both erenumab and Botox
- No adverse event costs applied (mostly non-severe; comparable across arms)

NICE MMD, monthly migraine days 30

Source: Company submission: section B.3.5 (pages 153-160)

Disease management resource use and costs comprised:

- Emergency department (A&E) visits
- Hospitalisations
- General practitioner visits
- Nurse practitioner visits
- Neurologist visits
- Migraine-specific medication (assumed to be represented by triptan use)
- Other medication (assumed to be represented by analgesics)

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ERG critique: utilities and costs

Utilities

- EQ-5D in line with NICE reference case and collected in LIBERTY; reason for not using EQ-5D-5L data is plausible but it does have a large impact on cost effectiveness analysis
- Values informed by data from full trial populations not the subgroup – inconsistent with effectiveness data
- Disutility from adverse events not included because mostly non-severe, however:
  - when having continuous treatment grade 1/2 adverse events may affect quality of life
  - adverse events may be XXXX in subgroup but small sample size so this is uncertain

Costs

- Informed by data from people with migraine not just those with ≥3 prior failed treatments – inconsistent with effectiveness data and no evidence that prior treatments don't affect costs
- Questionable whether data on monthly headache days can approximate monthly migraine days given that these are different outcomes
- Disease management medicine costs: sumatriptan injection costs assumed same as oral
- Unclear if acute medicine brands selected are representative of UK clinical practice

NICE 31

Source: ERG report: section 5.2.7 (page 82); section 5.2.8 (pages 85-86); section 5.2.9 (pages 88-89): Company's clarification response question A.9 (page 14)

Comparison of base case assumptions

	Company's base case	ERG's base case
Analysis	Pairwise	1) Incremental 2) Pairwise
Population	1) Whole population 2) Chronic migraine 3) Episodic migraine	1) Chronic migraine 2) Episodic migraine
Dose	1) Blended dose 2) 140 mg dose	1) 70 mg dose 2) 140 mg dose
Time horizon	10 years	Lifetime
Treatment effect	Maintained over time	1) Maintained over time 2) Wanes over 5 years
Stopping treatment	Revert to baseline monthly migraine days except non-responders who maintain any benefit seen at 12 weeks	Revert to non-responder monthly migraine days at 12 weeks
Utilities	MSQ results from full trial populations	MSQ results from full trial populations
Costs	Triptan injection price reflects the price of oral triptan	Triptan injection price reflects the price of triptan injections

NICE

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Company base case: Whole population

Treatment	Total		Incremental		ICER per QALY (with PAS)
	Costs	QALYs	Costs	QALYs	
Blended dose					
BSC	[redacted]	[redacted]			
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	£22,446
				Probabilistic	£22,309
140 mg dose					
BSC	[redacted]	[redacted]			
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,827
				Probabilistic	£19,472

Probability of cost-effectiveness	Blended dose	140 mg dose
At £20,000 per QALY gained threshold	35%	50%
At £30,000 per QALY gained threshold	70%	81%

NICE BSC, Best supportive care; QALY, Quality adjusted life year; ICER, Incremental cost-effectiveness ratio

33

Source: Company submission: section B.3.7.1 (page 164); section B.3.8.1 (pages 167; 168)

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Company chronic migraine results

Pairwise analyses	ICER per QALY (with PAS)
Blended dose vs. Botox	£18,893
140 mg dose vs. Botox	£17,832
Blended dose vs. BSC	£17,212
140 mg dose vs. BSC	£13,340

Incremental analyses			
Treatment	**Total costs**	**Total QALYs**	**ICER per QALY (with PAS)**
Blended dose			
BSC	[redacted]	[redacted]	
Botox	[redacted]	[redacted]	£15,953
Erenumab	[redacted]	[redacted]	£18,824
140 mg dose			
BSC	[redacted]	[redacted]	
Botox	[redacted]	[redacted]	£10,601
Erenumab	[redacted]	[redacted]	£17,795

NICE BSC, Best supportive care; QALY, Quality adjusted life year; ICER, Incremental cost-effectiveness ratio

34

Source: Company submission: section B.3.7.1 (pages 164-166)

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Company episodic migraine results

Treatment	Total		Incremental		ICER per QALY (with PAS)
	Costs	QALYs	Costs	QALYs	
Blended dose					
BSC	[redacted]	[redacted]			
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	£35,787
140 mg dose					
BSC	[redacted]	[redacted]			
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	£40,662

NICE BSC, Best supportive care; QALY, Quality adjusted life year; ICER, Incremental cost-effectiveness ratio

35

Source: Company submission: section B.3.7.1 (page 166)

Company scenarios: Whole population

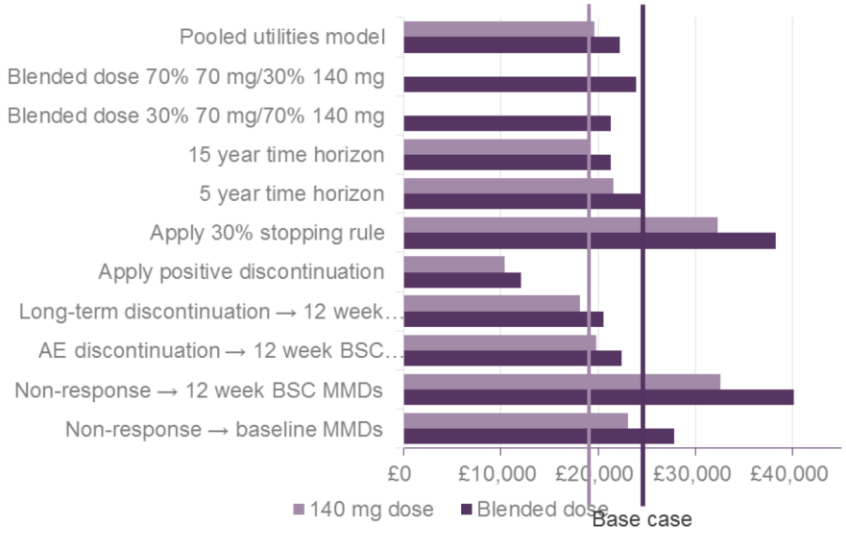
	Blended dose	140 mg dose
Company's base case	£22,446	£19,827
Non-response → baseline MMDs	£27,805	£23,098
Non-response → 12 week BSC MMDs	£40,102	£32,594
AE discontinuation → 12 week BSC MMDs	£22,378	£19,777
Long-term discontinuation → 12 week BSC MMDs	£20,585	£18,176
Apply positive discontinuation	£12,105	£10,422
Apply 30% stopping rule	£38,221	£32,293
5 year time horizon	£24,861	£21,577
15 year time horizon	£21,275	£19,015
Blended dose 30% 70 mg/70% 140 mg	£21,256	N/A
Blended dose 70% 70 mg/30% 140 mg	£23,899	N/A
Pooled utilities model	£22,232	£19,638

NICE MMD, Monthly migraine days; BSC, Best supportive care; AE, Adverse event

36

Source: Company submission: section B.3.8.3 (pages 179-180)

Company scenarios: Whole population



NICE MMD, Monthly migraine days; BSC, Best supportive care; AE, Adverse event

Company scenarios: Chronic migraine

	Vs. Botox Blended	Vs. Botox 140 mg	Vs. BSC Blended	Vs. BSC 140 mg
Non-response → baseline MMDs	↓ £16,046	↓ £14,384	↓ £16,340	↑ £14,789
Non-response → 12 week BSC MMDs	↑ £21,288	↑ £19,618	↑ £25,335	↑ £22,555
AE discontinuation → 12 week BSC MMDs	↑ £19,484	↑ £18,174	↓ £17,182	↓ £13,282
Long-term discont. → 12 week BSC MMDs	↓ £16,282	↓ £15,328	↓ £15,187	↓ £11,979
Apply positive discontinuation	↓ £8,979	↓ £8,340	↓ £8,868	↓ £6,815
Apply 30% stopping rule	↑ £21,426	↑ £19,582	↑ £24,803	↑ £20,017
5 year time horizon	↓ £16,137	↓ £15,119	↑ £18,011	↑ £14,354
15 year time horizon	↑ £20,384	↑ £19,468	↓ £17,123	↓ £12,908
Blended dose 30% 70 mg/70% 140 mg	↓ £18,432	N/A	↓ £15,402	N/A
Blended dose 70% 70 mg/30% 140 mg	↑ £19,414	N/A	↑ £19,547	N/A
Indication-specific utilities model	↑ £20,942	↑ £19,767	↑ £19,079	↑ £14,787
Method of administration disutility for Botox	↓ £4,367	↓ £4,593	N/A	N/A
ITC results using headache days outcomes	↑ £21,146	↓ £16,462	N/A	N/A

NICE

MMD, Monthly migraine days; BSC, Best supportive care; AE, Adverse event

38

Source: Company submission: section B.3.8.3 (pages 181-185)

Company scenarios: Episodic migraine

	Blended dose	140 mg dose
Non-response → baseline MMDs	£62,334	£45,010
Non-response → 12 week BSC MMDs	£69,167	£50,003
AE discontinuation → 12 week BSC MMDs	£35,760	£40,632
Long-term discontinuation → 12 week BSC MMDs	£35,069	£39,431
Apply positive discontinuation	£20,994	£22,418
Apply 30% stopping rule	£76,735	£74,077
5 year time horizon	£42,498	£44,091
15 year time horizon	£32,308	£39,268
Blended dose 30% 70 mg/70% 140 mg	£37,902	N/A
Blended dose 70% 70 mg/30% 140 mg	£33,404	N/A
Indication-specific utilities model	£34,761	£39,496
Utilities from EQ-5D LIBERTY (crosswalk 5L to 3L)	£68,080	£77,353

NICE MMD, Monthly migraine days; BSC, Best supportive care; AE, Adverse event 39

Source: Company submission: section B.3.8.3 (pages 186-188)

ERG base case: Chronic migraine

ERG changes (including fixing errors)	Incremental		Pairwise vs. BSC	
	70 mg	140 mg	70 mg	140 mg
Company's base case	Dominated	£17,832	£24,668	£13,340
1) Lifetime time horizon	Dominated	£27,038	£36,554	£11,855
2) Triptan injection costs	Dominated	£16,593	£23,633	£11,996
3) Non-responder MMD after stopping treatment	Dominated	£16,186	£23,556	£12,039
ERG base case (constant treatment effect)	**Dominated**	**£15,641**	**£25,818**	**£7,064**
ERG base case (effect waning over 5 years)	**Dominated**	**£36,659**	**£115,183**	**£30,881**

NICE

40

Source: ERG report: section 5.3 (page 96); section 6.1 (pages 102-103; 105-106); ERG erratum

Errors corrected by ERG:

- Discontinuation rate not applied in 1st cycle after response assessment
- Conversion between weekly and annual results
- Inconsistency regarding use of 24 week MMD distributions for responders

ERG base case: Episodic migraine

ERG changes (including fixing errors)	Incremental		Pairwise vs. BSC	
	70 mg	140 mg	70 mg	140 mg
Company's base case	£29,200	£73,282	£29,200	£40,662
1) Lifetime time horizon	£13,782	Dominated	£13,782	£36,510
2) Triptan injection costs	£27,613	£72,785	£27,613	£39,312
3) Non-responder MMD after stopping treatment	£28,106	£90,985	£28,106	£41,690
ERG base case (constant treatment effect)	**£10,207**	**Dominated**	**£10,207**	**£35,482**
ERG base case (effect waning over 5 years)	**£94,984**	**£310,725**	**£94,984**	**£143,414**

Note: Cost-effectiveness of 70 mg dose compared with 140 mg dose is inconsistent with clinical evidence. Effectiveness of 70 mg in patients for whom ≥3 prior treatments have failed not supported by evidence (no statistically significant results). Favourable cost-effectiveness driven by MMD frequency distribution for non-responders (lower than for 140 mg and BSC). Questionable whether there would be an advantage for 70 mg vs. 140 mg for non-responders.

NICE MMD, Monthly migraine days; BSC, Best supportive care 41

Source: ERG report: section 5.3 (page 96); section 5.4 (page 101); section 6.1 (pages 102-103; 105-106); ERG erratum

Errors corrected by ERG:

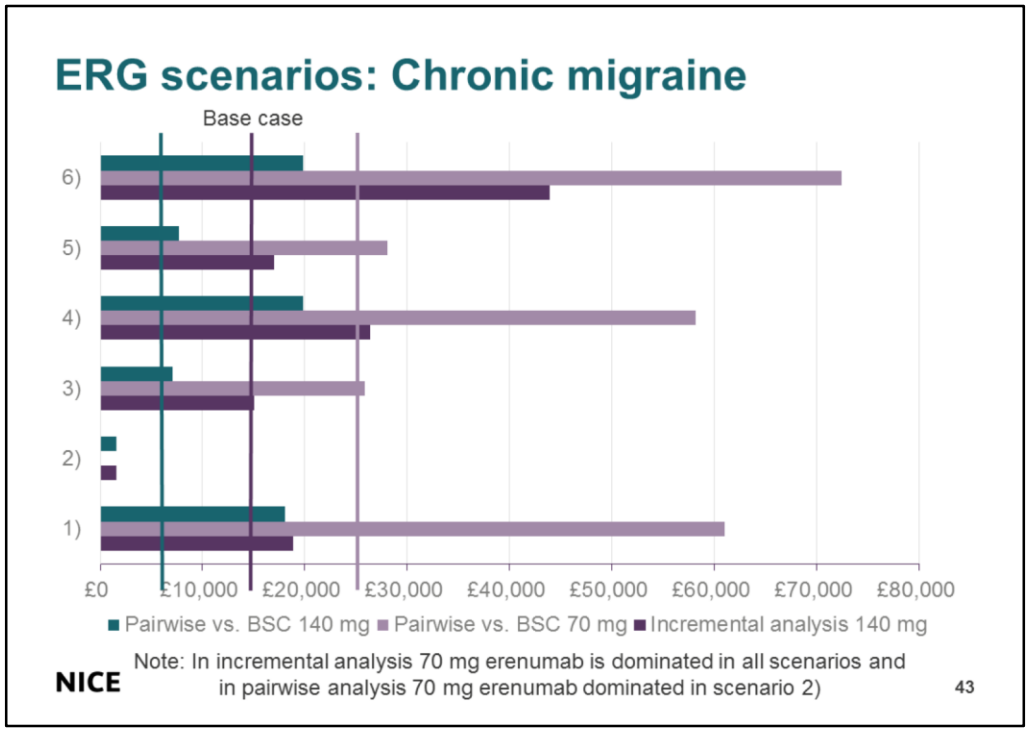
- Discontinuation rate not applied in 1st cycle after response assessment
- Conversion between weekly and annual results
- Inconsistency regarding use of 24 week MMD distributions for responders

ERG scenario analyses: chronic; episodic

	Incremental		Pairwise vs. BSC	
Chronic migraine	**70 mg**	**140 mg**	**70 mg**	**140 mg**
ERG base case (constant treatment effect)	Dominated	£15,641	£25,818	£7,064
1) Response definition ≥30% reduction	Dominated	↑ £18,862	↑ £60,941	↑ £18,862
2) Positive discontinuation	Dominated	↓ £1,549	Dominated	↓ £1,549
3) Botox response benefits after 12 weeks	Dominated	↓ £15,083	↔ £25,818	↔ £7,064
4) Treatment effect waning over 10 years	Dominated	↑ £26,351	↑ £58,135	↑ £19,787
5) Utilities from ≥3 prior subgroup	Dominated	↑ £17,000	↑ £28,061	↓ £7,678
6) Utilities from EQ-5D	Dominated	↑ £43,847	↑ £72,375	↑ £19,803
Episodic migraine				
ERG base case (constant treatment effect)	£10,207	Dominated	£10,207	£35,482
1) Response definition ≥30% reduction	↑ £90,984	Dominated	↑ £90,984	Dominated
2) Positive discontinuation	↓ £3,670	↓ £17,773	↓ £3,670	↓ £6,755
3) Treatment effect waning over 10 years	↑ £73,349	↑ £97,527	↑ £74,349	↑ £84,245
4) Utilities from ≥3 prior subgroup	↓ £7,528	Dominated	↓ £7,528	↓ £26,170
5) Utilities from EQ-5D	↑ £19,418	Dominated	↑ £19,418	↑ £67,498

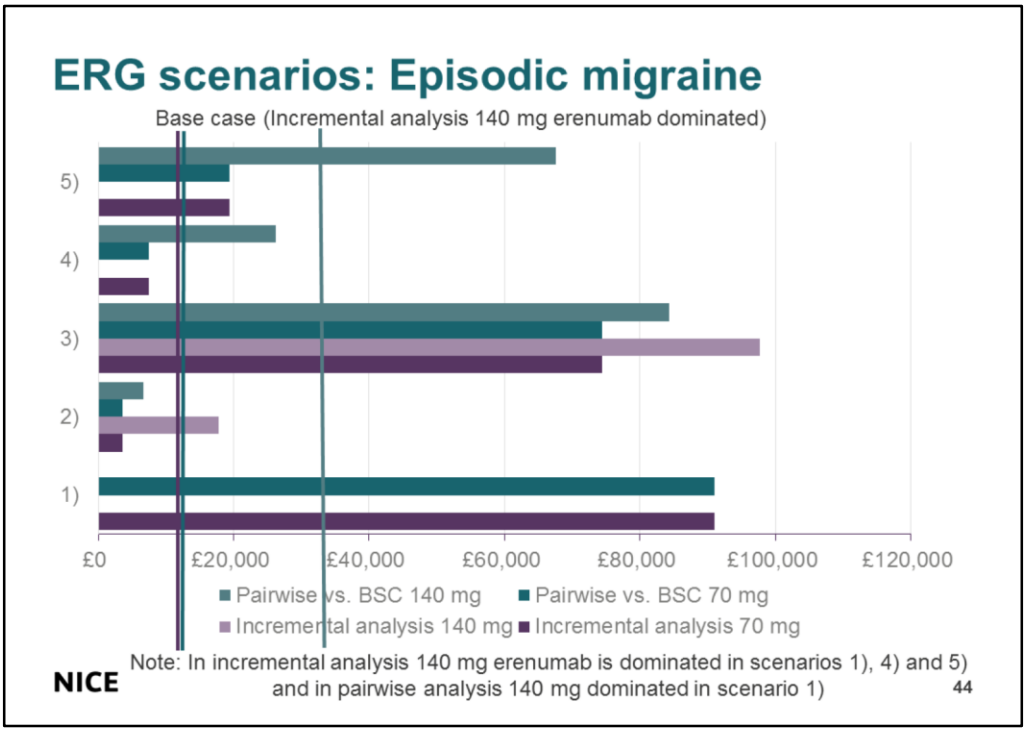
Source: ERG report: section 6.1 (pages 103-105; 106-107); ERG erratum

Note: scenario 3) Botox response benefits after 12 weeks – in the company's analysis response-specific utilities and costs were applied at 12 weeks for erenumab and 24 weeks for Botox but ERG consider that benefits of response may accrue beforehand, particularly before 24 weeks for Botox, so the ERG applied the response-specific utilities and costs for both erenumab and Botox at 12 weeks.



Scenarios

1) Response definition ≥30% reduction
2) Positive discontinuation
3) Botox response benefits after 12 weeks
4) Treatment effect waning over 10 years
5) Utilities from ≥3 prior subgroup
6) Utilities from EQ-5D



Scenarios

1) Response definition ≥30% reduction
2) Positive discontinuation
3) Treatment effect waning over 10 years
4) Utilities from ≥3 prior subgroup
5) Utilities from EQ-5D

High Frequency Episodic Migraine (HFEM)

- HFEM a recognised subgroup of episodic migraine patients who are considered to have a clinical burden similar to patients with chronic migraine, who have high unmet need because cannot access treatments recommended for chronic migraine (Botox)
- Company defines HFEM as 8-14 MHDs but analysis uses clinical data for 8-14 MHDs
- ERG questions using MMDs to approximate MHDs when these are separate outcomes

Company's subgroup analysis	
Whole population (chronic and HFEM)	
Blended dose: £22,260	140 mg: £19,239
Episodic migraine (restricted to people with HFEM)	
Blended dose: £37,607	140 mg: £37,749
ERG's subgroup analysis	
Assuming constant treatment effect	
70 mg Incremental: £10,782 70 mg Pairwise: £10,782	140 mg Incremental: Dominated 140 mg Pairwise: £29,259
Assuming effect waning over 5 years	
70 mg Incremental: £113,147 70 mg Pairwise: £113,147	140 mg Incremental: £125,865 140 mg Pairwise: £119,351
Alternative HFEM definition of 10-14 MHDs (Assuming constant treatment effect)	
70 mg Incremental: £13,556 70 mg Pairwise: £13,556	140 mg Incremental: Dominated 140 mg Pairwise: £40,972

NICE

MHD, Monthly headache days; MMD, Monthly migraine days

45

Source: Company submission: section B.3.2.1 (page 126); section B.3.9.1 (pages 191-192); ERG report: section B.5.2.3 (page 77); section B.5.3.3 (pages 99-100); ERG erratum

Innovation and equality issues

Innovation

- Erenumab is a 'step-change' in the management of migraine
- A first-in-class therapy
- Well tolerated, with few discontinuations because of adverse events
- Rapid onset of action
- Response maintained in longer-term
- Potential wider societal value of migraine prophylaxis
- More convenient and less resource-intensive alternative to Botox

Equality issues

- Migraine can be classed as a disability under the Equality Act 2010
- Migraine most common in people of working age and affects more women than men, therefore women further disadvantaged in the workplace by migraine
- Unequal access to specialist headache clinics and barriers to recommended treatments
- New treatment option may expose inequality of access to specialist services
- No issues raised by the company

NICE

46

Source: Company submission: section B.2.11 (pages 113-116)

Key issues: clinical effectiveness

- Are the trials generalisable to a UK population with migraine for whom ≥3 prior treatments failed?
- Is there sufficient clinical evidence to support long-term effectiveness of erenumab and durability of response?
- Do the trials adequately capture long-term safety data?
- Can it be assumed people with ≥15 headache days of which 4-7 are migraine are covered by the trial population?

NICE MMD, Monthly migraine days; MSQ, Migraine-specific quality of life questionnaire

Key issues: cost effectiveness

- Should the 'whole migraine population' be considered, or should chronic and episodic migraine populations be considered separately?
- Is it appropriate to consider a 'blended dose'?
- Should the 2 doses be considered together in an incremental analysis, or separately, in pairwise analyses?
- Should response to treatment be defined as ≥30% or ≥50% reduction in MMDs?
- What is the appropriate time horizon: 5 years? 10 years? 15 years? Lifetime?
- Is treatment effect likely to be constant or wane over time (over 5 years? 10 years?)
- Are people whose disease is responding likely to have treatment indefinitely?
- When treatment is stopped how is the disease likely to respond (revert to baseline or maintain any benefit seen at 12 weeks?) Is this likely to differ according to the reason treatment was stopped (i.e adverse events, non-response)?
- What is the most appropriate source of health utilities; MSQ scores from full trial or subgroup population, or EQ-5D? Are the utility values plausible?
- Are all relevant costs included?

NICE MMD, Monthly migraine days; MSQ, Migraine-specific quality of life questionnaire

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Erenumab for preventing migraine ID1188

Document B

Company evidence submission

September 2018

File name	Version	Contains confidential information	Date
NICE Erenumab Document B Final	**Final**	**Yes**	**December 2018**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

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Contents

Tables and figures

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

B.1.1 *Decision problem*

Erenumab was granted a marketing authorisation from the European Medicines Agency (EMA) on 26th July 2018 for the "prophylaxis of migraine in adults who have at least 4 migraine days per month when initiating treatment with erenumab". This submission addresses a decision problem that is based on part of the marketing authorisation for erenumab, focusing on migraine patients with ≥4 migraine days per month **for whom ≥3 prior prophylactic treatments have failed**. The optimisation to patients for whom ≥3 prior prophylactic treatments have failed is relevant and appropriate in the context of clinical practice within the National Health Service (NHS); erenumab would not be expected to be used in treatment-naïve patients due to the low cost of oral prophylactics. As such, at this position in the pathway, erenumab targets patients facing the highest unmet need and a lack of treatment options.

Migraine is a spectrum disorder, with patients in clinical practice distributed across a continuum of monthly migraine and headache day frequencies.[1-4] The decision problem addressed here is consistent with this as it considers patients with ≥4 monthly migraine days for whom ≥3 prior prophylactic treatments have failed as a single population of patients across the full spectrum of monthly migraine frequencies. This analysis is referred to as the "whole population base case".

In addition to the "whole population base case", the decision problem is also addressed by considering patients with chronic migraine and episodic migraine, with these two populations evaluated separately. Whilst these two populations are actively classified in some clinical guidelines (e.g. NICE CG150 and the International Classification of Headache Disorders [ICHD-III]),[5, 6] definitions of chronic and episodic migraine are not universally represented in clinical guidelines (e.g. the British Association for the Study of Headache [BASH] guidelines do not clearly define separate chronic and episodic populations).[7] Patient eligibility for each individual clinical trial of erenumab informing the marketing authorisation was distinguished using the terms of episodic and chronic migraine, though it should be noted that together these trials provide evidence across the entire population of patients with ≥4 monthly migraine days, and the marketing authorisation states that erenumab is licensed for migraine patients broadly, with no specific reference to chronic or episodic migraine. In addition, the only treatment currently recommended by NICE for the prophylaxis of migraine, botulinum toxin, is licensed and recommended by NICE for the treatment of chronic migraine patients only, consistent with the available evidence base for this therapy.[8] Feedback from eight headache expert UK neurologists has asserted that definitions of episodic and chronic migraine do not adequately capture the nature of migraine as a spectrum disorder in which patients may move between chronic and episodic migraine states over the duration of their disease and from month to month, and that these definitions therefore have limited relevance to clinical practice.[9] Nonetheless, in light of the relevance of definitions of chronic migraine and episodic migraine to clinical trial design and previous NICE guidance as noted above, this submission additionally presents analyses that separately consider the migraine population in terms of chronic migraine and episodic migraine, termed the "chronic migraine population" and "episodic migraine population", respectively. 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	People with migraine	Adults with migraine with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed. This represents an optimised use of erenumab in clinical practice. Specifically, this submission will address this decision problem by considering three populations: 1. Patients with ≥4 migraine days per month ["whole population base case"] 2. Patients defined as having chronic migraine (≥15 headache days a month of which at least eight are migraine) ["chronic migraine population"] 3. Patients defined as having episodic migraine (4–14 headache days per month) ["episodic migraine population"]	• Migraine is a spectrum disorder with patients distributed across a continuum of monthly migraine day frequencies; it is therefore appropriate to consider the population of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed as a whole • Some guidelines actively classify two populations of migraine (chronic and episodic) by frequency of monthly migraine or headache days,[5, 6] despite difficulties in distinguishing between these patients in practice.[9] It should be noted that these definitions are not universally represented in guidelines, and are of limited relevance in clinical practice. • The clinical trials for erenumab were also conducted in separate chronic and episodic populations in line with clinical trial guidelines, although the licence for erenumab does not distinguish between them as these trials showed efficacy in both populations and provided a simplified treatment algorithm • It was thus considered relevant to present evidence for the chronic and episodic migraine populations both together ("whole population base case") and separately
Intervention	Erenumab	Erenumab 70 mg or 140 mg once every 4 weeks	N/A – in line with NICE final scope
Comparator(s)	Established clinical management for migraine prophylaxis without erenumab	• BSC (for all three populations) • Botulinum toxin (for chronic migraine population only as per NICE recommendation[8])	• For the majority of patients for whom ≥3 prior prophylactic treatments have failed there are no further treatment options. Therefore, these patients would receive BSC • The exception to this is the availability of

			botulinum toxin, which is the only NICE-recommended therapy in the prophylaxis of migraine indication (and then for prophylaxis of chronic migraine only). Botulinum toxin is therefore a relevant comparator, though it is only recommended in a subset of patients who meet the definition of chronic migraine specified in the NICE guidance. Furthermore, it should be noted that the availability of botulinum toxin for these patients is restricted, and must be performed by trained expert physicians with specialist equipment, with only [redacted]% of NHS trusts in the UK estimated to be performing the procedure[10]
Outcomes	The outcome measures to be considered include: • 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 • Adverse effects of treatment • Health-related quality of life	• Frequency of migraine days per month o Change from baseline in mean monthly migraine days (MMDs) o Proportion of patients with ≥50% reduction in mean MMDs from baseline • Frequency of headache days per month o Change from baseline in mean MHDs • Severity of headaches and migraines o Change from baseline in monthly average severity of migraine pain o Change in pain interference with daily activities and migraine-specific impact from baseline, as measured by PROMIS (chronic migraine only) • Change from baseline in cumulative monthly headache hours • Change from baseline in monthly acute migraine-specific treatment days • Adverse effects of treatment	N/A – in line with NICE final scope

		• Health-related quality of life (EQ-5D-5L, HIT-6, MSQ v2.1, MIDAS and WPAI)	
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 PSS perspective.	• As per the NICE reference case, the cost-effectiveness of erenumab is expressed in terms of incremental costs per QALY, and costs have been considered from the perspective of the NHS and PSS. • A time horizon of 10 years is employed in the base case analysis, as this was considered an appropriate duration over which to fully capture the costs and benefits of erenumab, and is consistent with the time horizon used when evaluating biologics for other chronic diseases.[11-13]	N/A – in line with NICE final scope
Subgroups to be considered/ exploratory analyses	Not specified in final scope	The decision problem includes a subgroup analysis of the episodic migraine population, that considers only those patients within this population who have high frequency episodic migraine (8–14 MHDs). In addition, the submission presents exploratory analyses that consider the use of erenumab at an earlier line of therapy in patients for whom ≥2 prior prophylactic treatments have failed, and who face BSC as their only remaining treatment option due to contraindications, special warnings or precautions precluding use of a third oral prophylactic. As per the analyses in the ≥3 prior treatments population, results of this	The justification for the subgroup and exploratory analyses included in the submission is as follows: • HFEM is a recognised subgroup of episodic migraine, who are considered to have a clinical burden similar to those classified as having chronic migraine. However, these patients are unable to access botulinum toxin in line with its licensed indication and NICE recommendation, and therefore face a particularly high unmet need • Subgroup analyses are also presented in patients for whom ≥2 prior prophylactic treatments have failed, and who face BSC as their only remaining treatment option due to contraindications, special warnings or precautions precluding use of a third oral prophylactic, following feedback from UK

		exploratory analysis are presented for the whole population, the episodic migraine population and the chronic migraine population. Finally, analyses are presented in all three populations where all patients start treatment on the 140 mg dose of erenumab. The base case models a 50/50 split between patients receiving the 140 mg and 70 mg dose on initiation, which represents an assumption in the absence of long-term clinical experience of erenumab dosing in UK NHS clinical practice.	clinicians, which has indicated that there would be clinical desire to use erenumab at an earlier point in the treatment pathway • In the absence of long-term UK NHS clinical experience with erenumab, a conservative assumption, whereby 50% of patients would initiate treatment on erenumab 140 mg, and the remainder on erenumab 70 mg, is made in the base case analysis. However, the 140 mg dose may be more appropriate for patients for whom ≥3 prior prophylactic treatments have failed, as there is a trend towards better efficacy with the 140 mg dose in these more severe patients (see Section B.2.6.1). Analyses in which all patients initiate treatment on erenumab 140 mg are therefore also presented. Analyses in which all patients initiate treatment on erenumab 70 mg are presented in Appendix Z for completeness

Abbreviations: AE: adverse event; BSC: best supportive care; EQ-5D: EuroQol 5 dimensions; HFEM: high-frequency episodic migraine; HIT-6: Headache Impact Test; MHD: monthly headache day; MIDAS: Migraine Disability Assessment; MMD: monthly migraine day; MSQ-v2.1: Migraine-Specific Quality of Life Questionnaire Version 2.1; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PROMIS: Patient-Reported Outcomes Measurement Information System; PSS: Personal Social Services; QALY: quality-adjusted life year; WPAI: Work Productivity and Activity Impairment.

B.1.2 *Description of the technology being appraised*

A description of the technology being appraised (erenumab [Aimovig®]) is provided in Table 2 below.

Table 2: Technology being appraised

UK approved name and brand name	Erenumab (Aimovig®)
Mechanism of action	Erenumab is the only fully human monoclonal antibody CGRP receptor antagonist in clinical development for the prophylactic treatment of migraine. Erenumab is unique among the novel monoclonal antibody CGRP treatments for migraine as it is the only monoclonal antibody to target the receptor rather than the ligand, which is a more selective and targeted approach. CGRP is a pro-inflammatory vasodilating neuropeptide involved in migraine pathophysiology.[14] Erenumab binds to the CGRP receptor complex. It is designed to specifically inhibit CGRP biological activity through CGRP receptor signal transduction, irrespective of circulating CGRP levels. Therefore, the efficacy of erenumab is not affected by CGRP release or concentration. Binding to the receptor is competitive and can be reversible. By blocking the CGRP receptor, erenumab reduces the frequency and intensity of migraines experienced by patients.
Marketing authorisation/CE mark status	A marketing authorisation for erenumab in the indication relevant to this submission was received on 26th July 2018.[15]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Erenumab is indicated for the prophylaxis of migraine in adults who have at least four migraine days per month when initiating treatment.[16] Contraindications: • Hypersensitivity to the active substance or to any of the excipients Warnings and precautions for use: • Patients with certain major cardiovascular diseases were excluded from clinical studies. No safety data are available in these patients. • Latex-sensitive individuals: the removable cap of the erenumab pre-filled syringe contains natural rubber latex, which can cause allergic reactions in individuals sensitive to latex
Method of administration and dosage	Subcutaneous 70 mg or 140 mg Q4W. Treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine. The recommended dosage is 70 mg Q4W, although some patients may benefit from a dosage of 140 mg Q4W, which is administered as two consecutive injections of 70 mg each. Erenumab is available as a 70 mg pre-filled pen for self-injection; therefore two pre-filled pens are required per 140 mg dose. [redacted]

Additional tests or investigations	N/A
List price and average cost of a course of treatment	List price: £386.50 per 70 mg dose (1 x 70 mg pre-filled pen) The average cost of a course of treatment for a responder patient (assuming that 50% of patients initiate treatment on erenumab 70 mg, and 50% on erenumab 140 mg) is: [redacted] over 7 years (based on the median duration of treatment for responders of 7 years derived from the economic model). [redacted] The average cost of a course of treatment for a non-responder (12 weeks treatment) is: [redacted]
Patient access scheme (if applicable)	A simple PAS (confidential discount), making erenumab available at a fixed net price of £[redacted] per 70 mg dose was approved by the NHS England Commercial Medicines and Devices Investment Group on 1st May 2018. [redacted] Cost for non-responder (12 weeks treatment): £[redacted] Cost for responder patient: £[redacted] (confidential PAS price, based on modelled median duration of treatment for responders of 7 years)

Abbreviations: CGRP: calcitonin gene-related peptide; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; N/A: not applicable; PAS: patient access scheme; PASLU: Patient Access Scheme Liaison Unit; Q4W: every four weeks; SmPC: summary of product characteristics.

Appendix C: Health condition and position of the technology in the treatment pathway

Overview of the disease

- Migraine is a serious chronic neurological disorder, ranked as the third leading cause of disability in under 50's worldwide.[17]
- Migraine patients are distributed across a continuum of monthly migraine and headache day frequencies. An increasing frequency of migraine is associated with a greater clinical burden for patients, and a greater economic burden for the NHS.[18-20]
    - Some clinical guidelines actively classify migraine patients as having chronic migraine (≥15 headache days per month, of which ≥8 have features of migraine) or episodic migraine (0–14 headache days per month).[5, 7] Within episodic migraine, a subgroup of patients with high-frequency episodic migraine (HFEM) is also recognised as being associated with a higher burden of disease.[21]
    - However, these definitions are not universally represented in guidelines. Furthermore, eight headache expert UK neurologists provided feedback that these definitions can be of limited relevance to clinical practice, where patients may move between chronic and episodic migraine definitions over the duration of their disease and from month to month, and migraine is considered and treated more as a spectrum disorder.[1-4, 22]
- Migraine has a high burden of disease, with considerable effects on both individual patients and wider society. A migraine attack may last for up to 72 hours, during which time patients can experience a number of symptoms, including a severe throbbing pain in the head, nausea and vomiting.[6, 23] The effects also extend beyond the migraine itself, with patients consistently reporting compromised physical, mental and social wellbeing.[24-26]
- The intensity and frequency of migraine symptoms can be hugely debilitating, with patients often having a substantially decreased quality-of-life. Severe migraine attacks are classified among the most disabling illnesses by the World Health Organisation (WHO), comparable to dementia and active psychosis.[27]
- Migraine is the second most frequently cited cause of short-term absence,[28] accountable for an estimated 43 million absenteeism days of work lost each year in the UK.[29]
- In spite of the significant clinical and economic burden posed by migraine, its burden remains underappreciated, and it is the least publicly funded of all neurological illnesses relative to its economic impact.[30]

Clinical pathway of care

- Erenumab is positioned within this submission for the prophylaxis of migraine in patients for whom ≥3 prior prophylactic therapies have failed. This optimised positioning reflects the expected use of erenumab in the NHS, given the high burden of disease, the context of the availability of low cost oral prophylactics as initial treatment options and the high unmet need for these patients: as discussed below, the only recommended treatment option at this point in the pathway is botulinum toxin, which is recommended only for chronic migraine patients who have not responded to ≥3 prior prophylactic treatments.
- Current NICE clinical guidelines (CG150) recommend oral prophylactic treatments (typically topiramate, propranolol or amitriptyline) in the first instance for migraine patients.[5] Robust data to support the benefit-risk ratio of these treatments for the prophylaxis of migraine are limited. Furthermore, these options are associated with numerous different AEs, with patients frequently switching, discontinuing or delaying therapies due to a lack of

efficacy or poor tolerability, and real-world data showing that adherence rates range from 17–20% after only one year.[31-33]

- As such, patients can cycle through these treatment options quickly, with up to 20% of patients reaching a point where ≥3 prophylactic therapies have failed for them.[34] At this point, there are no further treatment options for the majority of patients, and these patients would therefore receive BSC. For some patients, contraindications, special warnings and precautions mean that they reach a point at which BSC is the only treatment option after ≥2 prophylactic therapies have failed for them.
- The exception to this is the availability of botulinum toxin, which is the only NICE-recommended therapy for the prophylaxis of migraine. Botulinum toxin is only available for patients who have not responded to ≥3 prior prophylactic treatments and who meet the definition of chronic migraine specified in the NICE guidance (TA 260).[8] Clinical trials of botulinum toxin in patients classified as having episodic migraine failed to meet their primary endpoints, meaning botulinum toxin is not an option for this patient population.[35, 36]
- The availability of botulinum toxin is highly restricted. The procedure must be performed by physicians with appropriate qualifications and expertise, using specialist equipment. As such, it is currently estimated to be available to migraine patients in [redacted]% of NHS trusts in the UK.[10] Therefore, botulinum toxin is a relevant comparator only for a small subgroup of patients within the chronic migraine population.
- As erenumab can be self-administered and is not restricted to specific specialist neurology centres, it has the potential to provide a treatment option that is not only easier for patients to use and less burdensome on the NHS than botulinum toxin, but that is available to a higher proportion of those patients currently facing a considerable unmet need. Erenumab also provides the benefit of being licensed across the spectrum of migraine.
- The recommended dosage of erenumab is 70 mg Q4W, however some patients may benefit from a higher dosage of 140 mg Q4W. Clinicians have the flexibility to select the dose they consider to be most appropriate for each patient. This means that patients with a high burden of disease and corresponding unmet need (e.g. patients for whom prior prophylactic treatments have failed) have the option to start treatment on the higher dose, which has been shown to be more effective in this more severe patient population (see Section B.2.6.1)

B.1.2.1 Overview of disease

Classification of migraine

Migraine is a serious chronic neurological disorder, having been ranked as the seventh most prevalent disorder and third leading cause of disability worldwide in the most recent Global Burden of Disease Survey.[37] In the UK, around 20% of the adult population, or 5.85 million people, are affected by migraine, amounting to 190,000 migraine attacks each day.[38]

In spite of this, migraine remains considerably underfunded, with research showing that it is the least publicly funded of all neurological illnesses relative to its economic impact in the European Union (EU).[30] This is compounded by similarly low rankings for anxiety and affective disorders, two of the most prevalent comorbidities of migraine.[30] Whilst this is likely the result of a combination of factors, the trivialisation of the condition as ‘just a headache’ is likely a key driving force behind its underappreciation.

There are no biological markers for migraine, and as such, diagnosis is based on both clinical history and the exclusion of other headache disorders. The ICHD-III provides a set of clinical criteria for the definition of migraine with or without aura, to guide diagnoses and subsequent treatment. These are outlined in Table 3 below.[6]

Table 3: Definition of migraine without aura and migraine with aura

Migraine without aura	Migraine with aura
• Recurrent headaches (at least five lifetime attacks) • Untreated or unsuccessfully treated headache duration of four to 72 hours • Headache with at least two of the following pain characteristics: o Unilateral o Pulsing o Moderate or severe intensity o Aggravated by physical activity • Associated with at least one of: o Nausea o Vomiting o Photophobia o Phonophobia	• At least two attacks fulfilling the below criteria: • One or more of the following fully reversible aura symptoms: o Visual o Sensory o Speech and/or language o Motor o Brainstem o Retinal • At least two of the following four characteristics: o At least one aura symptom spreading gradually over ≥5 minutes, and/or two or more symptoms occurring in succession o Each individual aura symptom lasts 5−60 minutes o At least one aura symptom is unilateral o Aura is accompanied, or followed within 60 minutes, by headache

Source: ICHD-III clinical critieria[6]

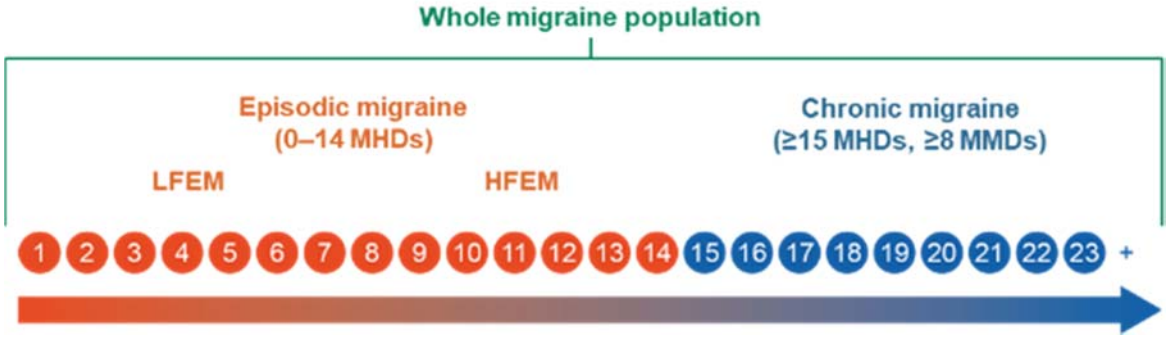
Migraine is a spectrum disorder with migraine patients distributed across a continuum of monthly migraine and headache day frequencies.[1-4] An increasing frequency of migraine days is associated with a greater clinical burden for patients, and a greater economic burden, both directly in terms of healthcare costs for the NHS, and indirectly, through productivity losses.[18] An increased migraine frequency is significantly associated with declines in both overall health utility and individual components including emotion and cognition.[19] Rates of depression and anxiety are also found to be associated with increasing frequencies of migraine.[20]

In some clinical guidelines, migraine patients are classified as having either chronic or episodic migraine dependent upon their monthly headache and migraine frequencies.[5, 6] The ICHD-III, for instance, defines episodic migraine as 0–14 headache days per month, and chronic migraine as 15 or more headache days per month, of which eight or more have features of migraine (with or without aura).[6] Episodic migraine patients may be further categorised into low-frequency episodic migraine (LFEM) and high-frequency episodic migraine (HFEM), with the latter having been recognised as having a higher burden of migraine more in line with patients who would be classified as having chronic migraine (Figure 1).[39]

These definitions are used to distinguish patients who have a higher frequency of headaches and migraines, and are likely to suffer more severely from their condition. However, the definitions are not universally represented in guidelines or applied in practice. For example, BASH guidelines refer to chronic migraine only as “migrainous headache occurring every day” and do not provide any active discussion of separate episodic or chronic populations, nor any definition of episodic migraine.[7] Furthermore, feedback from eight UK neurologists who specialise in headache management has stated that in practice, migraine is considered a spectrum disorder, with treatment decisions made not according to these discrete classifications, but on the basis of migraine frequency and severity.[9] Patients may move between migraine frequencies and cross from meeting one definition to another over their disease duration, or indeed on a monthly basis, limiting the practical relevance of definitions of episodic and chronic migraine.[1, 40, 41] Patients may

also experience a high degree of short-term variability in headache days per month, with one study showing that nearly three quarters of patients diagnosed with chronic migraine at baseline dropped below the diagnostic boundary of ≥15 MHDs over the course of one year.[40] This means that the diagnosis and management of migraine is challenging, and the interpretation of these definitions may differ between clinicians and individual patients. Where treatments are restricted to use in only either episodic or chronic migraine, but not both, this has the potential to pose challenges to effective management of the patient condition when considering that in reality patients may move between definitions of migraine over both the short- and long-term. The limited clinical relevance of classifying patients as either chronic or episodic migraine is highlighted by the emergence of the sub-categorisation of patients with HFEM. Studies suggest that these patients, although traditionally meeting the definition of episodic migraine, are much closer clinically to patients that might be categorised as chronic migraine patients.[9]

Figure 1: Classification of migraine by number of monthly migraine and headache days



Abbreviations: HFEM: high-frequency episodic migraine; LFEM: low-frequency episodic migraine; MHDs: monthly headache days; MMDs: monthly migraine days.
Source: Based on feedback from UK clinicians and Torres-Ferrus *et al*. (2017)[42]

Burden of disease

Migraine is a debilitating condition which has a considerable impact upon an individual's ability to work and socialise. Patients may suffer numerous migraine days per month, which are classified as any calendar day in which the patient experienced a qualified migraine headache (migraine headache defined as in Table 3), in either onset, continuation, or recurrence of the headache. An individual migraine typically lasts from four to 72 hours and may therefore span over multiple migraine days. During this time, patients experience a severe recurrent throbbing pain in their head, which is often accompanied by further disabling symptoms including nausea, vomiting, dizziness, fever and visual disturbances.[23] These acute physical symptoms have led to the classification of severe migraine attacks as one of the most disabling illnesses by the WHO, alongside conditions such as dementia and active psychosis.[27] Furthermore, headache is attributed as the leading neurological cause for accident and emergency (A&E) attendance, and in 2015/16, there were more than 85,000 hospital admissions and almost 71,000 emergency admissions where the primary diagnosis was headaches and migraine, an increase of 17% and 13%, respectively, from 2012/13.[43]

A migraine attack may be preceded by a prodrome phase in 30–40% of patients, and an aura phase in around 30% of patients. The prodrome comprises symptoms such as fatigue, irritability and food cravings, and can last for multiple days. The aura phase usually lasts for under an hour and is characterised by visual disturbances, numbness or weakness, slurred speech and sensitivity to light and sound. Around 70% of patients also experience a postdrome phase, which may include symptoms of fatigue and confusion.[44] In a survey of [redacted] people with migraine in the UK approximately [redacted]% of patients reported being somewhat/very/extremely limited after a

migraine attack.[45] The intensity, frequency and duration of the migraine can therefore be hugely debilitating, and studies have demonstrated that patients with migraine consistently report high levels of pain; 80% of those sampled in a US postal survey (n=3,577) experienced either 'severe' or 'extremely severe' pain,[46] and the average pain intensity in a study of 5,000 adult with migraine in England was reported as 7.5 out of ten.[47] Some patients who experience a high number of migraine days are left incapacitated for over half of the month, and are unable to work at all.[48]

The effects also extend beyond the duration of the attack itself, with more than three-quarters of sufferers reporting that their day-to-day activities are limited to some extent.[49] Patients with migraine report compromised physical, mental and social well-being, with multiple studies showing migraine patients to have a significantly lower health-related quality of life than the general population.[24-26] Migraine patients also are more likely to suffer from sleep-related problems including restless leg syndrome, sleep paralysis and daytime dysfunction.[50-52] Rates of common psychiatric disorders are higher in the migraine patient population, with the prevalence of depression and anxiety estimated to be as high as 50% and 60%, respectively.[53] Patients are also more likely to suffer from a range of other conditions, including epilepsy, chronic pain and ischaemic stroke, for which migraine patients have a two-fold risk compared to people who do not experience migraine.[54, 55] Furthermore, the impact of migraine extends into the personal and social lives of patients, with one study reporting that 45% of patients have missed family or social events, 50% believed that they were more likely to argue with their partners and children, and 32% reported avoiding making plans for fear of cancellation due to a migraine attack.[56] In a survey of [redacted] people with migraine in the UK over [redacted]% reported cancelling plans due to migraine.[45] As noted previously, migraine frequency is significantly associated with declines in both overall health utility, and individual components including emotion and cognition. Rates of depression and anxiety are also found to be associated with increasing frequencies of migraine.[19, 20]

In addition to the clinical burden on patients, migraine imposes substantial costs upon society, with the total financial burden in the UK estimated to be up to £9.7 billion per year.[29] Direct healthcare costs from outpatient care, investigation, prescription drugs and hospitalisations are in the region of almost £1 billion annually, and are compounded by several indirect costs, which are estimated to account for up to 93% of the total cost of migraine.[29, 57] As the second most frequently cited cause of short-term absence in non-manual workers, it is estimated that migraine accounts for up to 43 million days lost from work each year in the UK alone, at a cost of almost £4.4 billion.[28, 29] Furthermore, research suggests that people with migraine are more likely to go into work with symptoms present rather than be absent, meaning that presenteeism is likely to have a considerable impact on productivity losses.[58] Presenteeism is likely to be responsible for as much, if not more, lost productivity.[29] Additional costs are likely to arise during the interictal (i.e. between attacks) state, during which patients often exhibit anxiety and avoidance behaviour which has considerable impact on their quality of life, with further losses arising through the impact of migraine on career advancement and potential earnings.[29]

In summary, migraine poses a significant burden upon both patients and wider society, through its impact on health, quality of life, absenteeism and productivity. There is therefore a large unmet clinical need for well-tolerated and effective prophylaxis treatment for migraine patients.

Unmet need in prophylaxis of migraine

Acute migraine is initially treated with analgesics or triptans, with prophylaxis considered should these options prove unsuccessful. Prophylactic treatments are recommended to prevent the

onset of migraines, to reduce the attack frequency, severity and duration, and to improve responsiveness to treatment of acute attacks. They are deemed to be necessary for those patients with severe, frequent, or disabling migraine attacks. Prophylactic treatments may also prevent the problems of addiction and medication overuse which are associated with many of the acute pain-relieving medications available.[59, 60]

None of the prophylactic medications currently prescribed in the UK were developed specifically for use in migraine patients; all current treatments have instead been repurposed from uses in other patient populations. Furthermore, despite their widespread use, there is limited robust clinical evidence to support the effectiveness of most treatment options.[7, 61] Unpredictable variation in individual responses to treatment results in around 30% of patients failing to respond to any particular prophylactic medication, and evidence suggests that up to 20% of migraine patients do not respond to more than three different prophylactic treatment options.[34, 62] It is estimated that around 100,000 migraine patients in England and Wales fall under this category, which represents a large and continued unmet clinical need.[10]

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.[31-33] Less than half of patients on prophylactic treatments report being satisfied with their current treatment regimen, and many resort to over-the-counter medications.[63] Real-world data shows that adherence rates range from 17–20% after one year, and that persistence falls below the acceptable threshold of 80% after only six months.[32, 33] Adverse events (AEs) such as taste perversion, weight loss and paraesthesia are common in all 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.[64] Prophylaxis failure can also lead to overuse of acute migraine medication, which can perversely cause worsening migraine;[65] one study has shown that the use of acute medications on as few as five days per month can lead to an increase in the frequency of migraine days experienced.[66] 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 process.[7]

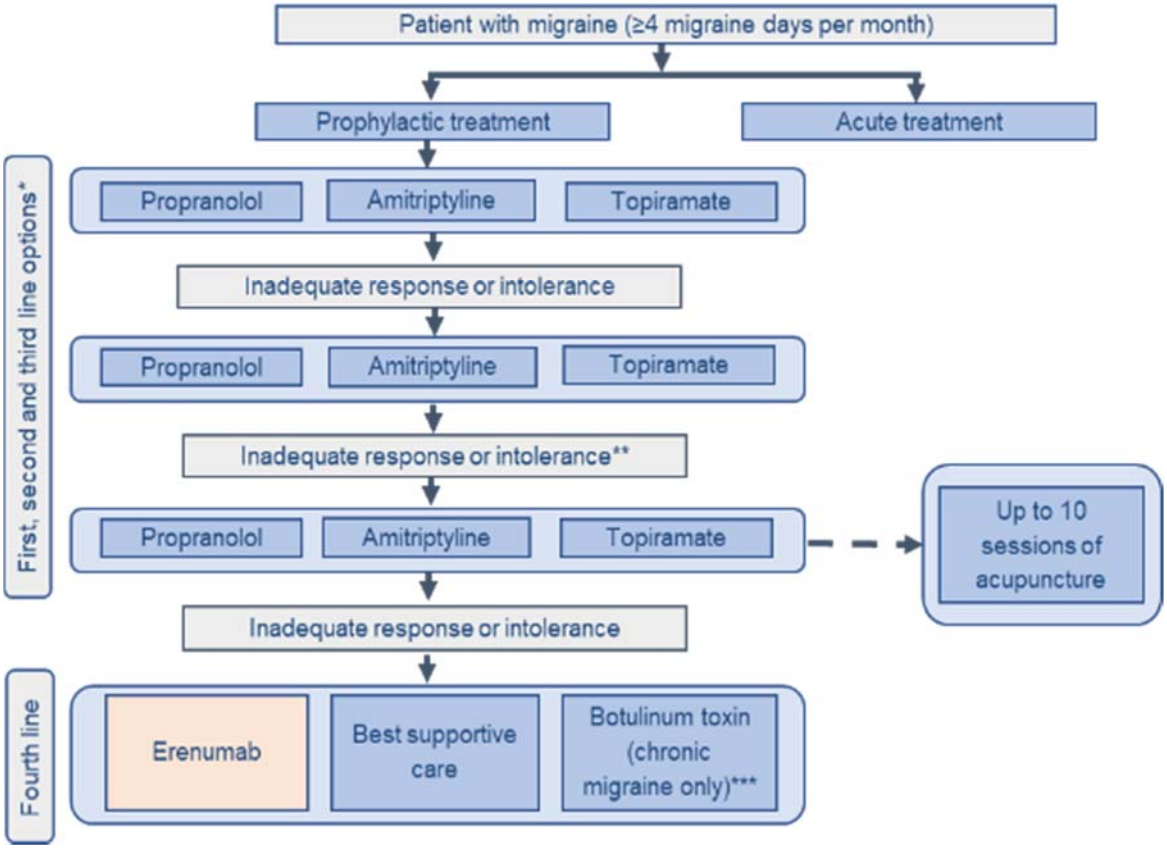
Issues of lack of efficacy, safety and tolerability described above mean that many patients do not respond to multiple prophylactic treatments, and quickly cycle through first-, second- and third-line options. At this point, the only option for the majority of patients is BSC, consisting of continued treatment with acute medication. Some patients may find that contraindications, special warnings and precautions concerning remaining oral prophylactic options mean that they face BSC as their only treatment option after just two prior oral prophylactic therapies. Patients receiving BSC are unlikely to achieve satisfactory outcomes in the long term, and can also suffer problems associated with medication overuse and migraine worsening as outlined above. It is therefore clear that there remains a considerable unmet need for well-tolerated and effective treatments for migraine prophylaxis, particularly for those patients for whom prior prophylactic treatments have failed.

B.1.2.2 Clinical pathway of care and relevant comparators to erenumab

The clinical pathway of care in the UK NHS for migraine patients with ≥4 MMDs (the population for which erenumab is licensed) is presented in Figure 2. This pathway is based on the NICE clinical pathway for the management of headaches in over 12s (CG150), in addition to the

section on migraine prophylaxis in BASH guidelines for the diagnosis and management of migraine, tension-type, cluster and medication-overuse headaches.[5, 7] These represent the guidelines of most relevance to UK practice. Guidance was also sought from eight UK neurologists who specialise in headache with regards to the use of specific therapies as first-, second- and third-line options.[9]

Figure 2: Clinical pathway of care for migraine patients with ≥4 migraine days per month



*If treatment at its maximum tolerated dose in the first-line is ineffective or poorly tolerated, the other two treatment classes may be considered for second-line. The same applies in moving from second-line to third-line treatment. No treatment should be tried twice in the pathway. **For those contraindicated to a third oral prophylactic, the remaining options would be BSC or erenumab. ***Botulinum toxin is recommended only for patients classified as having chronic migraine as per the NICE guidance for this therapy.[8]
Source: based on: NICE clinical guideline CG150: Headaches in over 12: diagnosis and management[5]; BASH Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type Headache, Cluster Headache and Medication-Overuse Headache (3rd Edition)[7]; NICE TA260: botulinum toxin type A for the prevention of headaches in adults with chronic migraine[8]; clinical expert opinion from an advisory board.[9]

The current NICE guideline (CG150) for the treatment of patients with migraine details treatment options for both acute and preventive (prophylactic) treatment.[5] For prophylaxis, topiramate, propranolol and amitriptyline are considered as initial options for migraine patients. The specific choice of treatment is made based on the patient's preference, comorbidities and the risk of AEs. If the first line therapy given is ineffective or poorly tolerated, then the other options not received as first-line are considered for second- and third-line treatments. Patients are reviewed three to six months after commencing treatment to assess the continuing need for migraine prophylaxis. As described in Section B.1.2.1, adherence to treatment is particularly poor in this disease area, and evidence suggests that up to 20% of migraine patients do not respond to three or more different prophylactic treatment options.[34, 62] Patients can be classified as not responding to treatment 6–8 weeks after dose titration,[7] meaning that they can cycle through treatment options relatively quickly.

Erenumab is positioned in this submission as a treatment option for migraine patients for whom ≥3 prior prophylactic treatments have failed. This reflects a patient population who face the continued burden of untreated or poorly managed migraine, as described in the section on current unmet need in prophylaxis of migraine: Section B.1.2.1. The optimisation to the population of migraine patients for whom ≥3 prior prophylactic treatments have failed is relevant and appropriate in the context of NHS clinical practice; erenumab would not be expected to be used in treatment-naïve patients due to the low cost of prophylactics. It is also in line with the NICE recommendation for botulinum toxin, although this is limited to the treatment of chronic migraine only, where treatment after three prior oral prophylactic therapy failures was considered a pragmatic approach for the NHS.[8] At this position in the treatment pathway, erenumab would be targeted for use in patients who face a high unmet need and a lack of treatment options.

It should be noted that feedback from UK clinicians has indicated that, if made available, there would be clinical desire to use erenumab at an earlier point in the treatment pathway: in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions.[9] Exploratory economic analyses considering this patient population are therefore also presented in Appendix Z. This submission also presents a subgroup analysis of patients classified as having HFEM for whom ≥3 prior prophylactic treatments have failed (see Section B.3.9.1). This is a recognised subgroup of episodic migraine patients who are considered to have a clinical burden similar to patients classified as having chronic migraine. However, unlike chronic migraine patients, patients with HFEM for whom ≥3 prior prophylactic treatments have failed are unable to access botulinum toxin in line with its NICE recommendation. The subgroup of HFEM patients therefore face a particularly high unmet need.[42]

As per the summary of product characteristics (SmPC), “the recommended dose [of erenumab] is 70 mg erenumab every 4 weeks”, but “some patients may benefit from a dose of 140 mg every 4 weeks”. Both doses were studied in the pivotal clinical trials for erenumab, reported in Section B.2. In the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, the optimised patient population in this submission, patients treated with erenumab 140 mg achieved numerically superior clinical outcomes compared to patients treated with erenumab 70 mg (see Section B.2.6.1), which may indicate that the higher dose is more suitable for these patients with more severe disease. Furthermore, the AE profiles of erenumab 70 mg and 140 mg are comparable, with no consistent dose-response trend observed. The 140 mg dose may therefore be most appropriate for the patient population considered in this submission; migraine patients for whom ≥3 prior prophylactic treatments have failed. This is supported by feedback from six expert UK neurologists, who considered that starting patients on the 140 mg dose may be the most efficient treatment approach for these difficult-to-treat patients, given the trend towards better efficacy with this dose, with no observed difference in adverse events.[67] The higher 140 mg dose is therefore considered to optimise the benefit-risk ratio for a subgroup of patients with a particularly high unmet need and limited therapeutic options, whilst the lower dose is considered to be appropriate for other patients, including those who are naïve to prophylactic treatment, or for whom prophylactic treatments have not failed. In this context, exploratory economic analyses have been presented where the proportion of patients starting on either the 70 mg or 140 mg dose of erenumab is varied (see Section B.3.8.3).

Relevant comparators to erenumab

For the majority of migraine prophylaxis patients for whom ≥3 prior prophylactic treatments have failed there are no further treatment options. As shown in Figure 2, these patients will receive

BSC in UK clinical practice, defined by continued treatment with acute medication and healthcare resource use in line with the monthly migraine days experienced. This is the only option for patients with episodic migraine at this point in the pathway and is also the only option for the majority of patients classified as having chronic migraine. The relevance of BSC as a comparator in this patient population is highlighted by the acceptance of BSC as the comparator in the only previous NICE appraisal in this disease area: botulinum toxin for chronic migraine (TA260).

Botulinum toxin has been recommended by NICE only for patients classified as having chronic migraine only, who have not responded to ≥3 prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse.[8] As such, botulinum toxin is a relevant comparator to erenumab in the subset of patients classified as having chronic migraine. Clinical trials of botulinum toxin in patients classified as having episodic migraine failed to meet their primary endpoints, meaning that botulinum toxin has not demonstrated effectiveness in this patient population.[35, 36] Treatment with botulinum toxin involves intramuscular injections to between 31 and 39 sites in the head and the back of the neck every 12 weeks.[8] This must be performed by a trained specialist, and as a result, it is estimated that only around [redacted]% of NHS Trusts in the UK currently use botulinum toxin for the prophylaxis of migraine.[10] Despite the positive NICE guidance for botulinum toxin in chronic migraine patients, availability of this treatment is restricted by these administration requirements and space in clinics, meaning that the majority of patients meeting the definition of chronic migraine will receive BSC in clinical practice. Erenumab is administered subcutaneously and can be self-administered by patients every four weeks following an initial hour-long nurse-led training session. It therefore has the potential to provide a treatment option that is easier to use for patients and less burdensome on the NHS than botulinum toxin. There is no restriction on neurology centres able to administer erenumab, meaning that it provides the only available treatment option for those patients who are unable to access the specialist centres that offer treatment with botulinum toxin. The relevant comparators for each migraine population considered in this submission are outlined below:

- Whole population base case: BSC
- Chronic migraine population: BSC and botulinum toxin (given in conjunction with BSC)
- Episodic migraine population: BSC

B.1.3 *Equality considerations*

It is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary of the clinical evidence

- Four clinical trials are considered to provide the key evidence for the clinical effectiveness of erenumab for migraine prophylaxis in this submission:
  - **Study 295:** phase II RCT (n=667) vs placebo in chronic migraine patients (70 mg and 140 mg).
  - **STRIVE:** phase III RCT (n=955) vs placebo in episodic migraine patients (70 mg and 140 mg).
  - **ARISE:** phase III RCT (n=577) vs placebo in episodic migraine patients (70 mg only).
  - **LIBERTY:** phase IIIb RCT (n=246) vs placebo in episodic migraine patients for whom 2–4 prior prophylactic treatments had failed (140 mg only).
- In the ITT population of each trial, patients treated with erenumab 70 mg and 140 mg achieved greater reductions in MMDs versus placebo, and a higher proportion of patients treated with erenumab also achieved a ≥50% reduction in MMDs versus placebo.
- The benefits of treatment with erenumab were consistent in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, the optimised patient population in this submission. Patients treated with erenumab 140 mg achieved greater reductions in MMDs than patients treated with erenumab 70 mg, in addition to improvements across several other outcomes, suggesting that the higher dose may be more suitable for this patient population, which has a high clinical burden and associated unmet need.
- As outlined in Section B.2.6, only a small number of patients in STRIVE and ARISE (n=74 and n=56, respectively) had received ≥3 prior prophylactic treatment categories. Analyses in these subgroups are therefore not considered to be meaningful across all outcome measures, and are presented for completeness only. LIBERTY provides more relevant clinical evidence in this subgroup as this was a study specifically designed to assess the efficacy and tolerability of erenumab in patients who have failed 2–4 previous migraine prophylactic treatments.

Study 295 efficacy results

- In *post-hoc* analyses of the subgroup of patients for whom ≥3 prior prophylactic treatment categories had failed (n=98, n=69 and n=65 in placebo, erenumab 70 mg and erenumab 140 mg arms), treatment with erenumab 70 mg and 140 mg resulted in a significantly greater mean reduction in MMDs from baseline to Week 12 than with placebo (difference in LSM versus placebo: −2.53 [95% CI: −4.27, −0.78; p=0.005] and −4.09 days [95% CI: −5.84, −2.33; p<0.001], respectively). In total, 34.8% of patients in the erenumab 70 mg arm, and 38.5% of patients in the erenumab 140 mg arm, achieved a ≥50% reduction in MMDs from baseline, compared to 15.3% in the placebo arm (OR: 2.96 [95% CI: 1.39, 6.27; p=0.004] and OR: 3.48 [95% CI: 1.64, 7.39; p=0.001], respectively).

STRIVE efficacy results

- In *post-hoc* analyses of the subgroup of patients for whom ≥3 prior prophylactic treatment categories had failed (n=27, n=24 and n=23 in placebo, erenumab 70 mg and erenumab 140 mg arms), patients treated with erenumab 70 mg and 140 mg achieved mean MMD reductions versus placebo of [redacted] (95% CI: [redacted]; [redacted]) and [redacted] (95% CI: [redacted]; [redacted]), respectively. In total, [redacted]% of patients in the erenumab 140 mg arm achieved a ≥50% reduction in MMDs from baseline, compared to [redacted]% in the placebo arm (OR: [redacted]; 95% CI: [redacted]; [redacted]). [redacted] ([redacted]%) patients in the erenumab 70 mg arm achieved a ≥50% reduction in MMDs from baseline to Week 12 (OR versus placebo: [redacted] [95% CI: [redacted]; [redacted]]).

ARISE efficacy results

- In *post-hoc* analyses of the subgroup of patients for whom ≥3 prior prophylactic treatment categories had failed (n= and n= in placebo and erenumab 70 mg arms), patients treated with erenumab 70 mg achieved greater reductions in mean MMDs from baseline compared to placebo (difference versus placebo: days [95% CI: ;). In total, patients (%) in the erenumab 70 mg arm, and patients in the placebo arm (%) achieved a ≥50% reduction in MMDs from baseline to Week 12 (OR: [95% CI: ;]).

LIBERTY efficacy results

- In *post-hoc* analyses of the subgroup of patients for whom ≥3 prior prophylactic treatments had failed, treatment with erenumab 140 mg resulted in greater reductions from baseline in MMDs compared to placebo (difference in LSM versus placebo: days [95% CI: ;]). In the erenumab 140 mg arm, % of patients achieved a ≥50% reduction in MMDs from baseline, compared to % of patients in the placebo arm (OR: [95% CI: ; p=]).

Summary of the results from the indirect treatment comparison

- The key comparator to erenumab is BSC, which is represented by the placebo arms of the four clinical trials informing the clinical efficacy of erenumab in this submission. Therefore, these trials provide direct relative efficacy data versus this comparator.
- In the absence of head-to-head trial data directly comparing erenumab to botulinum toxin in patients classified as having chronic migraine, an indirect treatment comparison (ITC) was conducted using data in the patient population for whom ≥3 prior prophylactic treatments have failed from Study 295 for erenumab, and the pooled PREEMPT study for botulinum toxin.
- 

Summary of safety evidence

- Overall, erenumab was well-tolerated and associated with an adverse event (AE) profile comparable to that of placebo. Erenumab 70 mg and 140 mg demonstrated similar safety profiles, with low numbers of AEs, SAEs and AEs leading to treatment discontinuation across both doses.
- The majority of AEs observed with erenumab were mild or moderate in nature, with serious adverse events (SAEs) being reported by only a minority of patients across all three treatment groups. SAEs were reported by 1.1%, 1.9% and 1.7% of patients treated with erenumab 140 mg in Study 295, STRIVE and LIBERTY, respectively, and by 3.2%, 2.5% and 1.1% of patients treated with erenumab 70 mg in Study 295, STRIVE and ARISE, respectively. These were similar to the number of SAEs observed in the placebo arms in each study (2.5%, 2.2%, 1.7% and 0.8% in Study 295, STRIVE, ARISE and LIBERTY).
- As noted in the SmPC, across the erenumab phase II and III clinical trial programme as a whole, the most frequently reported adverse drug reactions were injection-site reactions (4.5%), constipation (3.2%), muscle spasms (2.0%) and pruritus (1.8%).

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant clinical evidence from randomised controlled trials (RCTs), SLRs and (network) meta-analyses (NMAs) on the efficacy and safety of erenumab and botulinum toxin (as the only active comparator) for the prophylaxis of migraine. The SLR was conducted in February 2018, and subsequently updated in August 2018. In total the SLR identified 43 unique RCTs, of which 9 were studies of erenumab and 34 of botulinum toxin. No single study evaluated both treatments. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

Table 4 provides a summary of all studies of erenumab in the chronic or episodic migraine patient populations that were identified by the clinical SLR reported in Section B.2.1 and Appendix D, or available to Novartis as data on file. Although all such studies of erenumab are listed for transparency, only some studies are presented in full in this submission and used to inform the economic model, as detailed in Table 4.

Table 4: Overview of relevant clinical evidence informing the submission

Study	Presentation in submission	Does the study inform the clinical evidence base for the economic model?	Primary study reference(s)
Chronic migraine			
Study 295 (NCT02066415)	Key evidence, presented in full in Section B.2	Yes	Tepper *et al.* (2017)[68] Study 295 CSR[69] Ashina *et al*. (2018)[70]
NCT20130255	Supportive evidence. This was a multicentre, 13-month OLE of Study 295. It is summarised in Appendix L	Yes – this study supports a model assumption regarding long-term maintenance of erenumab efficacy (see Section B.3.3.4)	Amgen (2018)[71]
Episodic migraine			
STRIVE (NCT02456740)	Key evidence, presented in full in Section B.2	Yes	Goadsby *et al*. (2017)[72] STRIVE CSR[73]
LIBERTY (NCT03096834)	Supportive evidence, presented in Section B.2	Yes	Reuter *et al.* (2018)[74] LIBERTY data on file[75]
ARISE (NCT02483585)	Supportive evidence, presented in Section B.2	Yes	Dodick *et al*. (2018)[76] ARISE CSR[77]
NCT01952574	Supportive evidence. This study was a phase II study, and is	Yes – this study supports a model assumption regarding	Ashina *et al*. (2017)[78]

	therefore summarised only in brief in Appendix L	long-term maintenance of erenumab efficacy (see Section B.3.3.4)	
Other erenumab studies found in the SLR			
NCT01688739	Not presented in the submission – phase I study in healthy patients and patients with migraine	No – phase I study in healthy individuals and migraine patients to determine safety and tolerability of erenumab	de Hoon *et al.* (2017)[79]
NCT01723514	Not presented in the submission – phase I study in healthy patients and patients with migraine	No – phase I study in healthy individuals and migraine patients to determine safety and tolerability of erenumab	de Hoon *et al.* (2017)[79]

Abbreviations: CSR: clinical study report.
Source: Tepper *et al*. (2017)[68], Study 295 CSR[69], Goadsby *et al.* (2017)[72], STRIVE CSR[73], LIBERTY CSR, Dodick *et al*. (2018)[76], ARISE CSR[77], Ashina *et al.* (2017)[78], Amgen (2017)[80], Amgen (2018)[71]

As discussed in Section B.1.2.1, migraine is a spectrum disorder characterised by patients distributed across a continuum of migraine frequencies. Binary classifications of disease into chronic and episodic migraine may not adequately represent the reality of migraine treatment and patient experience in clinical practice.[1-4] Each identified trial of erenumab specified eligibility criteria leading to the recruitment of patients classified as having either episodic migraine or chronic migraine. As such, the relevant evidence base for erenumab in this submission is comprised of one trial in a population that can be considered to represent chronic migraine patients (Study 295), and three trials in populations that can be considered to represent episodic migraine patients (STRIVE, ARISE and LIBERTY).

The recruitment of separate episodic and chronic populations was considered to be appropriate based on EMA recommendations and International Headache Society (IHS) guidelines for controlled trials for drugs in migraine.[81] This decision was supported by consultations with several regulatory bodies, including the US Food and Drugs Administration (FDA), national Scientific Advice procedures in Europe, Health Canada, and the Medical Devices Agency (PDMA) in Japan. Taken together, the clinical evidence base for erenumab presented in this submission addresses both classifications of the migraine population and hence provides evidence of the efficacy and safety of erenumab across the population of migraine patients with ≥4 MMDs as a whole. Data from the separate trials in chronic and episodic migraine populations were submitted to the EMA as part of the marketing authorisation application and resulted in a licence for use of erenumab in all migraine patients who experience ≥4 migraine days per month (i.e. not defined in terms of episodic or chronic migraine).

As discussed in Section B.1.2.2, whilst the recommended dose of erenumab is 70 mg, some patients may benefit from a higher dose of 140 mg. Clinical efficacy data are available for both doses across the whole spectrum of migraine, as patients were treated with both erenumab 70 mg and 140 mg in Study 295 and STRIVE, with erenumab 70 mg in ARISE, and with erenumab 140 mg in LIBERTY. The patient population in LIBERTY included only those patients for whom ≥2 prior prophylactic treatments have failed and is therefore considered more severe; in this trial, only the 140 mg dose of erenumab was administered, indicating that treatment with the higher dose of 140 mg may be most suitable in this patient population. In the following sections, clinical efficacy outcomes are presented for both doses of erenumab.

Two further studies provide supportive evidence in this submission. Study NCT01952574 is a phase II study and is therefore summarised briefly in Appendix L. Study NCT20130255 was a 13-month open-label extension (OLE) of Study 295, and provides data to support the long-term safety and efficacy of erenumab. This study was used to support assumptions regarding the long-term efficacy of erenumab in the cost-effectiveness model.

Table 5: Clinical effectiveness evidence for erenumab in patients with migraine

Study	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT02483585)	LIBERTY (NCT03096834)
Study design	Phase II, multicentre, randomised, double-blind, placebo-controlled study. The study consisted of the following phases: screening, baseline, 12-week placebo-controlled double-blind treatment, 12-week safety follow-up and/or 52-week OLE	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The study consisted of the following phases: screening, baseline, 24-week placebo-controlled double-blind treatment, 28-week double-blind active treatment and 12-week safety follow-up	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The study consisted of the following phases: screening, baseline, 12-week placebo-controlled double-blind treatment, 28-week open-label treatment phase and 12-week safety follow-up	Phase IIIb, multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The study consisted of the following phases: screening, baseline, 12-week double-blind treatment phase, 52-week open-label treatment phase and 12-week follow-up
Population	Adults aged 18–65, with a history of chronic migraine, with or without aura (≥15 headache days per month, of which ≥8 days were migraine days)	Adults aged 18–65, with a history of episodic migraine (≥4 and <15 migraine days per month with <15 headache days per month) with or without aura for ≥12 months	Adults aged 18–65, with a history of episodic migraine (≥4 and <15 migraine days per month with <15 headache days per month) with or without aura for ≥12 months	Adults aged 18–65, with a history of episodic migraine (4–14 baseline migraine days) with <15 days per month of headache symptoms (i.e. migraine or non-migraine), who have failed 2–4 previous migraine prophylactic treatments for lack of efficacy or tolerability
Intervention(s)	Erenumab 70 mg or 140 mg Q4W	Erenumab 70 mg or erenumab 140 mg Q4W	Erenumab 70 mg Q4W	Erenumab 140 mg Q4W
Comparator(s)	Placebo	Placebo	Placebo	Placebo
Indicate if trial supports application for marketing authorisation	Yes	Yes	No[a]	No[b]
Indicate if trial used in the economic model	Yes	Yes	Yes	Yes
Rationale for use/non-use in the model	Study 295 is the pivotal trial for erenumab in the chronic migraine population,	STRIVE is the pivotal phase III study for erenumab in the episodic migraine population,	ARISE is a phase III study for erenumab in the episodic migraine population and	LIBERTY is a phase IIIb study for erenumab in the episodic migraine population

Study	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT02483585)	LIBERTY (NCT03096834)
	informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in the submission	informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in the submission	considers a population directly relevant to the decision problem addressed in the submission	for whom 2–4 previous migraine prophylactic treatments have failed. It considers a population directly relevant to the decision problem addressed in this submission
Reported outcomes specified in the decision problem	Primary Outcome: • **Change in MMDs from baseline to last four weeks of double-blind treatment phase** Secondary Outcomes: • **Achievement of at least 50% reduction from baseline in MMDs** • Change from baseline in monthly acute-migraine-specific days • Change from baseline in monthly cumulative hours of headache Exploratory Outcomes: • Change from baseline in monthly average severity of migraine pain • **Change from baseline in monthly headache**	Primary Outcome: • **Change from baseline in MMDs to the last three months of the double-blind treatment phase** Secondary Outcomes: • **Achievement of at least 50% reduction from baseline in MMDs** • Change from baseline in monthly acute migraine-specific medication treatment days Exploratory Outcomes: • **Change from baseline in mean monthly headache (migraine and non-migraine headache) days**	Primary outcome: • **Change in MMDs from baseline to last four weeks of double-blind treatment phase** Secondary Outcomes: • **Achievement of at least 50% reduction from baseline in MMDs** • Change from baseline in monthly acute migraine-specific medication treatment days Exploratory Outcomes: • **Change from baseline in mean monthly headache (migraine and non-migraine headache) days**	Primary Outcome: • **Achievement of at least a 50% reduction from baseline in MMDs in Month 3 (the final month) of the double-blind phase** Secondary Outcomes: • **Change from baseline to Month 3 (the final month) of the double-blind epoch in MMDs** • Change from baseline in monthly acute migraine-specific medication treatment days Exploratory Outcomes: • Change from baseline in headache impact scores, as measured by the HIT-6 • Change from baseline in

Study	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT02483585)	LIBERTY (NCT03096834)
	(migraine and non-migraine headache) days • **Effect of erenumab versus placebo on migraine-specific quality of life, as measured by the MSQ v2.1** • Effect of erenumab versus placebo on daily effects of headache, as measured by the HIT-6 • Effect of erenumab versus placebo on pain interference with daily activities and migraine-specific impact, as measured by the PROMIS Pain Interference Scale short form and migraine symptom interference questions • Effect of erenumab versus placebo on migraine-related disability, as measured by MIDAS Safety: • AEs	• Change from baseline in monthly hours of migraine headache • Change from baseline in severity of migraine pain • Change from baseline in headache impact scores, as measured by the HIT-6 • **Change from baseline in migraine-specific quality of life, as measured by the MSQ v2.1** • Effect of erenumab versus placebo on migraine-related disability, as measured by MIDAS Safety: • AEs	• Change from baseline in monthly hours of migraine headache • Change from baseline in severity of migraine pain • Change from baseline in headache impact scores, as measured by the HIT-6 • **Change from baseline in migraine-specific quality of life, as measured by the MSQ v2.1** • Effect of erenumab versus placebo on migraine-related disability, as measured by MIDAS Safety: AEs	EQ-5D-5L quality of life in the last month • Change from baseline in WPAI scores Safety: • AEs

Study	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT02483585)	LIBERTY (NCT03096834)
All other reported outcomes	• Change from baseline in monthly migraine attacks • Change from baseline in monthly moderate and severe headache (migraine and non-migraine) days • Change from baseline in monthly average severity of migraine-related symptoms (nausea, vomiting, phonophobia, photophobia) for qualified migraine headaches • Change in PI and impact on EA, as measured by the MPFID	• Change from baseline in mean monthly average physical impairment domain scores measured by MPFID • Change from baseline in mean monthly average everyday activity domain scores measured by MPFID • Effect of erenumab versus placebo in the month of onset of action, assessed by MMDs • Change from baseline in monthly migraine attacks • Achievement of at least 75% reduction from baseline in MMDs • Achievement of 100% reduction from baseline in MMDs • Change in PI and impact on EA, as measured by the MPFID	• Change from baseline in mean monthly average physical impairment domain scores measured by MPFID • Change from baseline in mean monthly average everyday activity domain scores measured by MPFID • Effect of erenumab versus placebo in the month of onset of action, assessed by MMDs • Change from baseline in monthly migraine attacks • Achievement of at least 75% reduction from baseline in MMDs • Achievement of 100% reduction from baseline in MMDs • Change in PI and impact on EA, as measured by the MPFID	• Achievement of at least 75% reduction from baseline in MMDs • Achievement of 100% reduction from baseline in MMDs • Change from baseline in monthly migraine attacks • Cumulative change from baseline of MMDs at the end of each month during the double-blind phase • Cumulative change form baseline on MMDs during the entire double-blind phase • Change form baseline of BDI-II psychometric test scores • Change in PI and impact on EA, as measured by the MPFID

Outcomes informing the cost-effectiveness model are highlighted in bold.
Footnotes: [a]This was not included in the original marketing authorisation application, which focused on the 140 mg dose of erenumab. [b]Trial results not available at time of the marketing authorisation application as the study was ongoing at this time.
Abbreviations: AE: adverse event; BDI-II: Beck Depression Inventory; EA: everyday activities; EQ-5D-5L: EuroQoL 5 dimensions 5 levels; HIT-6: Headache Impact Test; MFIQ: The Migraine Functional Impact Questionnaire; MIDAS: Migraine Disability Assessment; MMD: monthly migraine day; MPFID: Migraine Physical Function Impact Diary; MSQ: Migraine-Specific Quality of Life Questionnaire; OLE: open-label extension; PI: physical impairment; PROMIS: Patient-Reported Outcomes Measurement Information System; WPAI: work productivity and activity impairment.
Source: Study 295 CSR[69], STRIVE CSR[73], ARISE CSR[77], LIBERTY CSR[82]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Summary of trial methodology

Study 295

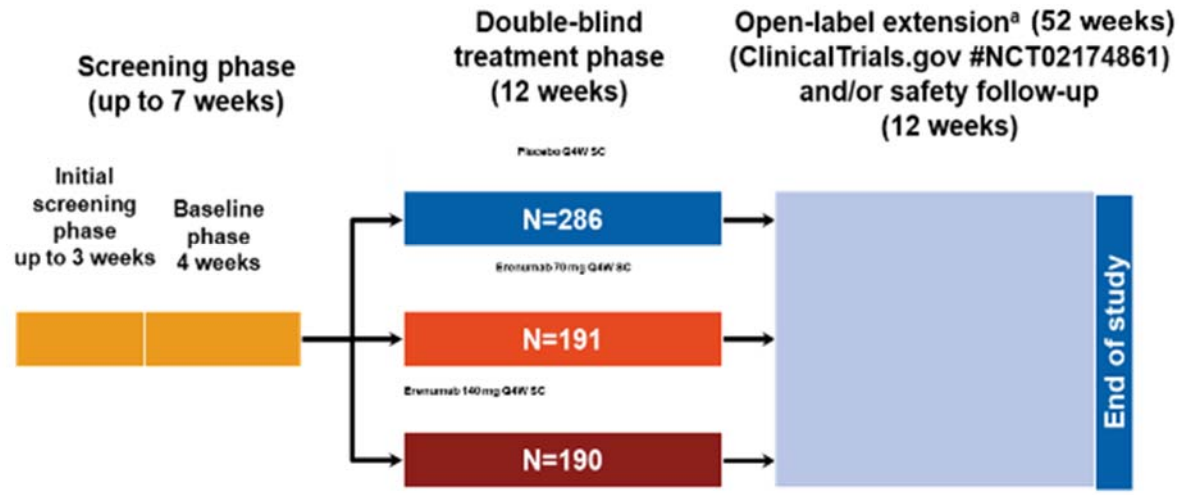
Study 295 was a phase II trial of erenumab in 667 adult patients classified as having chronic migraine, with or without aura. This large phase II study met all methodological standards for a phase III study for regulatory purposes. In order to enter the trial, patients were required to have experienced 15 or more headache days per month in each of the three months prior to screening, of which at least eight were migraine days.[68]

The trial consisted of four phases: screening, baseline, treatment, safety follow-up and/or OLE phase (see Figure 3). The initial screening phase lasted for up to three weeks, during which time patients were assessed for study eligibility according to pre-defined inclusion and exclusion criteria. All eligible patients were then enrolled into the baseline phase, which lasted for four weeks. During this time, patients recorded monthly migraine days, headache hours, headache days, migraine attacks and acute migraine-specific drug usage using an electronic diary (eDiary), to later be compared with scores from the final four weeks of the treatment phase. Patients were required to show at least 80% compliance with the eDiary during the baseline phase to be eligible to commence treatment.

Eligible patients were randomly assigned (3:2:2) to receive placebo, erenumab 70 mg, or erenumab 140 mg. Following the baseline phase, enrolled patients were treated with subcutaneous (SC) injections on Day 1, Week 4 and Week 8 of the 12-week double-blind phase, and patients recorded headache information using the eDiary. This allowed patients to enter details including incidence of headache, presence of aura, time of onset, time to resolution, severity, pain features and other symptoms of migraine.

The primary endpoint of Study 295 was the mean change in MMDs from baseline to the last four weeks of the double-blind treatment phase. This was calculated as the change in migraine days from the four-week baseline period to weeks 9–12 of the double-blind phase, where a migraine day was defined as any calendar day on which the patients had an onset, continuation, or recurrence of a qualified migraine. The 50% responder rate, which measured the proportion of patients with at least a 50% reduction from baseline in MMDs calculated using results from the primary endpoint, was measured as a secondary endpoint.

Figure 3: Study 295 study design and treatment schematic



[a]The objective of the open-label extension was to look at long-term safety and efficacy data, as well as secondary endpoints.
Abbreviations: CSR: clinical study report; Q4W: once every four weeks; SC: subcutaneous.
Source: Tepper *et al.* (2017)[68], Tepper *et al*. (2018)[83]

STRIVE

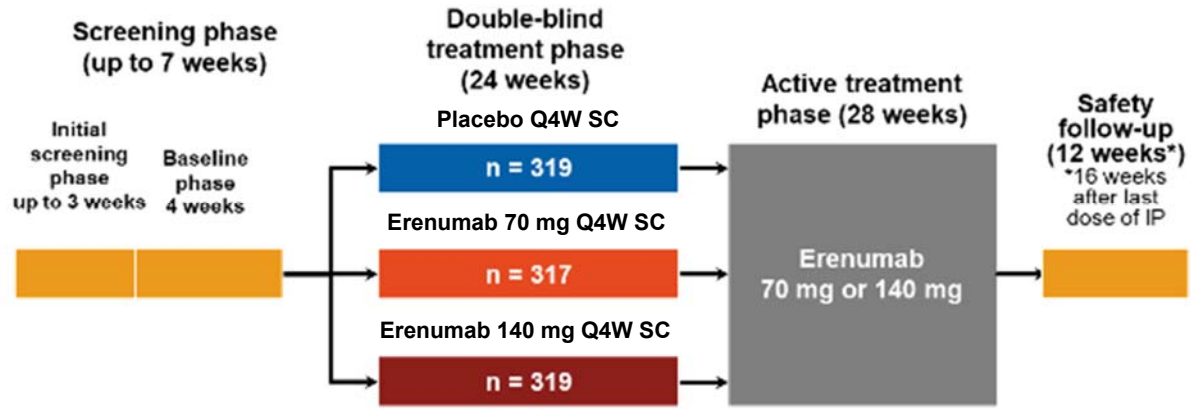
STRIVE was a phase III trial of erenumab in 955 adult patients classified as having episodic migraine. Within this study, episodic migraine was defined as patients with a history of migraine for at least 12 months and who experienced ≥4 and <15 migraine days per month, with or without aura, with <15 headache days per month.[72]

STRIVE consisted of four phases: screening and baseline, placebo-controlled double-blind treatment, active-treatment and a safety follow-up (see Figure 4). Screening and baseline phases followed the same protocol as Study 295, with eligible subjects recording several items, such as the incidence of headache, pain features and symptoms, and the use of acute medication to treat the headache using an eDiary, to be compared with values over the last three months of the double-blind treatment phase. During the double-blind phase, patients could be randomised to either placebo, erenumab 70 mg or erenumab 140 mg, with randomisation stratified by region and treatment status with current and prior migraine prophylactic treatment. During the active treatment phase, patients were re-randomised to receive either 70 mg or 140 mg doses of the investigational product. The doses were administered every four weeks (Q4W) SC by study staff during the both the double-blind and active treatment phases.[72]

Eligible patients were randomly assigned 1:1:1 to receive placebo, erenumab 70 mg or erenumab 140 mg once every four weeks by SC injection. Patients reported outcomes, including health-related quality of life (HRQoL) outcomes and characteristics of migraine in eDiaries, and these were used as the basis for clinical outcome assessments.

The primary endpoint of STRIVE was to evaluate the efficacy of erenumab by measuring the change from baseline to the final three months of the double-blind treatment phase in mean MMDs compared with placebo. The 50% responder rate, which evaluated the proportion of patients with at least 50% reduction from baseline in MMDs, was measured as a secondary endpoint.

Figure 4: STRIVE study design and treatment schematic



Abbreviations: IP: investigational product; Q4W: once every four weeks; SC: subcutaneous.
Source: Goadsby *et al.* (2017)[72]

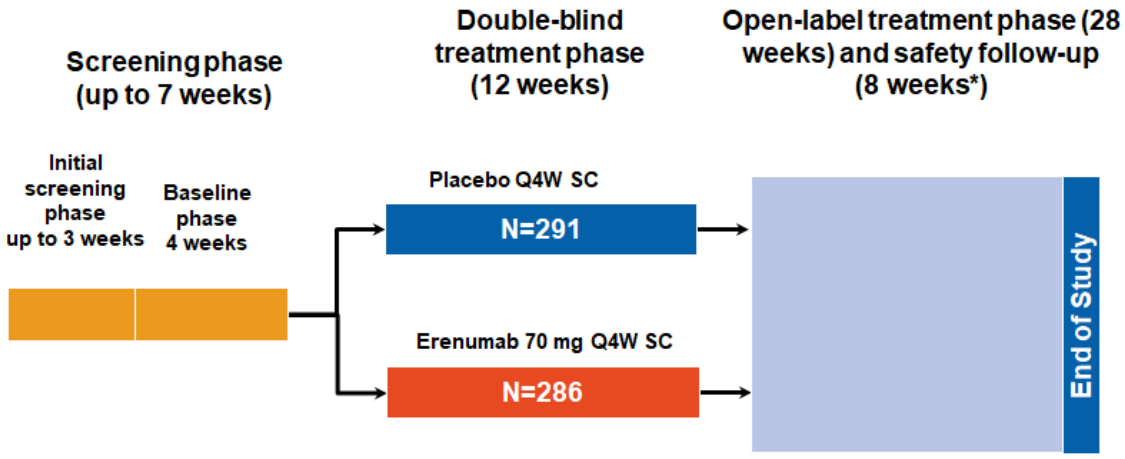
ARISE

ARISE was a phase III trial of erenumab in 577 adult patients classified as having episodic migraine. The definition of episodic migraine within this study was the same as for STRIVE (see above).[77]

ARISE consisted of five phases: screening, baseline, double-blind treatment, open-label treatment and safety follow-up (see Figure 5). Patients were assessed for trial eligibility according to pre-specified inclusion and exclusion criteria during the screening phase, which lasted for up to three weeks. During the 4-week baseline phase, patients recorded information on characteristics and frequency of migraine using an eDiary and eligibility for randomisation was assessed on this basis. During the double-blind phase, patients were randomised 1:1 to receive either placebo or erenumab 70 mg, with randomisation stratified by region and prior migraine prophylactic treatment. The doses were administered Q4W SC by study staff during the both the double-blind and active treatment phases.[77]

Patients reported outcomes, including HRQoL outcomes and characteristics of migraine in eDiaries; these were used as the basis for clinical outcome assessments. The primary endpoint of ARISE was to evaluate the efficacy of erenumab by measuring the change from baseline to the final month of the double-blind treatment phase in mean MMDs compared with placebo. The 50% responder rate was measured as a secondary endpoint.

Figure 5: ARISE study schema



*12 weeks after last dose of IP.
Abbreviations: IP: investigational product; Q4W: once every four weeks; SC: subcutaneous.
Source: Ashina et al. (2017)[78]

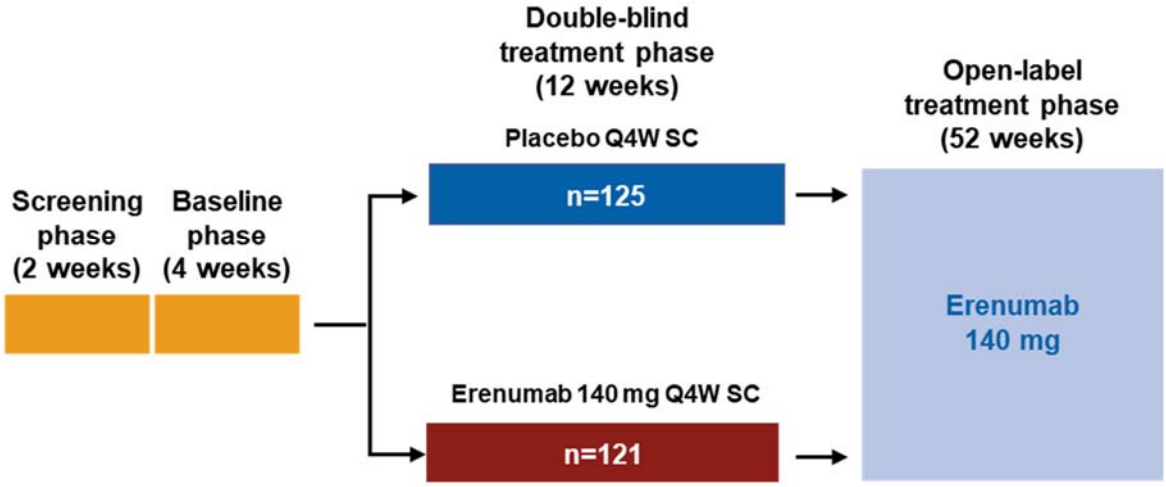
LIBERTY

LIBERTY was a phase IIIb trial in 246 adult patients classified as having episodic migraine. Inclusion criteria specified that patients had to have previously failed between two and four prophylactic treatments. Patients were further required to have a documented history of migraine, either with or without aura, for at least 12 months prior to screening, with specifically 4–14 days with migraine symptoms per month and <15 headache days per month. Patients enrolled into the double-blind treatment phase had a migraine frequency of 4–14 days per month during the baseline phase, as confirmed by the eDiary.

LIBERTY consisted of five phases: screening, baseline, double-blind treatment, open-label treatment and follow-up. Patients were assessed for trial eligibility according to pre-specified inclusion and exclusion criteria during the screening phase, which lasted for up to three weeks. During the 4-week baseline phase, patients recorded information on characteristics and frequency of migraine using an eDiary and eligibility for randomisation was assessed on this basis.

Eligible patients were randomly assigned 1:1 to receive placebo, or erenumab 140 mg once every four weeks by SC injection. Patients reported outcomes, including HRQoL outcomes and characteristics of migraine in eDiaries; these were used as the basis for clinical outcome assessments. The primary endpoint of LIBERTY was to evaluate the efficacy of erenumab by measuring the proportion of patients with at least 50% reduction from baseline in MMDs in Month 3 (the final month) of the double-blind epoch. The change from baseline in mean MMDs compared to placebo was collected as a secondary endpoint in the trial.

Figure 6: LIBERTY study design and treatment schematic



Abbreviations: Q4W: once every four weeks; SC: subcutaneous.
Source: LIBERTY data on file (2018)[84]

A summary of the methodologies used in Study 295, STRIVE, ARISE and LIBERTY is presented in Table 6. Full definitions of each outcome measure presented in the submission are provided in Appendix N.

Table 6: Summary of methodology for Study 295, STRIVE, ARISE and LIBERTY

Trial number (acronym)	NCT02066415 (Study 295)	NCT02456740 (STRIVE)	NCT02483585 (ARISE)	NCT03096834 (LIBERTY)
Location	International: 69 sites across Canada, Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, the UK (four sites, [redacted] patients) and the USA	International: 121 centres across Austria, Belgium, Canada, Czech Republic, Finland, Germany, the Netherlands, Poland, Slovakia, Sweden, Turkey, the UK (six sites, [redacted] patients) and the USA	International: 69 centres across Denmark, France, Greece, Portugal, Russia, Spain, Switzerland, and the USA	International: 68 locations across Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and the UK (five sites, [redacted] patients)
Trial design	Phase II, multicentre, randomised, double-blind, placebo-controlled, parallel-group study	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study	Phase IIIb, multicentre, randomised, double-blind, placebo-controlled, parallel-group study
Duration of study	• ≤3-week screening phase • 4-week baseline phase • 12-week double-blind treatment phase • 52-week open-label treatment epoch • Subsequent 12-week safety follow-up	• ≤3-week initial screening phase • 4-week baseline phase • 52-week treatment phase, consisting of the following: o 24-week placebo-controlled double-blind phase o 28-week active treatment phase • Subsequent 12-week safety follow-up	• ≤3-week initial screening phase • 4-week baseline phase • 12-week double-blind phase • 28-week open-label treatment phase • Subsequent 12-week safety follow-up	• 0–2 weeks screening • 4-week baseline epoch • 12-week double-blind epoch • 52-week open-label treatment epoch • Subsequent 12-week safety follow-up
Method of randomisation	Patients were randomised 3:2:2 to receive placebo, erenumab 70 mg or erenumab 140 mg, respectively. This was centrally executed by an interactive voice or web response system and was stratified by region (North America vs Europe) and medication overuse (presence vs absence)	Patients were randomised 1:1:1 to receive placebo, erenumab 70 mg or erenumab 140 mg. This was centrally executed by an interactive voice or web response system and was stratified by region (North America vs Other) and treatment status with migraine prophylactic medication (current or prior use, or no prior or current use)	Patients were randomised 1:1 to receive placebo or erenumab 70 mg. This was centrally executed by an interactive voice or web response system and was stratified by region (North America vs Other) and treatment status with migraine prophylactic medication (prior use, or no prior use)	Patients were randomised 1:1 to receive placebo or erenumab 140 mg. This was centrally executed by an interactive voice or web response system and was stratified by baseline MMDs (4–7 vs 8–14)
Method of blinding	Double-blind: patients, site personnel, and study personnel	Double-blind: patients, site personnel, sponsor study personnel and designees	Double-blind: patients, site personnel, sponsor study personnel and designees	Double-blind: patients, site personnel, sponsor study personnel and designees
Trial drugs and method of administration	Erenumab 70 mg, erenumab 140 mg or placebo administered Q4W subcutaneously	Erenumab 70 mg, erenumab 140 mg or placebo administered Q4W subcutaneously	Erenumab 70 mg or placebo administered Q4W subcutaneously	Erenumab 140 mg or placebo administered Q4W subcutaneously

Permitted and disallowed concomitant medication	Full details of permitted and disallowed concomitant medication are provided in Appendix M. Acute medications (migraine-specific and non migraine-specific) were permitted to treat acute migraine attacks. Any other concomitant medications or treatments deemed necessary were permitted, with the exception of those listed in Appendix M.	Full details of permitted and disallowed concomitant medication are provided in Appendix M. Acute medications (migraine-specific and non migraine-specific) were permitted to treat acute migraine attacks. Any other concomitant medications or treatments deemed necessary were permitted, with the exception of those listed in Appendix M.	Full details of permitted and disallowed concomitant medication are provided in Appendix M. Acute medications (migraine-specific and non migraine-specific) were permitted to treat acute migraine attacks. Any other concomitant medications or treatments deemed necessary were permitted, with the exception of those listed in Appendix M.	Full details of permitted and disallowed concomitant medication are provided in Appendix M. Acute medications (migraine-specific and non migraine-specific) were permitted to treat acute migraine attacks. Any other concomitant medications were not allowed unless in the context of a different pre-existing condition in stable doses for at least three months prior to baseline.
Primary outcomes (including scoring methods and timings of assessments)	Mean change in MMDs from baseline phase to final four weeks of the 12-week double-blind treatment phase, compared to placebo	Change from baseline in mean MMDs calculated using the MMDs from each of the last three months of the 24-week double-blind treatment phase	Mean change in MMDs from baseline phase to final four weeks of the 12-week double-blind treatment phase, compared to placebo	The achievement of at least a 50% reduction from baseline in MMDs in Month 3 (the final month) of the double-blind epoch
Secondary outcomes (including scoring methods and timings of assessments)	• Achievement of at least 50% reduction from baseline in MMDs (i.e. 50% responder rate) • Change from baseline in days on which acute migraine-specific drugs (triptans and ergot derivatives) were used • Change from baseline in cumulative headache hours (of any severity) • Safety: AEs, clinical laboratory values, vital signs, and anti-erenumab antibodies. All AEs were coded using MedDRA v19.0 and CTCAE v4 was used to grade AEs All efficacy endpoints were assessed using data from the last four weeks of the 12-week, double-blind treatment phase. Safety endpoints were assessed for the duration of the trial	• Achievement of at least a 50% reduction from baseline in mean MMDs • Change from baseline in mean monthly acute migraine-specific medication treatment days • Change from baseline in cumulative headache hours (of any severity) • Change from baseline in mean monthly average PI domain scores as measured by the MPFID • Change from baseline in mean monthly average impact on EA domain scores as measured by the MPFID • Safety: AEs All efficacy endpoints were measured over the last three months (months 4, 5 and 6) of the double-blind treatment phase, Safety endpoints were monitored throughout the trial	• Achievement of at least 50% reduction from baseline in MMDs • Change from baseline in monthly acute migraine-specific medication treatment days • Achievement of at least a 5-point reduction from baseline on average impact on everyday activities domain scores, as measured by the MPFID • Achievement of at least a 5-point reduction from baseline on average impact on physical impairment domain scores, as measured by the MPFID	• Change from baseline to Month 3 (the final month) of the double-blind epoch in MMDs • Change from baseline in mean monthly average PI domain scores as measured by the MPFID • Change from baseline in mean monthly average impact on EA domain scores as measured by the MPFID • Change from baseline in monthly acute migraine-specific medication treatment days • Achievement of at least 75% reduction from baseline in MMDs • Achievement of 100% reduction from baseline in MMDs • Safety: AEs

Pre-specified subgroup analyses	Primary and secondary endpoints were explored using subgroup analyses of:[69] • Age (by median age) • Sex • Race (White vs Other) • Region (North America vs Other) • Acute medication overuse (Yes vs No) • Selected acute medications for on-study use • Prior migraine prophylactic treatments • Failed migraine prophylactic medication use • Duration of disease • Body mass index (BMI) Other subgroup variables as deemed appropriate	The primary and secondary endpoints were analysed in the following subgroups: • Region • Prior/current treatment with migraine prophylactic medication • BMI (<median vs ≥median) • Baseline MMDs (<8 vs ≥8) Treatment failure of prior migraine prophylactic medications (failed vs non-failed)	The primary and secondary endpoints were analysed in the following subgroups: • Region (North America vs other) • Prior treatment with migraine prophylactic medication	The primary and secondary endpoints were analysed in the following subgroups: • Age • Gender • Baseline MMDs (<8 vs ≥8)

[a]ACE/ARBs, including lisinopril and candesartan specifically, are medicines used to control blood pressure.
Abbreviations: ACE: angiotensin-converting enzyme; AE: adverse event; ARB: angiotensin II receptor blockers; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EA: everyday activities; MedDRA: Medical Dictionary for Regulatory Activities; MMD: monthly migraine day; MPFID: migraine physical function impact diary; OLE: open-label extension; PI: physical impairment; Q4W: every four weeks.
Source: Tepper *et al.* (2017)[68], Supplementary Appendix, Tepper *et al.* (2017)[85], Study 295 CSR[69], Goadsby *et al.* (2017)[72], STRIVE CSR[73], STRIVE Protocol[86], Goadsby *et al.* (2017) Supplementary Appendix[87], ARISE CSR[77], Dodick *et al*. (2018)[76], LIBERTY ClinicalTrials.gov[88], LIBERTY CSR[82], LIBERTY Protocol[89].

Eligibility criteria of Study 295, STRIVE, ARISE and LIBERTY

Study 295, STRIVE, ARISE and LIBERTY enrolled adult patients, aged 18–65 years with a history of migraine (with or without aura), as per the IHS ICHD-III classification (see Table 3). Patients were excluded if they were older than 50 years at migraine onset and if they had a history of cluster headache or hemiplegic migraine headache. Key inclusion and exclusion criteria for which differed between trials, including the definition of a migraine headache, are outlined in Table 7. Patients were excluded from the studies if they had never experienced a response to a protocol-specified number of prophylactic treatments for migraine (see exclusion criteria). Full inclusion and exclusion criteria are provided in Appendix M.

Table 7: Inclusion and exclusion criteria, and definition of a migraine in Study 295, STRIVE, ARISE and LIBERTY

Term	Study 295	STRIVE	ARISE	LIBERTY
History of migraine	• ≥15 headache days per month • ≥8 days per month of migraine symptoms	• <15 headache days per month • 4–14 days per month (in at least two separate attacks) of migraine symptoms		• <15 headache days per month • 4–14 days per month (in at least two separate attacks) of migraine symptoms

			• Failed 2–4 prior migraine prophylaxis treatments
Definition of migraine	A qualified migraine headache was determined by the following criteria: • A migraine without aura, lasting for **≥4 continuous hours** and having met criteria a) and/or b): a) ≥2 of the following pain features: o Unilateral o Throbbing o Moderate to severe o Exacerbated with exercise/physical activity b) ≥1 of the associated symptoms: o Nausea and/or vomiting o Photophobia and phonophobia **OR** • A migraine with aura having met criteria c) and d) below, defined as: c) Meeting ≥1 of the following aura symptoms o **Visual** o **Sensory** o **Speech and/or language** o **Retinal** o **Brainstem** d) Aura accompanied, or followed within 60 minutes, by headache lasting for ≥4 continuous hours If the patient took an acute migraine-specific drug on a calendar day, then it	A qualified migraine headache was defined as a migraine with or without aura, lasting for ≥**30 minutes**, and meeting at least one of the following criteria: • ≥2 of the following pain features: o Unilateral o Throbbing o Moderate to severe o Exacerbated with exercise/physical activity • ≥1 of the following associated symptoms: o Nausea and/or vomiting o Photophobia and phonophobia If the patient took a migraine-specific medication during aura or to treat headache on a calendar day, then it was counted as a migraine day regardless of the duration and pain features/associated symptoms	

	was counted as a migraine day regardless of the duration and pain features/associated symptoms		
Exclusion criteria	No therapeutic response (reduction in frequency, duration or severity of headache) to ≥3 treatment categories	No therapeutic response (reduction in frequency, duration or severity of headache) to ≥2 treatment categories	No therapeutic response (reduction in frequency, duration or severity of headache) to ≥4 treatment categories

Note: Bold text in 'definition of migraine column' indicates differences in definition between the three trials.
Source: Study 295 Protocol[90], STRIVE Protocol[89], ARISE Protocol[91], LIBERTY Protocol[86]

B.2.3.2 Baseline characteristics

Study 295

Key baseline demographics, clinical characteristics and a summary of prior treatment usage and failure for the patients included in the randomisation analysis set in Study 295 are presented in Table 8. This set included all patients who were randomly assigned to treatment or placebo in the study.[68] Overall, seven patients (four in the placebo arm, one in the erenumab 70 mg arm and two in the erenumab 140 mg arm) did not receive their randomly assigned treatment, however these patients were still included within the randomisation analysis set.

The mean age of patients was 42.1 years, with a predominantly white (93.7%) and female (79.0%) population in all arms. Of all 667 patients in the randomisation analysis set, 67.9% had failed at least one prior preventative treatment due to lack of efficacy or tolerability, with almost 49.0% having failed at least two prior treatments. The proportion of patients who had failed prior treatments was similar across arms.

Between the three treatment arms, characteristics were generally similar, including age at migraine onset, with only a slight difference in mean monthly acute migraine-specific drug use days (9.5 days in the placebo group versus 8.8 days in the erenumab 70 mg group and 9.7 days in the erenumab 140 mg group). MMDs during the baseline period were comparable across treatment groups. Baseline characteristics observed in this study are representative of the typical migraine population in the UK, based on the results of a study of almost 90,000 migraine patients in the UK, and expert clinical opinion from a UK advisory board.[9, 92]

Baseline characteristics for the patients for whom ≥3 prior prophylactic treatments have failed (the population of interest in this submission) are reported in Section B.2.6.1, and for the patients for whom ≥2 prophylactic treatments have failed are reported in Appendix E. Overall, baseline characteristics were comparable between the ITT population and the patients for whom ≥3 prior prophylactic treatments have failed. The mean age in this subgroup was overall comparable, with patients in the erenumab 140 mg arm slightly older than in the ITT population (44.1 versus 42.9 years, respectively). Age at onset of migraine was slightly lower in patients for whom ≥3 prior prophylactic treatments have failed, however baseline MMDs were comparable.

Table 8: Baseline characteristics of patients in the ITT population in Study 295

Characteristic	Placebo (n=286)	Erenumab 70 mg (n=191)	Erenumab 140 mg (n=190)
Mean age, years (SD)	42.1 (11.3)	41.4 (11.3)	42.9 (11.1)
Range	18–66[a]	18–64	18–64
Sex, n (%)			
Women	226 (79)	166 (87)	160 (84)
Men	60 (21)	25 (13)	30 (16)
BMI, kg/m^2 (SD)	26.3 (5.1)	26.0 (5.3)	26.0 (5.4)
Ethnicity, n (%)			
White	268 (94)	176 (92)	184 (97)
Black or African American	11 (4)	10 (5)	6 (3)
Asian	4 (1)	4 (2)	0
Other[b]	3 (1)	1 (<1)	0

Age at migraine onset, years (SD)	20.4 (10.0)	21.1 (10.5)	21.5 (10.6)
Disease duration, years (SD)	22.2 (12.6)	20.7 (12.8)	21.9 (11.8)
History of migraine with aura, n (%)	124 (43)	81 (42)	71 (37)
Medication overuse	117 (41)	79 (41%)	78 (41)
History of previous preventative treatment failure, n (%)			
No drug failures[c]	86 (30)	64 (34)	64 (34)
Failure of ≥1 drug[d]	200 (70)	127 (67)	126 (66)
Failure of ≥2 drugs[d]	142 (50)	93 (49)	92 (48)
Previous use of preventative drug topiramate, n (%)	150 (52)	89 (47)	97 (51)
Previous use of botulinum toxin, n (%)	62 (23)	50 (26)	43 (23)
Baseline period, mean (SD)			
Monthly migraine days	18.2 (4.7)	17.9 (4.4)	17.8 (4.7)
Monthly headache hours	235.3 (126.1)	223.6 (126.6)	215.1 (123.5)
Monthly headache days	21.1 (3.9)	20.5 (3.8)	20.7 (3.8)
Monthly migraine attacks	4.2 (1.7)	4.5 (1.7)	4.3 (1.6)
Monthly acute migraine-specific drug use days[e]	9.5 (7.6)	8.8 (7.2)	9.7 (7.0)
Acute migraine-specific drug use, n (%)	225 (79)	143 (75)	149 (78)

Footnotes: [a]One patient was 65 years old at screening but turned 66 before randomisation. [b]Includes native Hawaiian and other Pacific Islander, multiple ethnic origins or other. [c]Includes treatment naïve patients and patients who had previous use of preventative drugs, but who did not have treatment failure due to lack of efficacy or tolerability. [d]Failure due to lack of efficacy of poor tolerability. [e]Triptans and ergot derivatives only.
Abbreviations: BMI: body mass index; SD: standard deviation.
Source: Tepper *et al.* (2017)[68]

STRIVE

Baseline demographics, clinical characteristics and a summary of prior treatment usage and failure of the patients included in the full analysis set in STRIVE are detailed in Table 9. Of the 955 patients randomised, the majority were white (89.1%) and female (85.2%), with the mean age being 40.9 years.

Across the three treatment arms in STRIVE, the number of MMDs was comparable, with a mean value of 8.23, 8.29 and 8.34 days in each of the placebo, erenumab 70 mg and erenumab 140 mg arms, respectively. The proportion of patients for whom prior prophylactic treatments have failed were similar between treatment arms.[73] Specifically, the percentage of patients for whom ≥2 prior treatments have failed were [redacted], [redacted] and [redacted] in the placebo, erenumab 70 mg and erenumab 140 mg arms, respectively. Baseline characteristics of the patients enrolled in this study are comparable to the wider UK migraine population, based on the results of a study of almost 90,000 migraine patients in the UK.[92] This was agreed by expert clinicians at a UK advisory board, although they noted that the mean MMDs at baseline may be slightly lower than those observed in UK clinical practice.[9]

Baseline characteristics for the patients for whom ≥3 prior prophylactic treatments have failed (the population of interest in this submission) are reported in Section B.2.6.1, and baseline

characteristics for the patients for whom ≥2 prophylactic treatments have failed are reported in Appendix E. Overall, baseline characteristics were comparable between the ITT population and the patients for whom ≥3 prior prophylactic treatments have failed. A higher proportion of patients in this subgroup is white, and patients in the subgroup have slightly higher MMDs at baseline.

Table 9: Baseline characteristics of patients in the ITT population in STRIVE

Characteristic	Placebo (n=319)	Erenumab 70 mg (n=317)	Erenumab 140 mg (n=319)
Mean age, years (SD)	41.3 (11.2)	41.1 (11.3)	40.4 (11.1)
Range	18–65	18–63	19–65
Sex, n (%)			
Women	274 (85.9)	268 (84.5)	272 (85.3)
Men	45 (14.1)	49 (15.5)	47 (14.7)
BMI (kg/m^2), mean (SD)	27.1 (6.3)	27.3 (5.9)	27.0 (6.2)
Ethnicity, n (%)			
White	277 (86.8)	281 (88.6)	293 (91.8)
Black or African American	24 (7.5)	24 (7.6)	18 (5.6)
Asian	8 (2.5)	5 (1.6)	4 (1.3)
Other[a]	10 (2.0)	7 (2.2)	4 (1.3)
Age at migraine[b] onset, years (SD)	21.2 (10.2)	21.4 (11.0)	20.7 (9.9)
Disease duration, years (SD)	20.5 (12.2)	19.8 (12.3)	19.7 (12.3)
Acute headache medication use, n (%)			
Migraine-specific[c]	191 (59.9)	179 (56.5)	192 (60.2)
Non-migraine-specific	244 (76.5)	243 (76.7)	256 (80.3)
Migraine-preventive medication use, n (%)[d]			
No current or previous use	178 (55.8)	175 (55.2)	187 (58.6)
Previous use only	131 (41.1)	133 (42.0)	124 (38.9)
Current use	10 (3.1)	9 (2.8)	8 (2.5)
History of previous preventative treatment failure[e], n (%)			
Lack of efficacy	90 (28.2)	89 (28.1)	83 (26.0)
Unacceptable side-effects	78 (24.5)	65 (20.5)	62 (19.4)
Baseline period, mean (SD)			
Monthly migraine days	8.2 (2.5)	8.3 (2.5)	8.3 (2.5)
Monthly headache days	9.3 (2.6)	9.1 (2.6)	9.3 (2.5)
Monthly migraine attacks	5.1 (1.5)	5.2 (1.5)	5.2 (1.4)
Monthly acute migraine-specific drug use days	3.4 (3.4)	3.2 (3.4)	3.4 (3.5)

Footnotes: [a]Other includes American Indian or Alaska native, multiple, native Hawaiian or other Pacific Islander and all other races. [b]Migraine with or without aura. [c]During the baseline phase, 557 patients (58.5%) used triptan-based medications and four patients (0.4) used ergotamine-based medications (safety analysis set). [d]The summary of treatment with migraine-preventive medictions is based on actual data collected rather than on randomisation stratification. [e]Treatment-failure categories were not mutually exclusive; a patient could be included in both categories.
Abbreviations: MPFID-EA: Migraine Physical Function Impact Diary, Everyday Activities domain; MPFID-PI: Migraine Physical Function Impact Diary, Physical Impairment domain; SD: standard deviation.
Source: Goadsby *et al.* (2017)[72], Goadsby *et al.* (2017) Supplementary Appendix[87], STRIVE CSR[73].

ARISE

Baseline demographics, clinical characteristics and a summary of prior treatment usage of the patients included in the full analysis set in ARISE are detailed in Table 10. Of the 577 patients randomised, the majority were female (85.3%) and white (89.8%), with a mean age of 42 years, and a mean disease duration of 21 years.

The number of MMDs at baseline was comparable between the treatment arms, with a mean value of 8.4 and 8.1 days in the placebo and erenumab 70 mg arms, respectively. Baseline characteristics of the patients enrolled in this study are comparable to the wider UK migraine population, based on the results of a study of almost 90,000 migraine patients in the UK.[92]

Baseline characteristics for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed are reported in Section B.2.6.1. Baseline characteristics for this subgroup were consistent with those in the full trial population, both in terms of patient demographics and baseline disease characteristics.

Table 10: Baseline characteristics of patients in the ITT population in ARISE

Characteristic	Placebo (n=291)	Erenumab 70 mg (n=286)
Mean age, years (SD)	42 (12)	42 (11)
Range	18–65	19–65
Sex, n (%)		
Women	247 (84.9)	245 (85.7)
Men	44 (15.1)	41 (14.3)
BMI, kg/m^2 (SD)	27.4 (6.1)	27.4 (6.3)
Ethnicity		
White	259 (89.0)	259 (90.6)
Black of African American	27 (9.3)	24 (8.4)
Asian	0 (0.0)	2 (0.7)
Other[a]	5 (1.7)	1 (0.3)
Age at migraine onset, years (SD)	22 (11)	21 (10)
Disease duration, years (SD)	20 (12)	22 (13)
Acute headache medication use, n (%)		
Migraine-specific	174 (59.8)	178 (62.2)
Non-migraine-specific	236 (81.1)	224 (78.3)
History of prior preventive treatment use		
History of prior preventive treatment use, n (%)	132 (45.4)	134 (46.9)
History of prior preventive treatment failure, n (%)	115 (87.1)	117 (87.3)
Baseline period, mean (SD)		
Monthly migraine days	8.4 (2.6)	8.1 (2.7)
Monthly headache days	9.3 (2.7)	9.1 (2.7)
Monthly migraine attacks	5.2 (1.5)	5.1 (1.5)
Monthly acute migraine-specific drug use days	3.4 (3.6)	3.7 (3.6)

Footnotes: [a]Other includes multiple, native Hawaiian or other Pacific Islander and all other races.
Abbreviations: BMI: body mass index; SD: standard deviation.
Source: Dodick *et al*. (2018)[76], ARISE CSR[77].

LIBERTY

Key baseline demographics, clinical characteristics and a summary of prior treatment usage and failure of the patients included in the full analysis set in LIBERTY are presented in Table 11. Of the 246 patients randomised, the majority were white (92.3%) and female (81.3%), with a mean age of 44.4 years.

Across the two treatment arms in LIBERTY, the number of MMDs were comparable, with a mean of 9.3 days in both the erenumab 140 mg and placebo groups. Out of all randomised patients, 38.6% had failed two prior prophylactic treatments, 37.8% had failed three, and 22.8% had failed four prior prophylactic treatments. Baseline characteristics are comparable to those observed in a UK study which included more than 30,000 patients who had received ≥2 prophylactic treatments.[92]

Baseline characteristics for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed are reported in Section B.2.6.1. Baseline characteristics for this subgroup were consistent with those in the full trial population, both in terms of patient demographics and baseline disease characteristics.

Table 11: Baseline characteristics of patients in the ITT population in LIBERTY

Characteristic	Placebo (n=125)	Erenumab 140 mg (n=121)
Mean age, years (SD)	44.2 (10.55)	44.6 (10.50)
Range	17, 64	18, 64
Sex, n (%)		
Women	103 (82.4)	97 (80.2)
Men	22 (17.6)	24 (19.8)
BMI, kg/m^2 (SD)	24.9 (5.12)	25.0 (4.19)
Ethnicity		
White	115 (92.0)	112 (92.6)
Black of African American	0 (0)	0 (0)
Asian	1 (0.8)	0 (0)
Other[a]	9 (7.2%)	9 (7.4)
Age at migraine onset, years (SD)	20.5 (10.90)	18.0 (9.35)
Disease duration, years (SD)	23.7 (10.91)	26.6 (12.12)
Acute headache medication use, n (%)		
Migraine-specific	109 (87.2)	102 (84.3)
Non-migraine-specific	14 (11.2)	13 (10.7)
History of previous preventative treatment failure, n (%)[b]		
2	52 (41.6)	43 (35.5)
3	49 (39.2)	44 (36.4)
4	23 (18.4)	33 (27.3)
Baseline period, mean (SD)		

Monthly migraine days	9.3 (2.71)	9.3 (2.58)
Monthly headache days	10.1 (2.68)	10.1 (2.81)
Monthly acute migraine-specific drug use days	4.4 (2.84)	4.8 (2.95)
Acute migraine-specific drug use, n (%)	109 (87.2)	102 (84.3)

Footnotes: [a]'Other' includes unknown (n=1 in placebo arm). [b]Two patients (one in each arm) had a history of less than 2 prior preventative treatment failures.
Abbreviations: BMI: body mass index; SD: standard deviation.
Source: LIBERTY data on file (2018)[84], Reuter *et al.* (2018)[93]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 Trial populations in Study 295, STRIVE, ARISE and LIBERTY

Definitions of the patient populations used within Study 295, STRIVE, ARISE and LIBERTY are provided in Table 12. The statistical analyses used for primary endpoints, alongside sample size calculations and methods for handling missing data, are presented in Table 13. Full CONSORT diagrams of the study population flow, and reasons for study drug discontinuation and discontinuation from the study, are provided in Appendix D.

A total of 953 patients were screened in Study 295, with 667 randomised to receive placebo, erenumab 70 mg, and erenumab 140 mg. Of these, 660 patients (99.0%) went on to receive at least one dose of investigational product (erenumab or placebo), which formed the safety analysis population. The Week 8 dose was completed by 637 patients (95.5%) and 631 (94.6%) completed the study (i.e., completed the full 12-week assessment). Reasons for study drug discontinuation included subject request, loss to follow-up, AEs and non-compliance.

Of the 1,492 patients screened in STRIVE, 955 were enrolled and randomised to receive placebo, erenumab 70 mg and erenumab 140 mg. Of these, 952 patients (99.7%) went on to receive at least one dose of investigational product (erenumab or placebo) during the double-blind treatment phase with 858 (90.6%) completing this phase. In the following active treatment phase of the study, 844 patients received one or more doses of either erenumab 70 mg or erenumab 140 mg, with 14 patients not continuing from the double-blind phase. As of the data cut-off date (5th September 2016), 91 patients had completed the active treatment phase, 716 were continuing, and 37 patients from the 844 randomised had discontinued.

Of the 877 patients screened in ARISE, 577 were enrolled and randomised to receive placebo or erenumab 70 mg. Of these, 572 patients (99.1%) went on to receive at least one dose of investigational product (erenumab or placebo) during the double-blind treatment phase with 546 (94.6%) completing this phase. In the following active treatment phase of the study, 538 patients received one or more doses of erenumab 70 mg, with 8 patients not continuing from the double-blind phase. As of the data cut-off date (11th July 2016), 101 patients had completed the active treatment phase, 405 were continuing, and 32 patients from the 577 randomised had discontinued.[94]

Of the 333 patients screened in LIBERTY, 246 were enrolled and randomised to receive placebo and erenumab 140 mg. Of these 243 went on to receive at least one dose of investigational product (erenumab or placebo) during the double-blind treatment phase with 240 (97.6%)

completing this phase. All patients who completed the double-blind treatment phase entered the open-label treatment phase.[75, 84]

Table 12: Trial populations for Study 295, STRIVE, ARISE and LIBERTY

Analysis	Trial population			
	Study 295	**STRIVE**	**ARISE**	**LIBERTY**
Randomisation analysis (RA) set	**RA set (n=667) -** All patients in the study who were randomly assigned to treatment Data analysed: Demographic data, baseline disease characteristics, subject disposition, and important protocol deviations	N/A	N/A	**RA set (n=246) -** All patients who were randomly assigned to treatment
Full analysis (FA) set	N/A	**FA set (n=955) -** All patients randomised in the study Data analysed: Used to tabulate demographics and baseline characteristics, patient disposition, and important protocol deviations	**FA set (n=577) -** All patients randomised in the study Data analysed: Used to tabulate demographics and baseline characteristics, patient disposition, and important protocol deviations	**FA set (n= 243) -** All patients who started study medication and have completed at least one post-baseline monthly migraine day measurement in the double-blind phase Data analysed: Efficacy endpoints
Efficacy analysis(EA) set	**EA set (n=656) -** All patients in the randomisation analysis set who received at least one dose of investigational product and completed at least one post-baseline monthly eDiary measurement Data analysed: Efficacy endpoints	**EA set (n=946) -** Patients in the full analysis set who received at least one dose of investigational product and completed at least one post-baseline MMD measurement in the double-blind treatment phase. Data analysed: Used for analyses of efficacy endpoints and patient-reported outcomes	**EA set (n=570) -** Patients in the full analysis set who received at least one dose of investigational product and completed at least one post-baseline MMD measurement in the double-blind treatment phase. Data analysed: Used for analyses of efficacy endpoints and patient-reported outcomes	N/A

Safety analysis (SA) set	**SA set (n=660) -** All randomly assigned patients who received at least one dose of investigational product Data analysed: Used for safety endpoints and investigational product administration	**SA set (n=952) -** All randomised patients who received at least one dose of investigational product Data analysed: Used for safety endpoints and summary of investigational product administration	**SA set (n=572) -** All randomised patients who received at least one dose of investigational product Data analysed: Used for safety endpoints and summary of investigational product administration	**SA set (n=243) -** All randomised patients who received at least one dose of investigational product Data analysed: Used for safety endpoints
Per protocol (PP) set	**PP set (n=612) -** For the final analysis at week 12, patients who received the Week 8 investigational product and did not have important protocol deviations or GCP violations. Any patients who did not have an observed MMD value at Week 12 were excluded Data analysed: Sensitivity analyses on primary and secondary endpoints	**PP set (n=808) -** Subset of the efficacy analysis set that included patients who completed the 24-week double-blind treatment phase with no major protocol violations Data analysed: Sensitivity analyses on primary and secondary efficacy endpoints	**PP set (n=522) -** Subset of the efficacy analysis set that included patients who completed the 12-week double-blind treatment phase with no major protocol violations Data analysed: Sensitivity analyses on primary and secondary efficacy endpoints	N/A

Abbreviations: MMD: monthly migraine day; N/A: not applicable.
Source: Tepper *et al.* (2017)[68], Study 295 CSR[69], STRIVE CSR[73], ARISE CSR[77], LIBERTY CSR[82]

Interim analyses and patient stopping guidelines

Study 295

An administrative interim analysis was conducted by an independent statistical group after all randomised patients completed the double-blind treatment phase on 23rd February 2016. At this point, the study drugs were no longer administered and all efficacy assessments had been collected. The analysis, which included, but was not limited to, the primary endpoint in the randomisation analysis set, was planned to provide information on dose selection and device development for erenumab. Results in this submission are presented from the final analysis, conducted at the end of the study after the double-blind treatment phase and the safety follow-up phase.

STRIVE

A blinded interim analysis was conducted by the sponsor after approximately 30% of patients had completed the first three months of the double-blind treatment phase. The purpose of this interim analysis was to re-estimate the sample size by providing information on the variance for the trial, relative to the planning assumptions used in the sample size calculation. The type 1 error of the primary analysis was maintained as treatment assignment remained blinded and the study was not stopped early. The data presented in this submission are the results of the double-blind treatment phase.

ARISE

A blinded interim analysis was conducted by the sponsor after 28% of patients completed the double-blind treatment phase, to re-estimate the sample size by providing information on the variance for this trial relative to the planning assumptions used in the sample size calculation. No specific hypotheses were tested and treatment assignment remained blinded to all involved parties. The data presented in this submission are the results of the double-blind treatment phase.

LIBERTY

No interim analysis was conducted during this trial. The data presented in this submission are the results of the double-blind treatment phase.

Statistical tests

A summary of the statistical tests for the primary analysis of Study 295, STRIVE, ARISE and LIBERTY is presented in Table 13.

Table 13: Statistical tests for the primary analysis of Study 295, STRIVE, ARISE and LIBERTY

Trial number (acronym)	NCT02066415 (Study 295)	NCT02456740 (STRIVE)	NCT02483585 (ARISE)	NCT03096834 (LIBERTY)
Hypothesis objective	The primary endpoint was the mean change in MMDs from baseline to the last four weeks of the 12-week double-blind treatment phase. Null hypothesis (H_0): There was no difference between erenumab 70 mg or 140 mg from placebo in terms of change from baseline in MMDs. Alternative hypothesis (H_A): At least one dose of erenumab reduced MMDs from baseline to a greater extent than placebo.	The primary endpoint was the change from baseline in MMDs. The mean MMDs was calculated using the MMDs from each of the last three months (Months 4, 5, and 6) of the 24-week double-blind treatment phase. Null hypothesis (H_0): Neither erenumab 70 or 140 mg differ from placebo with respect to change in MMDs from baseline to the last 3 months (Months 4, 5, and 6) of the double-blind treatment phase. Alternative hypothesis (H_A): At least one erenumab dose reduced MMDs from baseline to a greater extent than placebo.	The primary endpoint was the mean change from baseline in MMDs from baseline to the last four weeks (Month 3) of the double-blind treatment phase. Null hypothesis (H_0): There was no difference between 70mg and placebo with respect to change in MMDs from baseline to the last four weeks (Month 3) of the double-blind treatment phase. Alternative hypothesis (H_A): At least one erenumab dose reduced MMDs from baseline to a greater extent than placebo	The primary endpoint was the achievement of at least a 50% reduction from baseline in MMDs in the last four weeks (Month 3) of the double-blind treatment epoch. Null hypothesis (H_0): There was no difference between erenumab 140 mg from placebo in terms of the number of patients who achieved at least a 50% reduction from baseline in MMDs to the last four weeks (Month 3) of the double-blind treatment epoch. Alternative hypothesis (H_A): Erenumab 140 mg was associated with a greater proportion of patients who achieved at least a 50% reduction from baseline in MMDs to the last four weeks of the double-blind treatment epoch than placebo.
Statistical tests	LSM was calculated at each timepoint based on a generalised linear mixed effects model. This model included treatment group, baseline MMDs value, stratification factors (region and medication	Observed data and mean MMDs at Months 4, 5, and 6 were used to produce summary statistics by visit. LSM calculated based on a generalised linear mixed effects	Primary analyses for continuous efficacy endpoints were based on a linear mixed effects model which included treatment group, baseline MMDs value, stratification factors, scheduled visit, and the interaction of	The first analysis was conducted on all patient data at the end of the double-blind treatment epoch. After the open-label treatment phase ended, a second set of analyses of all data was conducted.

	overuse), scheduled visit, and the interaction of treatment group with scheduled visit using observed data as covariates and assuming a first-order autoregressive covariance structure. Pairwise treatment difference and linear trend were tested using a contrast from the mixed effects model	model. This mixed model included treatment group, baseline MMDs value, stratification factors (region and prior/current treatment with migraine prophylactic medication), scheduled visit, and the interaction of treatment group with scheduled visit using observed data as covariates. The model assumed a first-order autoregressive covariance structure. Pairwise treatment difference and linear trend was tested using a contrast from the given mixed effect model.	treatment group with scheduled visit using observed data as covariates and assuming a first-order autoregressive covariance structure. For dichotomous efficacy endpoints, a stratified CMH test was used. A sequential testing procedure was used to maintain the 2-sided study-wise type I error at 0.05 between the primary and secondary endpoints.	A CMH test stratified by the migraine frequency was used under a 2-sided significance level of 0.05 to evaluate association between the 50% responder rate and treatment. The corresponding p-value, and estimated odds ratio between erenumab and placebo, along with the 95% CI was reported.
Sample size, power calculation	Within the erenumab 70 mg group, the treatment effect and common SD compared with placebo was assumed to be −1.9 days and 6.1, respectively. Using a two-sample t-test with a two-sided significance level of 0.04, the planned sample sizes for the placebo group (n=279) and the erenumab 70 mg group (n=186) provided 85% power in detecting superiority of erenumab in the primary endpoint.	A planned enrolment of 284 patients per treatment group provided ≥90% power to detect treatment differences of −1.12 MMDs for erenumab 70 mg and −1.30 MMDs for erenumab 140 mg versus placebo, with a common SD of 3.78, using two-sided t-tests with a significance level of 0.05. The sample size calculation assumed a 10% drop-out rate. The assumed treatment effect was based on results observed in the phase II trial of erenumab in episodic migraine.[72, 95]	A planned enrolment of 270 subjects per group provided 90% power to detect treatment differences of −1.12 MMDs for the erenumab 70 mg group versus placebo, using two-sided t-tests with a significance level of 0.05, assuming a common SD of 3.78. The planned sample sizes also provided 95% power to detect a difference of 15.5% in the proportion of subjects with ≥50% reduction in MMDs using a stratified CMH test with a significance level of 0.04, and 97% power to detect a difference of 0.96 days in the	The treatment effect of erenumab 140 mg compared to placebo observed in STRIVE at Month 3 for the full population, patients with ≥1 treatment failures, and patients with ≥2 treatment failures was used to inform sample size calculations. Assuming a treatment effect similar to the effect observed in STRIVE, under 2-sided 0.05 alpha level, with 90% power, it takes 220 patients (110 per treatment group) to detect approximately a 20% improvement on the response rate of 50%, assuming 18%

			mean change in monthly migraine-specific medication treatment days as compared to placebo with a significance level of 0.04 and a common SD of 2.65 days.	response rate in the placebo group.
Data management, patient withdrawals	Missing data was not replaced with any substituted values for analysis of the primary endpoint. Patients could withdraw from the study at any time at their own request, or they could be withdrawn at any time at the discretion of the sponsor for safety or behavioural reasons, or the inability of the patient to comply with the protocol-specified criteria.	No imputation for missing data. Patients could withdraw from the study at any time at their own request, or they could be withdrawn at any time at the discretion of the sponsor for safety or behavioural reasons, or the inability of the patient to comply with the protocol-specified criteria.	No imputation for missing data was performed for continuous endpoints. For dichotomous endpoints, missing data were imputed as non-response. Patients could withdraw from the study at any time at their own request, or they could be withdrawn at any time at the discretion of the sponsor for safety or behavioural reasons, or the inability of the patient to comply with the protocol-specified criteria.	Patients with missing MMDs data at Month 3 of the double-blind treatment phase were imputed as non-responders. Note that missing data was not imputed for safety endpoints.

Abbreviations: CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; SD: standard deviation.
Source: Tepper *et al.* (2017)[68], Study 295 CSR[69], Goadsby et al. (2017) Supplementary Appendix[87], STRIVE CSR[73], Dodick *et al*. (2018)[76], ARISE CSR[77], ARISE Protocol[91], LIBERTY CSR[82], LIBERTY Protocol[89]

B.2.4.2 Quality assessment of the relevant clinical effectiveness evidence

Study 295

Overall, Study 295 was well-designed, with appropriate randomisation, concealment of treatment and blinding. Participants were assigned a unique subject identification number upon entrance to the screening phase, with randomisation based on a schedule generated by the sponsor before the start of the study, and centrally executed using an interactive voice/web response system. The study was double-blinded, with the patients, site personnel and sponsor study personnel masked to the randomisation treatment group assignment. The study was funded by Amgen.

STRIVE

STRIVE was well-designed, with appropriate randomisation, concealment of treatment and blinding. Patients were assigned a unique subject identification number upon entrance to the screening phase, and randomisation was based on a schedule generated by the sponsor before the start of the study, and centrally executed using an interactive voice/web response system. The study was funded by Amgen.

ARISE

ARISE was well-designed, with appropriate randomisation, concealment of treatment and blinding. Patients were assigned a unique subject identification number upon entrance to the screening phase, and randomisation was based on a schedule generated by the sponsor before the start of the study, and centrally executed using an interactive voice/web response system. The study was funded by Amgen.

LIBERTY

LIBERTY was well-designed, with appropriate randomisation, concealment of treatment and blinding. Patients were assigned a unique subject identification number upon entrance to the screening phase, and randomisation was based on a schedule generated by the sponsor before the start of the study, and centrally executed using an interactive voice/web response system. The study was double-blinded, with the patients, site personnel and sponsor study personnel masked to the randomisation treatment group assignment. The study was funded by Novartis.

A summary of quality assessments across all four studies is provided in Table 14. Full quality assessments of each study individually can be found in Appendix D.

Table 14: Overview of quality assessments for studies of erenumab

Trial number (acronym)	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT NCT02483585)	LIBERTY (NCT03096834)
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study	Yes	Yes	Yes	Yes

in terms of prognostic factors?				
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	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	No

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[96]

B.2.5 *Clinical effectiveness results of the relevant trials*

B.2.5.1 Key clinical effectiveness results from the relevant trials

All four trials met their primary endpoint at the time of their analyses, demonstrating that erenumab is associated with a significant reduction in MMDs from baseline versus placebo across the migraine spectrum, including in both chronic migraine and episodic migraine patients. A brief overview of the key endpoints for all four trials is provided below. As discussed in Section B.1.1, this submission focuses on patients for whom ≥3 prior prophylactic treatments have failed. Presentation and discussion of the efficacy results for this subgroup of each trial is provided in Section B.2.6. It is the results in these populations that inform the economic model presented in Section B.3.

Study 295

A summary of the clinical effectiveness results at Week 12 in Study 295 is provided in Table 15. All scope-defined efficacy outcomes available from this study are summarised in this table. Compared with placebo, treatment with erenumab was associated with significant reductions from baseline in mean MMDs, MHDs and acute migraine-specific treatment days, as well as a significantly higher ≥50% responder rate. Study 295 met its primary endpoint, with a mean

reduction in MMDs from baseline of −6.6 days in both erenumab arms, compared to −4.2 days in the placebo arm, corresponding to a LSM difference versus placebo of −2.5 days in both erenumab arms (95% CI: −3.5, −1.4; p<0.0001). Significant differences were observed from as early as Week 1, and were maintained for the duration of the assessment period.[97] In total, 75 (40%) and 77 (41%) patients in the erenumab 70 mg and erenumab 140 mg arms, respectively, achieved a ≥50% reduction in MMDs from baseline, compared to 66 patients (23%) in the placebo arm. This corresponded to an odds ratio of response versus placebo of 2.2 (95% CI: 1.5, 3.3; p=0.0001) and 2.3 (95% CI: 1.6, 3.5; p<0.0001) for erenumab 70 mg and erenumab 140 mg respectively. This means that patients treated with erenumab 70 mg and 140 mg had over two times the odds of achieving a reduction in MMDs of at least 50% from baseline, compared to patients treated with placebo.

On an individual patient level, reductions of headache frequency from baseline of more than 30% are generally considered clinically relevant. Reductions by more than one day per month are considered to be the minimally important difference at a population level.[98] Against these clinical criteria, erenumab demonstrated clinically meaningful efficacy. Erenumab achieved reductions in both migraine frequency and headache frequency from baseline of multiple days per month, as well as a significant increase in the proportion of patients achieving the even more stringent measure of more than 50% reduction in migraine days per month.

In addition, results summarised in Table 15 and Table 16 demonstrate that, compared to placebo, erenumab provides significant reductions in the requirement for acute migraine-specific treatment, as well as numerical reductions in average severity of migraine pain and cumulative monthly headache hours. Taken together, these results support the efficacy of erenumab in alleviating the burden of disease in adults with disabling migraine symptoms.

Table 15: Overview of key clinical effectiveness results from Study 295 at Week 12

Outcome	Placebo (n=281)	Erenumab 70 mg (n=188)	Erenumab 140 mg (n=187)
Change from baseline in MMDs[a]			
Baseline			
Mean (SE)	18.24 (0.28)	17.94 (0.32)	17.78 (0.34)
Median	18.06	17.68	17.63
Q1, Q3	14.82, 21.78	15.00, 20.37	14.48, 21.00
Minimum, Maximum	5.6, 28.0	8.1, 28.0	8.1, 28.0
Change from baseline at Week 12			
Mean (SE)	−4.2 (0.4)	−6.6 (0.4)	−6.6 (0.4)
Difference (95% CI)	-	−2.5 (−3.5, −1.4)	−2.5 (−3.5, −1.4)
p-value	-	<0.0001	<0.0001
Change from baseline in MHDs[a]			
Baseline			
Mean (SE)	21.16 (0.23)	20.60 (0.27)	20.78 (0.27)
Median	21.00	20.06	20.28
Q1, Q3	18.00, 24.00	17.56, 23.00	17.92, 23.63
Minimum, Maximum	9.3, 28.0	14.5, 28.0	14.0, 28.0

Change from baseline at Week 12			
Mean (SE)	[redacted]	[redacted]	[redacted]
Difference (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]
Proportion of patients with ≥50% reduction in MMDs from baseline at Week 12[b]			
Responders, n (%)	66 (23.5)	75 (39.9)	77 (41.2)
Difference versus placebo, %	-	16.4	17.7
Odds ratio (95% CI)	-	2.18 (1.46, 3.27)	2.34 (1.56, 3.51)
p-value	-	<0.001	<0.001

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment. [b]The adjusted odds ratios and p-values were obtained from a CMH test after the missing data were imputed as non-response, stratified by stratification factors region and medication overuse. The same analysis was repeated for each visit. P-values for pairwise comparisons are nominal p-values obtained from the CMH test using data including placebo and corresponding erenumab dose group only.
Abbreviations: CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; Q1: first quartile; Q3: third quartile; SE: standard error.
Source: Study 295 CSR[69], Tepper *et al.* (2017)[68], Tepper *et al.* Supplementary material[85]

Table 16: Overview of other effectiveness results from Study 295 at Week 12[a]

	Placebo (n=281)	Erenumab 70 mg (n=188)	Erenumab 140 mg (n=187)
Monthly acute migraine-specific medication treatment days			
Baseline			
Mean (SE)	9.42 (0.45)	8.77 (0.53)	9.68 (0.51)
Median	9.00	9.83	10.40
Q1, Q3	2.00, 15.00	0.00, 14.00	2.07, 15.56
Minimum, Maximum	0.0, 27.0	0.0, 26.0	0.0, 23.6
Change from baseline at Week 12			
LSM (SE)	−1.58 (0.24)	−3.45 (0.29)	−4.13 (0.29)
95% CI of LSM	−2.05, −1.11	−4.02, −2.87	−4.70, −3.56
Difference (95% CI)	-	−1.86 (−2.60, −1.13)	−2.55 (−3.28, −1.82)
p-value	-	<0.001	<0.001
Cumulative monthly headache hours			
Baseline			
Mean (SE)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Change from baseline at Week 12			
LSM (SE)	–55.22	–64.76	–74.53
95% CI of LSM	–66.38, –44.06	–78.34, –51.17	–88.05, –61.01

Difference (95% CI)	-	-9.54 (-26.98, 7.90)	–19.31 (–36.71, –1.92)
p-value	-	0.28	0.030
Change from baseline in monthly average severity of migraine pain			
Baseline			
Mean (SE)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Change from baseline at Week 12			
LSM (SE)	[redacted]	[redacted]	[redacted]
95% CI of LSM	[redacted]	[redacted]	[redacted]
Difference (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; LSM: least squares mean; Q1: first quartile; Q3: third quartile; SE: standard error.
Source: Study 295 CSR[69], Tepper *et al*. (2017)[68]

STRIVE

A summary of the key clinical effectiveness results from baseline to the last three months of the double-blind treatment phase in STRIVE is provided in Table 17 and Table 18. All scope-defined efficacy outcomes available from this study are summarised in these tables. STRIVE met its primary endpoint, with erenumab demonstrating a significantly greater reduction in MMDs from baseline compared to placebo. Patients treated with erenumab 70 mg and 140 mg achieved significantly greater reductions from baseline to the last three months of the 24-week double-blind treatment phase compared to placebo for several further key endpoints, including frequency of MHDs and monthly acute migraine-specific treatment days. In terms of reduction in the frequency of MMDs, the differences in LSM versus placebo were −1.4 days (95% CI: −1.9, −0.9; p<0.001) and −1.9 days (95% CI: −2.3, −1.4; p<0.001) for the erenumab 70 mg and erenumab 140 mg arms, respectively. As in Study 295, significant differences were observed from as early as Week 1, highlighting the rapid onset of action of erenumab.[99] Over the last three months of the double-blind treatment phase, 135 (43.3%) and 159 (50.0%) patients in the erenumab 70 mg and 140 mg arms achieved a ≥50% reduction in mean MMDs from baseline, compared to 84 (26.6%) patients in the placebo arm. The odds ratios for response for the 70 mg and 140 mg arms versus placebo were 2.13 (95% CI: 1.52, 2.98; p<0.001) and 2.81 (95% CI: 2.01, 3.94; p<0.001) respectively. Patients treated with erenumab 140 mg achieved numerically greater reductions in MMDs and MHDs from baseline compared to those treated with erenumab 70 mg, and a higher proportion of patients achieved a ≥50% reduction in mean MMDs compared to the erenumab 70 mg arm.

Table 17: Overview of key clinical effectiveness results from STRIVE over months 4, 5 and 6

	Placebo (n=316)	Erenumab 70 mg (n=312)	Erenumab 140 mg (n=318)
Change from baseline in MMDs[a]			
Baseline			
N	316	312	318
Mean (SE)	8.25 (2.51)	8.31 (2.47)	8.33 (2.48)
Median	8.00	8.00	8.00
Q1, Q3	6.00, 10.00	6.40, 10.00	6.76, 10.00
Minimum, Maximum	3.0, 14.9	3.5, 14.5	3.2, 16.0
Change from baseline over months 4, 5, and 6			
LSM estimate (SE)	–1.83 (0.18)	–3.23 (0.18)	–3.67 (0.18)
95% CI of LSM	–2.18, –1.48	–3.58, –2.88	–4.02, –3.33
Difference in LSM (95% CI)	-	–1.40 (–1.88, –0.92)	–1.85 (–2.33, –1.37)
p-value	-	<0.001	<0.001
Change from baseline in MHDs[a]			
Baseline			
Mean (SE)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Change from baseline over months 4, 5, and 6			
LSM estimate (SE)	[redacted]	[redacted]	[redacted]
95% CI of LSM	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]
Proportion of patients with ≥50% reduction in baseline MMDs over months 4, 5 and 6[b]			
Responders, n (%)	84 (26.6)	135 (43.3)	159 (50.0)
Odds ratio versus placebo (95% CI)	-	2.13 (1.52, 2.98)	2.81 (2.01, 3.94)
p-value	-	<0.001	<0.001

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment. [b]The adjusted odds ratios and p-values were obtained from a CMH test after the missing data were imputed as non-response, stratified by stratification factors region and medication overuse. The same analysis was repeated for each visit. P-values for pairwise comparisons are nominal p-values obtained from the CMH test using data including placebo and corresponding erenumab dose group only.
Abbreviations: CI: confidence interval; LSM: least squares mean; MMD: monthly migraine day; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: Goadsby *et al.* (2017)[72], Goadsby *et al.* (2017) Supplementary Appendix[87], STRIVE CSR[73]

Table 18: Overview of other clinical effectiveness results from STRIVE over months 4, 5 and 6[a]

	Placebo (n=316)	Erenumab 70 mg (n=312)	Erenumab 140 mg (n=318)
Change from baseline in monthly acute migraine-specific days			
Baseline			
Mean (SD)	3.43 (3.43)	3.24 (3.40)	3.42 (3.48)
Median	3.29	3.00	3.00
Q1, Q3	0.00, 6.00	0.00, 5.87	0.00, 6.00
Minimum, Maximum	0.0, 12.0	0.0, 14.0	0.0, 12.6
Change from baseline over months 4, 5, and 6			
LSM estimate	−0.20	−1.13	−1.61
95% CI of LSM	−0.41, 0.02	−1.34, −0.92	−1.83, −1.40
Difference in LSM (95% CI)	-	−0.94 (−1.23, −0.64)	−1.42 (−1.71, −1.12)
p-value	-	<0.001	<0.001
Change from baseline in monthly average severity of migraine pain			
Baseline			
Mean (SE)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Change from baseline over months 4, 5, and 6			
LSM estimate (SE)	[redacted]	[redacted]	[redacted]
95% CI of LSM	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]
Change from baseline in monthly hours of migraine headache			
Baseline			
Mean (SE)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]
Change from baseline over months 4, 5, and 6			
LSM estimate (SE)	[redacted]	[redacted]	[redacted]
95% CI of LSM	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; LSM: least squares mean; MMD: monthly migraine day; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: Goadsby *et al.* (2017)[72]; Goadsby *et al*. (2017) Supplementary Appendix[87]; STRIVE CSR[73]

ARISE

A summary of the key clinical effectiveness results from baseline to the last month of the double-blind treatment phase (Month 3) in ARISE is provided in
Table 19. Compared with placebo, treatment with erenumab was associated with significant reductions from baseline in mean MMDs, MHDs and acute migraine-specific treatment days, as well as a significantly higher ≥50% responder rate. ARISE met its primary endpoint, with a mean reduction in MMDs from baseline of −2.9 days in the erenumab 70 mg arm, compared to −1.8 days in the placebo arm, corresponding to a LSM difference versus placebo of −1.0 days (95% CI: −1.6, −0.5; p<0.001). In total, 112 (39.7%) patients in the erenumab 70 mg arm, and 85 (29.5%) patients in the placebo arm achieved a ≥50% reduction in MMDs from baseline, corresponding to an odds ratio of response of 1.59 (95% CI: 1.12, 2.27; p=0.010).

Other clinical efficacy results summarised in
Table 19 and Table 20 indicate that, compared to placebo, treatment with erenumab leads to significant reductions in the use of acute migraine-specific treatment, average severity of migraine pain, and monthly hours of migraine headache.

Table 19: Overview of key clinical effectiveness results from ARISE at Week 12

	Placebo (n=288)	Erenumab 70 mg (n=282)
Change from baseline in MMDs[a]		
Baseline		
Mean (SD)	8.4 (2.6)	8.1 (2.7)
Median	8.24	8.00
Q1, Q3	6.50, 10.00	6.32, 9.66
Minimum, Maximum	2.8, 16.6	2.4, 15.4
Change from baseline at Week 12		
Mean (SE)	−1.8 (0.2)	−2.9 (0.2)
Mean difference (95% CI)	-	−1.0 (−1.6, −0.5)
p-value	-	<0.001
Change from baseline in MHDs[a]		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]
Change from baseline at Week 12		
Mean (SE)	[redacted]	[redacted]

Mean difference (95% CI)	-	[redacted]
p-value	-	[redacted]
Proportion of patients with ≥50% reduction in MMDs from baseline at Week 12[b]		
Responders, n (%)	85 (29.5)	112 (39.7)
Odds ratio versus placebo (95% CI)	-	1.59 (1.12, 2.27)
p-value	-	0.010

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment. [b]The adjusted odds ratios and p-values were obtained from a CMH test after the missing data were imputed as non-response, stratified by stratification factors region and medication overuse. The same analysis was repeated for each visit. P-values for pairwise comparisons are nominal p-values obtained from the CMH test using data including placebo and corresponding erenumab dose group only.
Abbreviations: CI: confidence interval; LSM: least squares mean; MMD: monthly migraine day; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: Dodick *et al*. (2018)[76], ARISE CSR[77]

Table 20: Overview of other effectiveness results from ARISE at Week 12[a]

	Placebo (n=288)	Erenumab 140 mg (n=282)
Change from baseline in monthly acute migraine-specific medication days		
Baseline		
Mean (SD)	3.4 (3.6)	3.7 (3.6)
Median	2.59	3.61
Q1, Q3	0.00, 6.76	0.00, 7.00
Minimum, Maximum	0.0, 12.4	0.0, 13.5
Change from baseline at Week 12		
Mean (SE)	−0.6 (0.1)	−1.2 (0.1)
Mean difference (95% CI)	-	−0.6 (−1.0, −0.2)
p-value	-	0.002
Change from baseline in monthly average severity of migraine pain		
Baseline		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]
Change from baseline at Week 12		
Mean (SE)	[redacted]	[redacted]
Mean difference (95% CI)	-	[redacted]
p-value	-	[redacted]
Change from baseline in monthly hours of migraine headache		
Baseline		

Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]
Change from baseline at Week 12		
Mean (SE)	[redacted]	[redacted]
Mean difference (95% CI)	-	[redacted]
p-value	-	[redacted]

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; LSM: least squares mean; MMD: monthly migraine day; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: Dodick *et al*. (2018)[76], ARISE CSR[77]

LIBERTY

A summary of the key clinical effectiveness results from baseline to the last month of the double-blind epoch (Month 3) in LIBERTY is provided in Table 21 below. The number of cumulative hours of migraine and severity of migraine pain were not recorded in LIBERTY, and therefore no data are available for these endpoints.

LIBERTY met its primary endpoint, with a significantly greater proportion of patients achieving ≥50% reduction in baseline MMDs in the erenumab 140 mg arm versus placebo. Patients in the erenumab 140 mg arm also experienced a significant reduction in the number of acute migraine-specific medication days at Week 12 versus placebo (p<0.001). The LIBERTY study required eligible patients to have failed 2–4 prior migraine prophylaxis treatments, thereby building upon the evidence provided by STRIVE and ARISE to consider a patient population with a high burden of disease and very few further treatment options.

Table 21: Overview of key clinical effectiveness results from LIBERTY at Week 12

	Placebo (n=124)	Erenumab 140 mg (n=119)
Change from baseline in MMDs[a]		
Baseline		
Mean (SD)	9.3 (2.71)	9.3 (2.58)
Median	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]
Change from baseline at Week 12		
Mean (SE)	−0.15 (0.41)	−1.76 (0.44)
Mean difference (95% CI)	-	−1.61 (−2.70, −0.52)
p-value	-	0.004
Change from baseline in MHDs[a]		
Baseline		
Mean (SD)	[redacted]	[redacted]

Median	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]
Change from baseline at Week 12		
Mean (SE)	[redacted]	[redacted]
Mean difference (95% CI)	-	[redacted]
p-value	-	[redacted]
Proportion of patients with ≥50% reduction in MMDs from baseline at Week 12[a]		
Responders, n (%)	17 (13.7)	36 (30.3)
Odds ratio versus placebo (95% CI)	-	2.73 (1.43, 5.19)
p-value	-	0.002
Change from baseline in monthly acute migraine-specific medication days[b]		
Baseline		
Mean (SD)	4.41 (2.83)	4.85 (2.96)
Median	4.50	5.19
Minimum, Maximum	0.0, 10.0	0.0, 13.2
Change from baseline at Week 12		
Mean (SE)	0.48 (0.29)	−1.26 (0.24)
Mean difference (95% CI)	-	−1.73 (−2.46, −1.01)
p-value	-	<0.001

[a]Statistical analysis utilises a CMH test adjusting for stratification factor (4–7 vs. 8–14 migraine days at baseline) after missing data are imputed as non-response (NRI). [b]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming an unstructured covariance matrix. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment. [b]The adjusted odds ratios and p-values were obtained from a CMH test after the missing data were imputed as non-response, stratified by stratification factors region and medication overuse. The same analysis was repeated for each visit. P-values for pairwise comparisons are nominal p-values obtained from the CMH test using data including placebo and corresponding erenumab dose group only.
Abbreviations: CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; SE: standard error.
Source: LIBERTY data on file (2018)[84], Reuter *et al.* (2018)[93]

B.2.5.2 Health-related quality of life in the full patient populations

The results of key patient-reported outcomes for the full populations in Study 295, STRIVE, ARISE and LIBERTY are presented in below. Patients treated with erenumab achieved improvements in HRQoL across all four trials, measured by MSQ-v2.1, HIT-6, MIDAS, PROMIS and MPFID scores versus placebo.

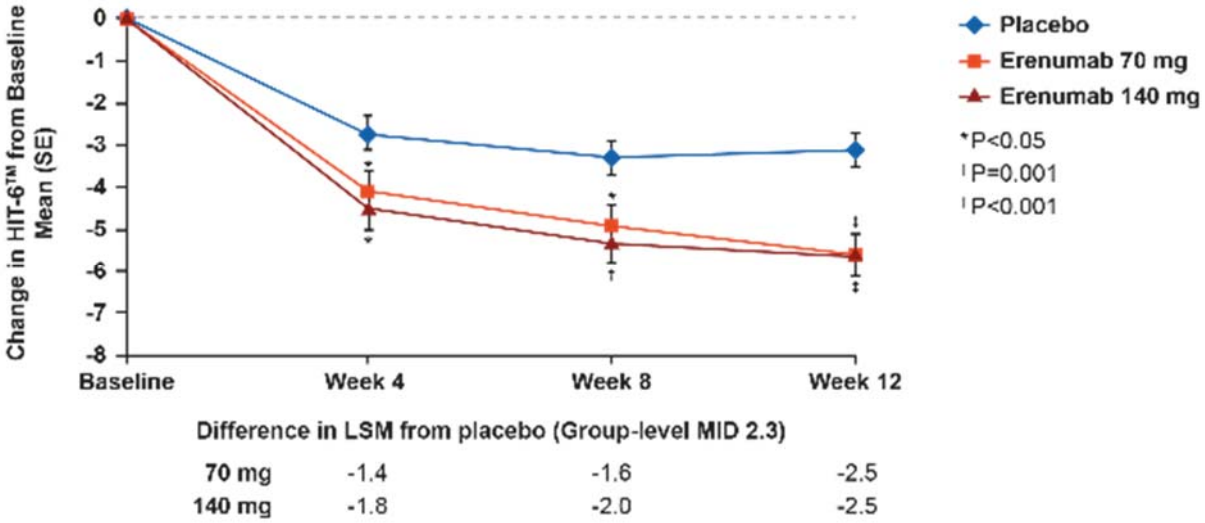
Study 295

Erenumab was associated with a statistically significant reduction in HIT-6 score versus placebo

The HIT-6 score is a patient-reported outcome (PRO) that captures multiple aspects of the impact on daily living, covering severe pain, limitation of daily activity, wanting to lie down when headache is experienced, feeling too tired to work due to headache and feelings of irritation due

to headache, as outlined in Appendix N. The change from baseline for HIT-6 scores in each arm is presented in Figure 7, which shows a significant reduction in HIT-6 scores at all assessment timepoints in the erenumab 70 mg and 140 mg arms compared with placebo. This indicates that patients treated with erenumab experienced a significant improvement in the impact of headache on daily living compared with placebo, with differences observed as early as the Week 4 assessment timepoint.

Figure 7: Change from baseline in total HIT-6 score in the efficacy analysis set[a]

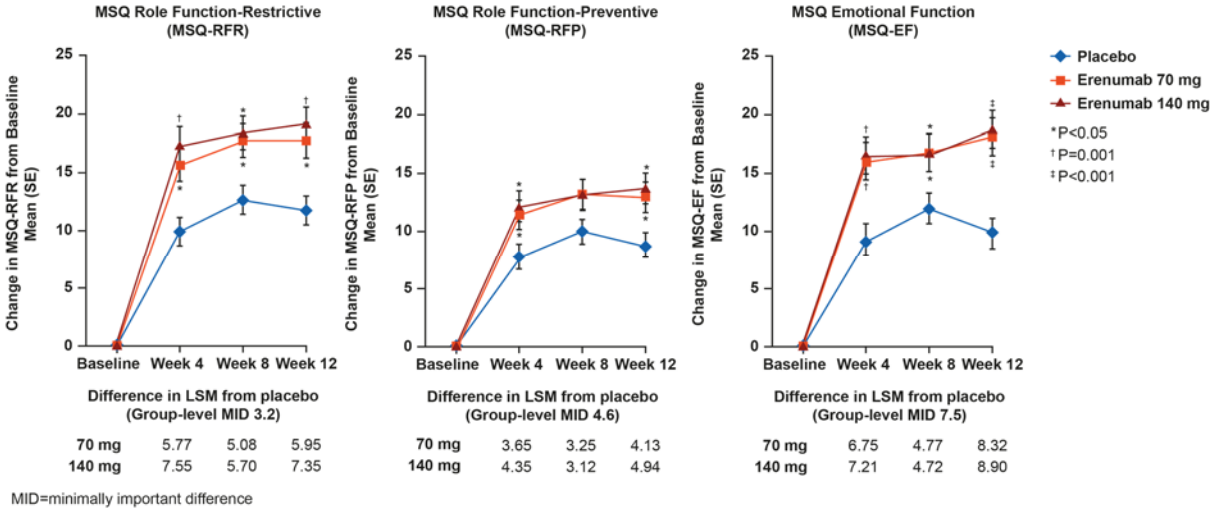


[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: HIT-6: Headache Impact Test; LSM: least squares mean; MID: minimally important difference; SE: standard error.
Source: Study 295 CSR[69]

MSQ 2.1 scores improved in erenumab patients, across all three subdomains of role-functioning restrictive, role-functioning preventative and emotional-function

MSQ v2.1 is a self-administered instrument that captures migraine-specific quality of life. Three sub-domain scores of the MSQ, role-function restrictive (RFR), role-function preventative (RFP) and emotional-function (EF), were individually measured and are presented in Figure 8. These demonstrated significant improvements relative to placebo in all three domains for erenumab 70 mg and 140 mg at nearly all assessment timepoints. Furthermore, the difference in LSM between erenumab 140 mg and placebo exceeded the group-level minimally important difference (MID) at all timepoints, indicating important quality of life benefits with erenumab 140 mg treatment. In summary, these results indicate that patients within the erenumab 70 and 140 mg arms experienced a significant improvement in the extent to which migraine limited daily activities and impacted related emotions compared to patients who received placebo.

Figure 8: Change from baseline in MSQ-RFR, RFP and EF scores in the efficacy analysis set[a]

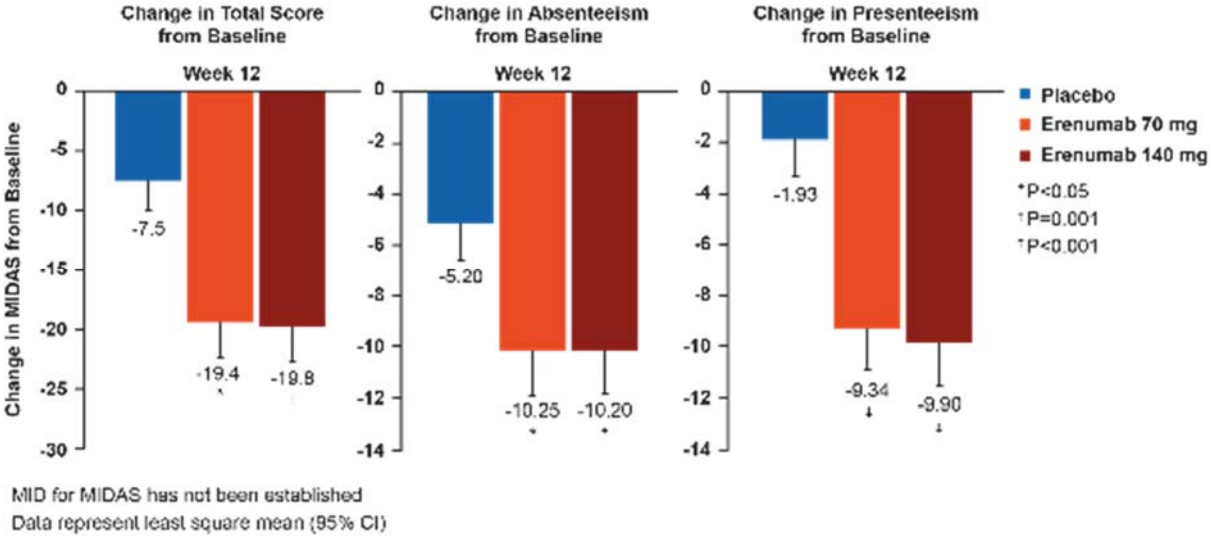


[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: LSM: least squares mean; MID: minimally important difference; MSQ-EF: Migraine-Specific Quality-of-Life Questionnaire-Emotional Function; MSQ-RFR: Migraine-Specific Quality-of-Life Questionnaire-Role Function-Restrictive; MSQ-RFP: Migraine-Specific Quality-of-Life Questionnaire-Role Function-Preventive; SE: standard error.
Source: Adapted from Study 295 CSR[69]

Patients treated with erenumab experienced significant reductions in both absenteeism and presenteeism MIDAS scores

MIDAS scores capture disease-related disability in family, social and leisure activities, and the impact on productivity both at home and in the workplace. MIDAS scores from the double-blind treatment phase of Study 295 are provided in Figure 9. As illustrated, there were significant reductions in both absenteeism and presenteeism in the erenumab 70 mg and 140 mg arms compared to placebo.

Figure 9: Change from baseline in MIDAS results in the efficacy analysis set[a]

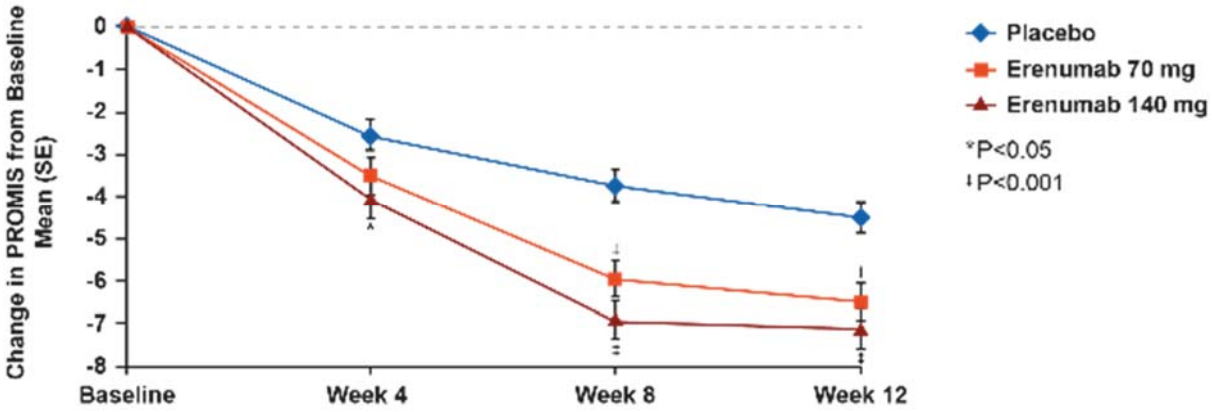


[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; MID: minimally important difference; MIDAS: Migraine Disability Assessment.
Source: Study 295 CSR[69]

Erenumab significantly reduced pain and migraine symptoms versus placebo, as measured by PROMIS

Data collected by the PROMIS Pain Interference Scale short form and single pain and migraine symptom interference questions is presented graphically in Figure 10, summarised as the change from baseline in monthly average scores. A significant reduction in scores was observed in both erenumab 70 mg and 140 mg arms at Week 12 when compared to placebo, indicating a greater improvement in pain and migraine symptoms for those treated with erenumab over placebo. For the erenumab 140 mg arm, significant differences were observed as early as the Week 4 assessment timepoint.

Figure 10: Change from baseline in monthly average PROMIS score in the efficacy analysis set[a]



[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
MID for PROMIS has not been established.
Abbreviations: PROMIS: Patient Reported Outcomes Measurement Information System Pain Interference Scale short form; SE: standard error.
Source: Study 295 CSR[69]

STRIVE

Erenumab significantly reduced HIT-6 scores in patients compared to placebo

As discussed above, the HIT-6 test measures impact of headache on daily living, specifically including aspects such as limitation of daily activity in household, work, school and social aspects, along with severe pain and feeling of irritation due to headache. The observed results show a significant reduction in HIT-6 scores at during Months 4, 5 and 6 in both erenumab arms when compared with placebo (Table 22).

Table 22: Change from baseline in HIT-6 total score in the efficacy analysis set[a]

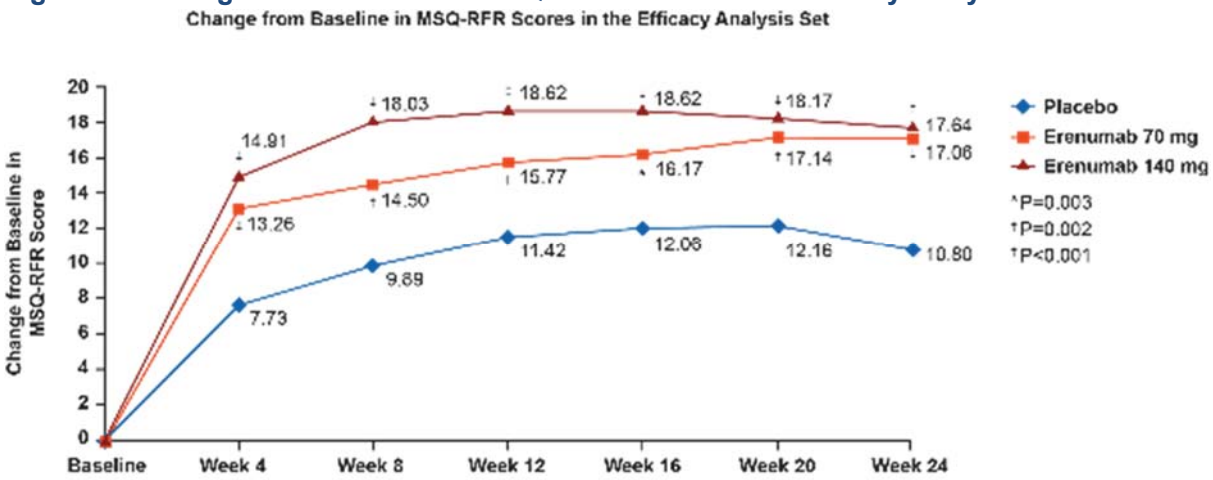
	Placebo (n=316)	Erenumab 70 mg (n=312)	Erenumab 140 mg (n=318)
Baseline			
Mean (SE)	59.8 (0.3)	60.3 (0.3)	59.2 (0.4)
Median	61.0	61.0	60.0
Q1, Q3	57.0, 64.0	57.0, 64.0	55.0, 63.0
Minimum, Maximum	40, 78	44, 78	38, 76
Mean over months 4, 5, and 6			
LSM estimate (SE)	−4.6 (0.4)	−6.7 (0.3)	−6.9 (0.3)
95% CI of LSM	−5.3, −4.0	−7.4, −6.0	−7.6, −6.3
Difference in LSM (95% CI)	-	−2.1 (−3.0, −1.1)	−2.3 (−3.2, −1.3)
p-value	-	<0.001	<0.001

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; HIT-6: Headache Impact Test; LSM: least squares mean; MMD: monthly migraine day; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: STRIVE CSR[73]

Summary of results for MSQ v2.1

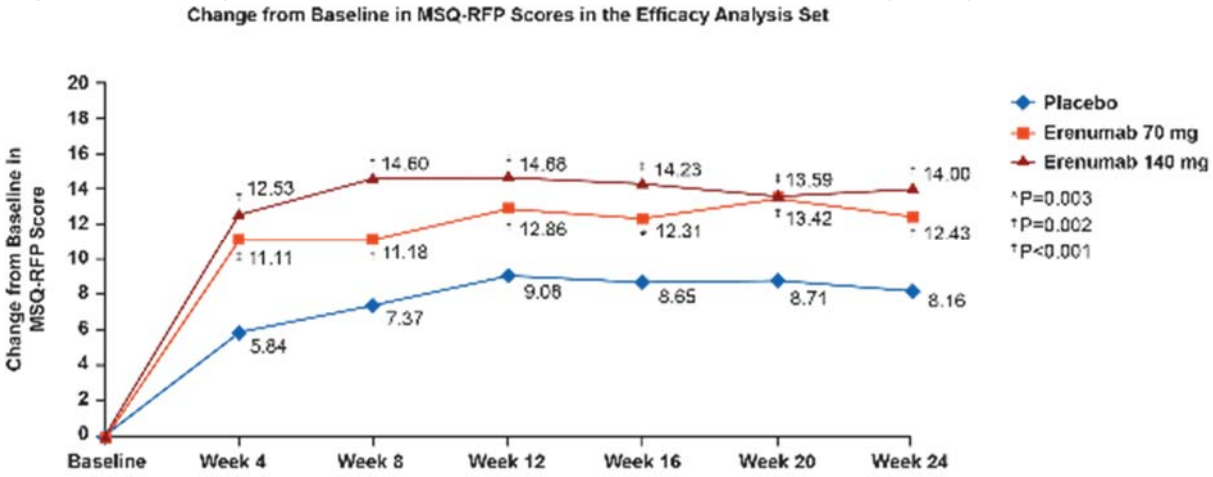
Three sub-domain scores of the MSQ v2.1, RFR, RFP and EF domains were individually measured and are presented in Figure 11, Figure 12 and Figure 13, respectively. The results illustrate that patients within the erenumab arms had a statistically greater reduction in MSQ scores across all three sub-domains in patients with episodic migraine. Patients treated with erenumab 140 mg experienced improvements in MSQ scores earlier than patients treated with erenumab 70 mg, and sustained higher scores throughout the double-blind period.

Figure 11: Change from baseline in MSQ-RFR scores in the efficacy analysis set[a]



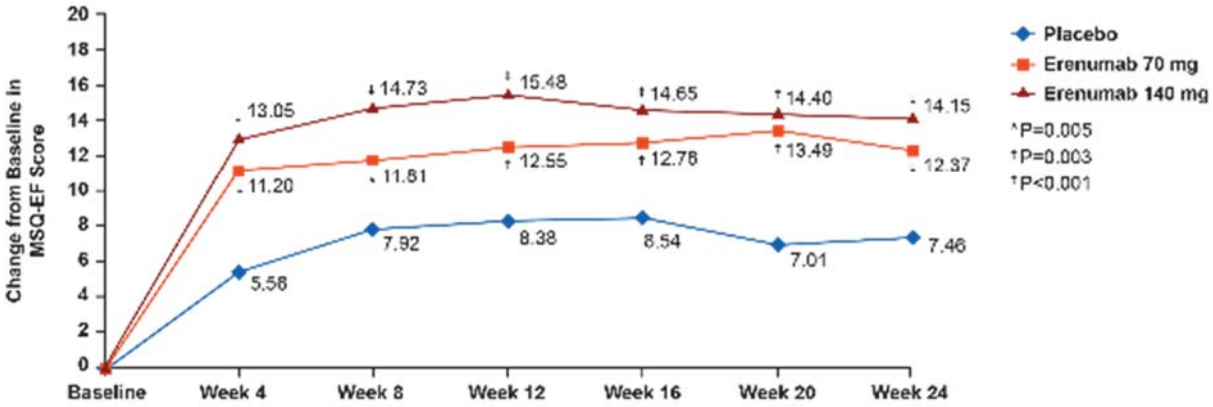
[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: MSQ-RFR: Migraine-Specific Quality of Life Questionnaire-Role Function-Restrictive.
Source: Adapted from STRIVE CSR[73]

Figure 12: Change from baseline in MSQ-RFP scores in the efficacy analysis set[a]



[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: MSQ-RFP: Migraine-Specific Quality-of-Life Questionnaire-Role Function-Preventive.
Source: Adapted from STRIVE CSR[73]

Figure 13: Change from baseline in MSQ-EF scores in the efficacy analysis set[a]



[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: MSQ-EF: Migraine-Specific Quality of Life Questionnaire-Emotional Function.
Source: Adapted from STRIVE CSR[73]

Erenumab decreased MIDAS scores, indicating a reduction in disease-related disability

MIDAS scores from the double-blind treatment phase of STRIVE are provided in Table 23. The mean change from baseline over months 4, 5 and 6 illustrate a significant reduction in MIDAS scores in erenumab 70 mg and erenumab 140 mg arms versus placebo. This indicates a reduction in disease-related disability and impact on productivity for patients receiving erenumab for episodic migraine compared with placebo.

Table 23: Change from baseline in modified MIDAS total score in the efficacy analysis set[a]

	Placebo (n=316)	Erenumab 70 mg (n=312)	Erenumab 140 mg (n=318)
Baseline			
Mean (SE)	14.9 (0.6)	14.5 (0.7)	12.9 (0.5)
Median	12.5	12.0	11.0
Q1, Q3	7.0, 20.0	7.0, 20.0	5.0, 18.0
Minimum, Maximum	0, 63	0, 105	0, 68
Mean over months 4, 5, and 6			
LSM estimate (SE)	−4.6 (0.4)	−6.7 (0.4)	−7.5 (0.4)
95% CI of LSM	−5.5, −3.8	−7.6, −5.9	−8.3, −6.6
Difference in LSM (95% CI)	-	−2.1 (−3.3, −0.9)	−2.8 (−4.0, −1.7)
p-value	-	<0.001	<0.001

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; LSM: least squares mean; MIDAS: Migraine Disability Assessment; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: STRIVE CSR[73]

Treatment with erenumab led to reductions in the physical activity and everyday activities domains of the MPFID compared to placebo

At assessment timepoints during the double-blind treatment phase, change from baseline in mean monthly average PI sub-domain scores was measured by the MPFID and recorded, with data presented in Table 24. The difference in LSM versus placebo in the change from baseline to the last three months of the double-blind treatment phase was –1.86 (95% CI: –2.95, –0.77) for erenumab 70 mg and –2.43 (95% CI: –3.51, –1.35) for erenumab 140 mg. The corresponding p-values were <0.001 for both comparisons. Thus, these data provide statistically significant evidence that erenumab, of either 70 mg or 140 mg doses, reduced mean monthly average PI domain scores to a greater extent than placebo in patients with migraine.

Table 24: Reduction from baseline of mean monthly average PI domain scores, as measured by the MPFID in the efficacy analysis set[a]

	Placebo (n=316)	Erenumab 70 mg (n=312)	Erenumab 140 mg (n=318)
Baseline			
Mean (SE)	12.24 (0.53)	12.56 (0.55)	11.98 (0.50)
Median	10.16	10.16	10.24
Q1, Q3	5.33, 16.51	5.99, 15.53	5.18, 16.43
Minimum, Maximum	0.3, 51.2	0.0, 62.2	0.0, 47.3
Change from baseline in mean over months 4, 5, and 6			
LSM estimate (SE)	–2.38 (0.40)	–4.24 (0.40)	–4.81 (0.40)
95% CI of LSM	–3.16, –1.59	–5.02, –3.45	–5.59, –4.03
Difference in LSM (95% CI)	-	-1.86 (–2.95, –0.77)	–2.43 (–3.51, –1.35)

p-value	-	<0.001	<0.001

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; LSM: least squares mean; MPFID: Migraine Physical Function Impact Diary; Q1: first quartile; Q3; third quartile; PI: physical impairment; SE: standard error.
Source: STRIVE CSR[73]

As with the observed PI sub-domain scores, MPFID EA sub-domain scores were recorded and results for this outcome are presented in Table 25. There was a significantly greater mean reduction in mean monthly average EA sub-domain scores from baseline to Months 4, 5, and 6 of the double-blind treatment phase for erenumab, in either dose, compared to placebo. Specifically, the difference in LSM was –2.22 (95% CI: –3.28, –1.16) for erenumab 70 mg and –2.57 (95% CI: –3.62, –1.51) for erenumab 140 mg versus placebo. These statistically significant observations for EA sub-domain scores of the MPFID highlight the significant effect of erenumab, relative to placebo, in improving migraine patients' ability to carry out everyday activities.

Table 25: Reduction from baseline of mean monthly average EA domain scores, as measured by the MPFID in the efficacy analysis set[a]

	Placebo (n=316)	Erenumab 70 mg (n=312)	Erenumab 140 mg (n=318)
Baseline			
Mean (SE)	13.65 (0.51)	14.04 (0.50)	13.0 (0.46)
Median	11.85	11.66	11.02
Q1, Q3	6.49, 18.37	8.20, 17.17	7.14, 17.24
Minimum, Maximum	0.0, 49.4	0.1, 52.3	0.0, 46.2
Change from baseline in mean over months 4, 5, and 6			
LSM estimate (SE)	–3.30 (0.39)	–5.52 (0.39)	–5.86 (0.39)
95% CI of LSM	–4.06, -2.53	–6.28, –4.75	–6.62, –5.10
Difference in LSM (95% CI)	-	–2.22 (–3.28, –1.16)	–2.57 (–3.62, –1.51)
p-value	-	<0.001	<0.001

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; EA: everyday activities; LSM: least squares mean; MPFID: Migraine Physical Function Impact Diary; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: STRIVE CSR[73]

ARISE

Patients treated with erenumab 70 mg achieved significantly greater reductions in HIT-6 scores versus placebo

Treatment with erenumab led to a significantly greater reduction in the impact of headache on daily living (measured by HIT-6) compared to placebo. At Week 12, patients treated with erenumab 70 mg and placebo achieved reductions in HIT-6 scores of –4.9 and –2.6, respectively, corresponding to a LSM difference of –2.3 (–3.3, –1.3; p<0.001), as shown in Table 26).

Table 26: Change from baseline in HIT-6 total score in the efficacy analysis set[a]

	Placebo (n=288)	Erenumab 70 mg (n=282)
Baseline		
Mean (SE)	59.5 (0.4)	59.8 (0.3)
Median	60.0	61.0
Q1, Q3	56.0, 64.0	56.0, 63.0
Minimum, Maximum	42, 74	42, 78
Change from baseline at Week 12		
LSM estimate (SE)	–2.6 (0.4)	–4.9 (0.4)
Difference in LSM (95% CI)	-	–2.3 (–3.3, –1.3)
p-value	-	<0.001

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; HIT-6: Headache Impact Test; LSM: least squares mean; MMD: monthly migraine day; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: Dodick *et al*. (2018)[100], ARISE CSR[77]

Treatment with erenumab 70 mg led to significantly greater reductions across all domains of the MSQ v2.1 compared to placebo

The change from baseline in MSQ v2.1 scores at Week 12 are shown in Table 27 below. Patients treated with erenumab 70 mg achieved significantly greater reductions across MSQ-RFR, MSQ-RFP and MSQ-EF scores at Week 12 versus placebo. This demonstrates that treatment with erenumab leads to improvements in several dimensions of HRQoL in patients with migraine, including the extent to which migraine interferes with work and daily activities.

Table 27: Change from baseline in MSQ v2.1 domain scores in the efficacy analysis set in ARISE[a]

	Placebo (n=288)	Erenumab 70 mg (n=282)
MSQ-RFR		
Baseline		
Mean (SE)	58.89 (1.03)	57.85 (0.99)
Median	60.00	60.00
Q1, Q3	48.57, 71.43	48.57, 68.57
Minimum, Maximum	8.6, 97.1	0.0, 100.0
Change from baseline at Week 12		
LSM estimate (SE)	9.71 (0.98)	15.20 (0.98)
Difference in LSM (95% CI)	-	5.48 (2.81, 8.16)
p-value	-	<0.001
MSQ-RFP		
Baseline		
Mean (SE)	72.44 (1.15)	70.50 (1.18)
Median	75.00	75.00
Q1, Q3	60.00, 90.00	60.00, 85.00
Minimum, Maximum	5.0, 100.0	0.0, 100.0

Change from baseline at Week 12		
LSM estimate (SE)	8.44 (0.90)	12.01 (0.91)
Difference in LSM (95% CI)	-	3.57 (1.11, 6.04)
p-value	-	0.005
MSQ-EF		
Baseline		
Mean (SE)	72.03 (1.39)	70.47 (1.38)
Median	80.00	73.33
Q1, Q3	60.00, 93.33	60.00, 93.33
Minimum, Maximum	0.0, 100.0	0.0, 100.0
Change from baseline at Week 12		
LSM estimate (SE)	7.28 (1.05)	11.76 (1.06)
Difference in LSM (95% CI)	-	4.48 (1.60, 7.35)
p-value	-	0.002

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; LSM: least squares mean; MSQ-EF: Migraine-Specific Quality of Life Questionnaire-Emotional Function MSQ-RFP: Migraine-Specific Quality-of-Life Questionnaire-Role Function-Preventive; MSQ-RFR: Migraine-Specific Quality of Life Questionnaire-Role Function-Restrictive; Q1: first quartile; Q3; third quartile; SE: standard error.
Source: Dodick *et al*. (2018)[100], ARISE CSR[77]

Patients treated with erenumab achieved greater reductions in MPFID domain scores compared to placebo

Patients treated with erenumab achieved greater reductions in MPFID physical impairment and impact on everyday activities domain scores compared to placebo, and experienced a greater reduction in the number of monthly days with impairment from baseline to Week 12 (see

Table 28). At Week 12, patients treated with erenumab 70 mg achieved a reduction from baseline of −3.18 and −4.33 in physical impairment and impact on everyday activities scores, respectively, compared to −1.88 and −3.23 in the placebo arm. This corresponded to LSM differences of −1.30 (95% CI: −2.40, −0.19, p=0.021) and −1.10 (95% CI: −2.25, 0.05; p=0.061) for physical impairment and impact on everyday activities domain scores, respectively. Patients treated with erenumab 70 mg also achieved a mean reduction in the monthly days with impairment of −2.45 days, versus −1.75 in the placebo arm, corresponding to an LSM difference of −0.70 (95% CI: −1.42, 0.02; p=0.058).

Table 28: Change from baseline in MPFID scores at Week 12 in efficacy analysis set in ARISE[a]

	Placebo (n=288)	Erenumab 70 mg (n=282)
Physical impairment score		
Baseline		
Mean (SE)	11.38 (0.53)	10.73 (0.53)
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]

Minimum, Maximum	[redacted]	[redacted]
Change from baseline at Week 12		
LSM estimate (SE)	−1.88 (0.40)	−3.18 (0.41)
Difference in LSM (95% CI)	-	−1.30 (−2.40, −0.19)
p-value	-	0.021
Impact on everyday activities score		
Baseline		
Mean (SE)	13.59 (0.52)	12.99 (0.52)
Median	12.12	11.15
Q1, Q3	7.03, 18.75	7.41, 16.41
Minimum, Maximum	0.0, 52.3	0.0, 45.7
Change from baseline at Week 12		
LSM estimate (SE)	−3.23 (0.42)	−4.33 (0.42)
Difference in LSM (95% CI)	-	−1.10 (−2.25, 0.05)
p-value	-	0.061
Monthly days with impairment		
Baseline		
Mean (SE)	7.54 (0.29)	7.23 (0.27)
Median	6.79	6.89
Q1, Q3	4.00, 9.91	4.00, 9.94
Minimum, Maximum	0.0, 28.0	0.0, 27.0
Change from baseline at Week 12		
LSM estimate (SE)	−1.75 (0.27)	−2.45 (0.27)
Difference in LSM (95% CI)	-	−0.70 (−1.42, 0.02)
p-value	-	0.058

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; LSM: least squares mean; MPFID: Migraine Physical Function Impact Diary; Q1: first quartile; Q3; third quartile; PI: physical impairment; SE: standard error.
Source: Dodick *et al*. (2018)[76], ARISE CSR[77]

LIBERTY

Treatment with erenumab led to significantly greater reductions in HIT-6 scores at Week 12 versus placebo

At Week 12, patients treated with erenumab 140 mg achieved a mean reduction in HIT-6 scores of [redacted], compared to [redacted] for patients treated with placebo. This corresponded to an LSM difference of [redacted]. Significant differences were observed from [redacted], and were maintained for the duration of the study period, as shown in Table 29.

Table 29: Change from baseline in HIT-6 to Week 12 in the full analysis set of LIBERTY, mixed model repeated measures[a]

	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Baseline		

n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]
Change from baseline at Week 4		
LSM estimate (SE)	[redacted]	[redacted]
Difference in LSM (95% CI)	-	[redacted]
p-value	-	[redacted]
Change from baseline at Week 8		
LSM estimate (SE)	[redacted]	[redacted]
Difference in LSM (95% CI)	-	[redacted]
p-value	-	[redacted]
Change from baseline at Week 12		
LSM estimate (SE)	[redacted]	[redacted]
Difference in LSM (95% CI)	-	[redacted]
p-value	-	[redacted]

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming an unstructured covariance matrix. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; HIT-6: Headache Impact Test; LSM: least squares mean; SD: standard deviation; SE: standard error.
Source: LIBERTY data on file[75]

EQ-5D-5L scores provided a further measure of HRQoL outcomes in LIBERTY

Minimal differences were observed in EQ-5D-5L over the course of the trial in either arm (Table 30). The EQ-5D-5L questionnaire reflects a patient's self-assessment at a single point in time as it requires patients to complete the questionnaire based on how they feel "today". Therefore, it is likely to be an insensitive measure for capturing the quality of life impact of migraine. EQ-5D was only collected at treatment appointments. Thus, the majority of patients would not have been experiencing a migraine at the time of EQ-5D measurement and those patients experiencing a migraine are very likely to have postponed their visits to a time they were without migraine. As such, EQ-5D information was not typically collected during a migraine episode for most patients and instead better reflects the health status of patients during the periods between migraines. EQ-5D-5L values were not therefore considered to provide an adequate representation of the HRQoL of patients in LIBERTY but have been provided here for completeness.

Table 30: Change from baseline in EQ-5D-5L to Week 12 in the full analysis set in LIBERTY, mixed model repeated measures[a]

	Placebo (n=[redacted])	**Erenumab 140 mg (n=[redacted])**
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]
Change from baseline at Week 4		
LSM estimate (SE)	[redacted]	[redacted]

Difference in LSM (95% CI)	-	[redacted]
p-value	-	[redacted]
Change from baseline at Week 8		
LSM estimate (SE)	[redacted]	[redacted]
Difference in LSM (95% CI)	-	[redacted]
p-value	-	[redacted]
Change from baseline at Week 12		
LSM estimate (SE)	[redacted]	[redacted]
Difference in LSM (95% CI)	-	[redacted]
p-value	-	[redacted]

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming an unstructured covariance matrix. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; EQ-5D-5L: EuroQol 5 Dimension 5 Level questionnaire; LSM: least squares mean; SD: standard deviation; SE: standard error.
Source: LIBERTY data on file[75]

Greater differences in WPAI scores were observed in patients treated with erenumab 140 mg compared to placebo

Patients treated with erenumab 140 mg achieved numerically greater reductions in all WPAI scores from baseline to Week 12 compared to patients treated with placebo. These differences were significant for the percent impairment when working due to the problem, the percent overall work impairment due to the problem, and the percent activity impairment due to the problem. Full results are reported in Table 31.

Table 31: Change from baseline in WPAI to Week 12 in the full analysis set in LIBERTY, mixed model repeated measures[a]

	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Percent work time missed due to problem		
n	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
Difference (95% CI)	-	[redacted]
p-value	-	[redacted]
Percent impairment while working due to problem		
n	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
Difference (95% CI)	-	[redacted]
p-value	-	[redacted]
Percent overall work impairment due to problem		
n	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
Difference (95% CI)	-	[redacted]
p-value	-	[redacted]
Percent activity impairment due to problem		
n	[redacted]	[redacted]

Change from baseline	[redacted]	[redacted]
Difference (95% CI)	-	[redacted]
p-value	-	[redacted]

[a]Adjusted analysis utilised a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming an unstructured covariance matrix. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
Abbreviations: CI: confidence interval; LSM: least squares mean; SD: standard deviation; SE: standard error; WPAI: Work Productivity and Activity Impairment.
Source: LIBERTY data on file[75]

B.2.6 *Subgroup analysis*

Clinical effectiveness results and patient-reported outcomes in patients for whom ≥3 prior prophylactic treatments have failed

- Consistent with results in the full trial population, erenumab demonstrated clinical effectiveness in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, the key population considered in this submission.
- Patients treated with erenumab 140 mg achieved greater reductions in MMDs, and a higher proportion achieved a ≥50% reduction in MMDs from baseline, compared to patients treated with erenumab 70 mg. This suggests that patients for whom ≥3 prior prophylactic treatments have failed may benefit from starting treatment on the higher 140 mg dose.
- It should be noted that the number of patients who had received ≥3 prior prophylactic treatments in STRIVE and ARISE was small (n=[redacted] and n=[redacted], [redacted]% and [redacted]% of the study populations, respectively). Analyses across all outcome measures in these subgroups are not therefore considered to be meaningful, and are presented in this section for completeness. LIBERTY provides more relevant clinical evidence in this subgroup as this was a study specifically designed to assess the efficacy and tolerability of erenumab in patients who have failed 2–4 previous migraine prophylactic treatments.

Study 295:

- Patients treated with erenumab 70 mg and 140 mg achieved statistically significant reductions in mean MMDs from baseline to Week 12 compared to placebo (difference in LSM versus placebo: −2.53 [95% CI: −4.27, −0.78; p=0.005] and −4.09 [95% CI: −5.84, −2.33; p<0.001], respectively).
- In total, 34.8% and 38.5% of patients in the erenumab 70 mg and 140 mg arms achieved a ≥50% reduction in MMDs from baseline, compared to 15.3% of patients in the placebo arm (OR: 2.96 [95% CI: 1.39, 6.27; p=0.004] and 3.48 [95% CI: 1.64, 7.39; p=0.001], respectively).

STRIVE:

- Patients treated with erenumab 70 mg and 140 mg achieved greater reductions in adjusted mean MMDs from baseline to the last three months of the double-blind treatment phase versus placebo (difference versus placebo: [redacted] (95% CI: [redacted]) and of [redacted] (95% CI: [redacted] respectively).
- In total, [redacted] and [redacted]% of patients in the erenumab 70 mg and 140 mg arms achieved a ≥50% reduction in adjusted mean MMDs from baseline, compared to [redacted]% of patients in the placebo arm (OR: [redacted]; 95% CI: [redacted] and OR: [redacted] (95% CI: [redacted], respectively).

ARISE:

- Patients treated with erenumab 70 mg achieved greater reductions in mean MMDs from baseline compared to placebo (difference versus placebo: [redacted] days; 95% CI: [redacted]; [redacted]).
- In total, [redacted] patients ([redacted]%) in the erenumab 70 mg arm, and [redacted] patients in the placebo arm ([redacted]%) achieved a ≥50% reduction in MMDs from baseline to Week 12 (OR: [redacted] [95% CI: [redacted]; [redacted]]).

LIBERTY:

- Patients treated with erenumab 140 mg achieved a clinically meaningful reduction in mean MMDs from baseline to Week 12, with numerically greater reductions compared to placebo (difference in LSM versus placebo: [redacted] days [95% CI: [redacted]; [redacted]]).
- In total, [redacted]% of patients in the erenumab 140 mg arm achieved a ≥50% reduction in MMDs from baseline, compared to [redacted]% of patients in the placebo arm (OR: [redacted] [95% CI: [redacted]; p=[redacted]]).

Key clinical effectiveness results in patients for whom ≥2 prior prophylactic treatments have failed

- Erenumab demonstrated clinical effectiveness in the subgroup of patients for whom ≥2 prior prophylactic treatments have failed, with statistically significant reductions in MMDs and a greater ≥50% responder rate compared to placebo.
    - **Study 295:** Patients treated with erenumab 70 mg and 140 mg achieved a significantly greater reduction in mean MMDs from baseline (difference vs placebo: −2.71 [95% CI: −4.20, −1.21] and −4.28 [95% CI: −5.75, −2.80], respectively). Patients treated with erenumab 70 mg and 140 mg also had a significantly greater ≥50% response rate (OR: 2.81 [95% CI: 1.39, 5.67; p=0.003] and OR: 3.96 [95% CI: 2.01, 7.82; p=0.019], respectively), compared to placebo.
    - **STRIVE:** Patients treated with erenumab 70 mg had a higher reduction from baseline in mean MMDs at Week 24 compared to placebo (difference: −1.32 [95% CI: −2.64, 0.00; p=0.051, and a significantly higher ≥50% response rate [OR: 2.89 [95% CI: 1.00, 8.33; p=0.045]. Patients in the erenumab 140 mg arm had a significantly greater reduction from baseline in mean MMDs at Week 24 compared to placebo (difference: −2.70; 95% CI: (−3.97, −1.44), and a significantly higher ≥50% response rate (OR: 4.54; 95% CI: 1.66, 12.39; p=0.002).
    - **ARISE:** Patients treated with erenumab 70 mg had a higher reduction in MMDs from baseline to Week 12 versus placebo (difference: [redacted] [95% CI: [redacted]; [redacted]], and a higher ≥50% response rate [OR: [redacted] [95% CI: [redacted]; [redacted]].
    - **LIBERTY:** Patients treated with erenumab 140 mg achieved a significantly greater reduction from baseline in mean MMDs at Week 12 versus placebo (difference: −1.61; 95% CI: −2.70, −0.52; p=0.004), and a significantly higher proportion achieved ≥50% reductions in MMDs from baseline at Week 12 (OR: 2.73; 95% CI: 1.43, 5.19; p=0.002).

Key clinical effectiveness results in patients with HFEM

- **STRIVE**:
    - Patients in the erenumab 140 mg arm achieved a significantly greater mean reduction in MMDs from baseline to Week 24 versus placebo (difference: [redacted] days [95% CI: [redacted]; [redacted]]).

- In the erenumab 140 mg arm, [redacted]% of patients achieved ≥50% reductions in MMDs from baseline to Week 24 compared to [redacted]% of patients in the placebo arm (OR: [redacted] [95% CI: [redacted]; [redacted]]).

- **ARISE:**
  - Patients in the erenumab 70 mg arm achieved greater reductions in MMDs at Week 12 versus placebo (difference: [redacted] [95% CI: [redacted]; [redacted]]).
  - At Week 12, [redacted] patients ([redacted]%) treated with erenumab 70 mg, and [redacted] patients ([redacted]%) treated with placebo achieved reductions in MMDs of ≥50% from baseline (OR: [redacted] [95% CI: [redacted]; [redacted]]).
- **LIBERTY**:
  - Patients treated with erenumab 140 mg achieved a numerically greater reduction in mean MMDs from baseline versus placebo (difference: [redacted] days [95% CI: [redacted]; [redacted]]).
  - In the erenumab 140 mg arm, [redacted]% of patients achieved a ≥50% reduction in mean MMDs from baseline at Week 12, compared to [redacted]% of patients in the placebo arm (OR: [redacted] [95% CI: [redacted]; [redacted]]).

The results of the pre-specified subgroup analyses performed for the trial ITT populations on various patient characteristics that are detailed in Table 6 are provided in Appendix E.

The key analyses presented in this submission are as follows:

- Patients for whom ≥3 prior prophylactic treatment categories have failed (*post-hoc* analysis). This is a patient population with a high unmet need and a lack of treatment options, as discussed in Section B.1.2.2. Patients may cycle through the available prophylactic treatments relatively quickly due to a lack of efficacy or poor tolerability, and at this point in the pathway, BSC would be the only option available for the majority of patients. Analyses presented in the clinical effectiveness section across multiple outcome measures are for patients for whom ≥3 prior prophylactic treatments have failed, comprising those who had failed on treatments from >3 protocol-defined categories; for example, prior non-responders to a beta-blocker, a tricyclic antidepressant and topiramate (please see CSR for full list of protocol defined categories).
- Patients with HFEM for whom ≥3 prior prophylactic treatments have failed (*HFEM was a stratification factor at randomisation*) also represent a subgroup of clinical interest. Patients with HFEM have a similar clinical burden to patients classified as having chronic migraine, but are able to access only BSC at this point in the treatment pathway (see Section B.1.2.1)
- Patients for whom ≥2 prior prophylactic treatments have failed (pre-specified analysis in Study 295; *post-hoc* analysis of STRIVE; *post-hoc* analysis of ARISE; full trial population of LIBERTY). Consideration of the efficacy of erenumab in this subgroup is relevant as feedback from UK clinicians has suggested that erenumab may be an appropriate therapy in patients for whom ≥2 prior prophylactic treatments have failed and are unsuitable for treatment with a further treatment with a prophylactic therapy as a result of contraindications, special warnings and precautions (see Section B.1.2.2)

B.2.6.1 Clinical effectiveness results in patients for whom ≥3 prior prophylactic treatments have failed

Baseline characteristics in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in each of the studies are provided in Table 32, Table 33, Table 34 and Table 35

below. In general, baseline characteristics were comparable to those in the full trial populations of each study (Table 8, Table 9, Table 10 and Table 11, respectively).

A summary of the clinical effectiveness results in this subgroup in each trial, structured by outcome of relevance to the decision problem, is provided below.

Table 32: Baseline characteristics of patients for whom ≥3 prior prophylactic treatments have failed in Study 295

Characteristic	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])	Erenumab 140 mg (n=[redacted])
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Women	[redacted]	[redacted]	[redacted]
Men	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]
Age at migraine[b] onset, years (SD)	[redacted]	[redacted]	[redacted]
Disease duration, years (SD)	[redacted]	[redacted]	[redacted]
Previous use of preventative drug topiramate, n (%)	[redacted]	[redacted]	[redacted]
Previous use of botulinum toxin, n (%)	[redacted]	[redacted]	[redacted]
Acute headache medication use, n (%)			
Migraine specific[c]	[redacted]	[redacted]	[redacted]
Non-migraine specific	[redacted]	[redacted]	[redacted]
Baseline period, mean (SD)			
Monthly migraine days	[redacted]	[redacted]	[redacted]
Monthly headache days	[redacted]	[redacted]	[redacted]
Monthly migraine attacks	[redacted]	[redacted]	[redacted]
Monthly acute migraine-specific drug use days	[redacted]	[redacted]	[redacted]

[a]Other includes American Indian or Alaska native, multiple, native Hawaiian or other Pacific Islander and all other races. [b]Migraine with or without aura. [c]During the baseline phase, 557 patients (58.5%) used triptan-based medications and four patients (0.4) used ergotamine-based medications (safety analysis set). [d]The summary of treatment with migraine-preventive medications is based on actual data collected rather than on randomisation stratification. [e]Treatment-failure categories were not mutually exclusive; a patient could be included in both categories.
Abbreviations: BMI: body mass index; SD: standard deviation.
Source: Study 295 *post-hoc* analysis, data on file (2018)[101]

Table 33: Baseline characteristics of patients for whom ≥3 prior prophylactic treatments have failed in STRIVE

Characteristic	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])	Erenumab 140 mg (n=[redacted])
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Women	[redacted]	[redacted]	[redacted]
Men	[redacted]	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Baseline period, mean (SD)			
Monthly migraine days	[redacted]	[redacted]	[redacted]
History of previous preventative treatment failure, n (%)			
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
>4	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; SD: standard deviation.
Source: STRIVE post-hoc analysis, data on file (2018)[102]

Table 34: Baseline characteristics of patients for whom ≥3 prior prophylactic treatments have failed in ARISE

Characteristic	Placebo (n=29)	Erenumab 70 mg (n=27)
Mean age, years (SD)	[redacted]	[redacted]
Range	[redacted]	[redacted]
Sex, n (%)		
Women	[redacted]	[redacted]
Men	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]
Ethnicity, n (%)		
White	[redacted]	[redacted]
Monthly migraine days at baseline, mean (SD)	[redacted]	[redacted]
History of previous preventative treatment failure, n (%)		
3	[redacted]	[redacted]
4	[redacted]	[redacted]
>4	[redacted]	[redacted]

Abbreviations: SD: standard deviation.
Source: ARISE *post-hoc* analysis, data on file (2018)[103]

Table 35: Baseline characteristics of patients for whom ≥3 prior prophylactic treatments have failed in LIBERTY

Characteristic	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Mean age, years (SD)	[redacted]	[redacted]
Range	[redacted]	[redacted]
Sex, n (%)		
Women	[redacted]	[redacted]
Men	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]
Ethnicity, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]
Age at migraine[b] onset, years (SD)	[redacted]	[redacted]
Disease duration, years (SD)	[redacted]	[redacted]
Acute headache medication use, n (%)		
Migraine specific	[redacted]	[redacted]
Non-migraine specific	[redacted]	[redacted]
History of previous preventative treatment failure, n (%)		
3	[redacted]	[redacted]
4	[redacted]	[redacted]
>4	[redacted]	[redacted]
Baseline period, mean (SD)		
Monthly migraine days	[redacted]	[redacted]
Monthly headache days	[redacted]	[redacted]
Monthly acute migraine-specific drug use days	[redacted]	[redacted]
Acute migraine-specific drug use, n (%)	[redacted]	[redacted]

[a]Other includes Native American, Pacific Islander, unknown, and all other races. [b]Migraine with or without aura.
Abbreviations: BMI: body mass index; SD: standard deviation.
Source: LIBERTY *post-hoc* analysis, data on file (2018)[104]

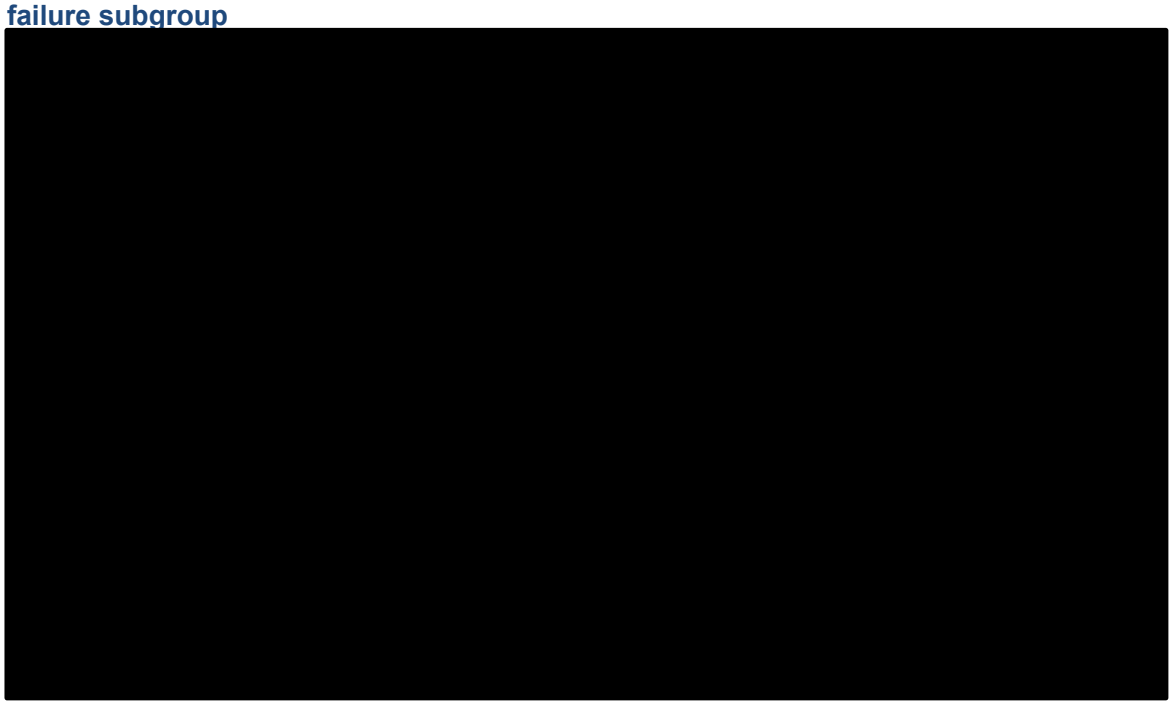
Change from baseline in MMDs, ≥3 prior prophylactic treatment failure subgroup

Study 295

Treatment with erenumab was associated with a statistically significant reduction in MMDs compared to placebo, as measured from baseline to Week 12 (see Figure 14). Patients treated with erenumab 70 mg and erenumab 140 mg achieved mean reductions in MMDs from baseline of [redacted] and [redacted] days respectively, compared to [redacted] days in the placebo arm. This corresponded to respective LSM differences versus placebo of −2.53 days (95% CI: −4.27, −0.78; p=0.005) and −4.09 days (95% CI: −5.83, −2.33, p<0.001). Greater reductions in MMDs were observed in the erenumab 140 mg compared to the erenumab 70 mg arm at all time points. This indicates that the higher dose is numerically superior to the 70 mg dose in this subgroup, in

contrast to the ITT population, for whom minimal differences were observed between the two doses (Table 15), and supports the suitability of erenumab 140 mg in this patient population.

Figure 14: Change from baseline in MMDs in Study 295, ≥3 prior prophylactic treatment failure subgroup



Abbreviations: LSM: least square means.
Source: Study 295 *post-hoc* analysis, data on file (2018)[101]

STRIVE

At baseline, patients in the erenumab 70 mg, 140 mg and placebo arms had mean MMDs of , and days, respectively. Patients treated with erenumab 140 mg achieved reduction of X days in mean MMDs from baseline to the last three months of the double-blind treatment phase compared to days in the placebo arm. The corresponds to a difference in MMDs of (95% CI:). Patients treated with erenumab 70 mg had a change of days in mean MMDs from baseline to the last three months of the double-blind treatment phase compared to days in the placebo arm. The corresponds to a difference in MMDs of (95% CI).

ARISE

At baseline, patients in the erenumab 70 mg and placebo groups had mean MMDs of and days, respectively. At Week 12, patients treated with erenumab 70 mg achieved reductions of days, compared to days in the placebo arm, which corresponded to a difference of (95% CI: ;).

LIBERTY

At baseline, patients in the erenumab 140 mg and placebo arms had mean MMDs of and days, respectively. Patients treated with erenumab 140 mg achieved numerically greater reductions in MMDs versus placebo. At Week 12, patients achieved mean reductions in MMDs from baseline of and days in the erenumab 140 mg and placebo arms, respectively. This corresponded to a difference of days (95% CI: ;). As discussed

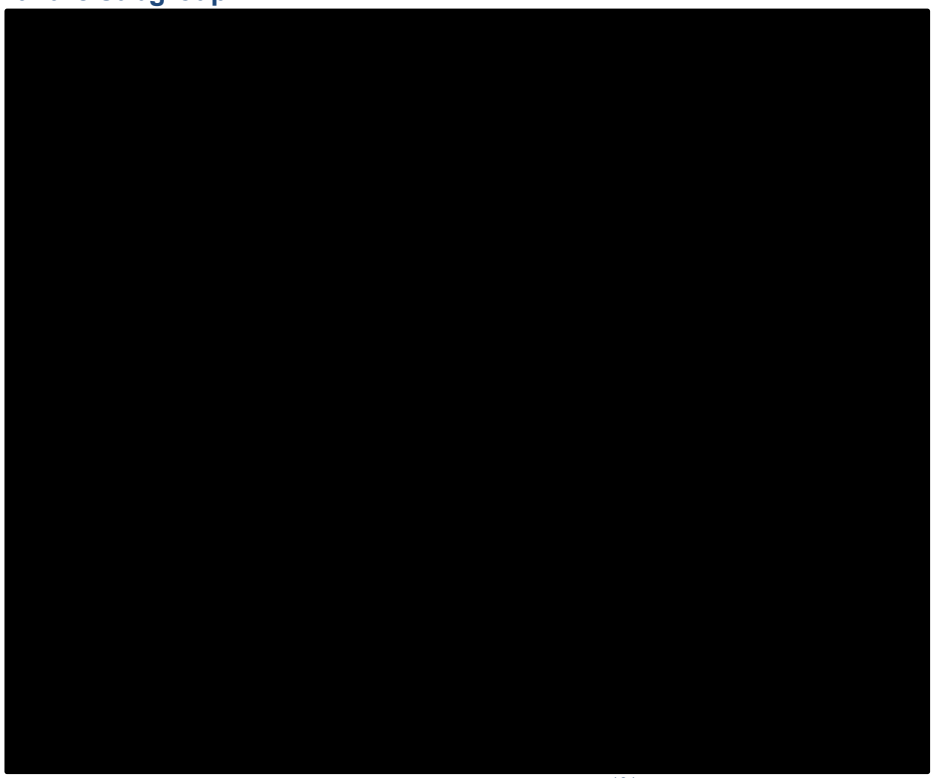
previously, reductions in MMDs of more than one day represent a clinically meaningful change for patients with a high unmet need.

≥50% responder rates (MMDs), ≥3 prior prophylactic treatment failure subgroup

Study 295

A significantly higher proportion of patients treated with erenumab 70 mg and 140 mg achieved a ≥50% reduction in MMDs from baseline to Week 12 versus placebo (Figure 15). In total, 23 (34.8%) of the patients in the erenumab 70 mg arm and 25 (38.5%) of the patients in the erenumab 140 mg arm achieved a ≥50% reduction in MMDs from baseline, compared to 15 patients (15.3%) in the placebo arm. This corresponded to an odds ratio versus placebo of 3.0 (95% CI: 1.4, 6.3; p=0.004) and 3.5 (95% CI: 1.6, 7.4; p=0.001) for the erenumab 70 mg and erenumab 140 mg arms respectively. In the erenumab 140 mg arm, significantly greater ≥50% responder rates versus placebo were observed from as early as Week 4, and were maintained over the entire assessment period. Again, erenumab 140 mg was shown to be more effective than erenumab 70 mg in this subgroup, as a higher proportion of patients treated with erenumab 140 mg achieved a ≥50% reduction in MMDs from baseline at all assessed timepoints.

Figure 15: ≥50% responder rate (MMDs) in Study 295, ≥3 prior prophylactic treatment failure subgroup



Source: Study 295 *post-hoc* analysis, data on file (2018)[101]

STRIVE

A higher proportion of patients treated with erenumab 140 mg achieved a ≥50% reduction in MMDs from baseline from baseline to the last three months of the double-blind treatment phase compared to placebo. In total, [redacted] ([redacted]%) patients in the erenumab 140 mg arm achieved a ≥50% reduction in MMDs from baseline to the last three months of the double-blind treatment phase, compared to [redacted] ([redacted]%) patients in the placebo arm, corresponding to an odds ratio versus placebo of [redacted] (95% CI: [redacted]). [redacted] ([redacted]%) patients in the erenumab 70

mg arm achieved a ≥50% reduction in MMDs from baseline to the last three months of the double-blind treatment phase corresponding to an odds ratio versus placebo of [redacted]; 95% CI: [redacted]; [redacted]), again demonstrating the numerical superiority of erenumab 140 mg in this subgroup.

ARISE

A higher proportion of patients treated with erenumab 70 mg achieved a ≥50% reduction in MMDs from baseline to Week 12 versus placebo. In total, [redacted] patients ([redacted]%) in the erenumab 70 mg arm, and [redacted] patients in the placebo arm ([redacted]%) achieved a ≥50% reduction in MMDs from baseline to Week 12. This corresponded to an odds ratio versus placebo of [redacted] (95% CI: [redacted]; [redacted]).

LIBERTY

A significantly higher proportion of patients treated with erenumab 140 mg achieved a ≥50% reduction in MMDs from baseline to Week 12 versus placebo. In total, [redacted] ([redacted]%) patients in the erenumab 140 mg arm achieved a ≥50% reduction in MMDs from baseline, compared to [redacted] ([redacted]%) patients in the placebo arm. This corresponded to an odds ratio versus placebo of [redacted] (95% CI: [redacted]; [redacted]).

Change from baseline in MHDs, ≥3 prior prophylactic treatment failure subgroup

Study 295

Patients had mean MHDs at baseline of [redacted], [redacted] and [redacted] days in the erenumab 70 mg, erenumab 140 mg and placebo arms, respectively. At Week 12, patients treated with erenumab 70 mg and 140 mg achieved LSM mean reductions in MHDs from baseline of [redacted] days and [redacted] days respectively, compared to [redacted] days in the placebo arm. This corresponded to LSM differences versus placebo of [redacted] days (95% CI: [redacted]; [redacted]) and [redacted] days (95% CI: [redacted]; [redacted]) in the erenumab 70 mg and 140 mg arms, respectively. Similar to the change in MMDs, these results demonstrate that in the subgroup of patients for whom ≥3 prior treatments have failed, treatment with erenumab 140 mg leads to greater reductions in MHDs from baseline compared to treatment with erenumab 70 mg.

Figure 16: Change from baseline in MHDs in Study 295, ≥3 prior prophylactic treatment failure subgroup

Abbreviations: LSM: least square means.
Source: Study 295 *post-hoc* analysis, data on file (2018)[101]

STRIVE

Patients treated with erenumab 140 mg achieved greater reduction in mean MHDs from baseline to the last three months of the double-blind treatment phase compared to placebo. Patients in the erenumab 140 mg and placebo arms achieved mean reductions in MHDs of [redacted] and [redacted] days from baseline to the last three months of the double-blind treatment phase compared to placebo, respectively. This corresponded to a difference of [redacted] days (95% CI: [redacted]; [redacted]).Patients in the erenumab 70 mg and placebo arms achieved mean reductions in MHDs of [redacted] and [redacted] days from baseline to the last three months of the double-blind treatment phase compared to placebo, respectively. This corresponded to a difference of [redacted] days (95% CI: [redacted]; [redacted]).

ARISE

Patients treated with erenumab 70 mg achieved numerically greater reductions in mean MHDs from baseline to Week 12 versus placebo. Patients in the erenumab 70 mg and placebo arms achieved mean reductions in MHDs of [redacted] and [redacted] days at Week 12, respectively. This corresponded to a difference of [redacted] days (95% CI: [redacted]; [redacted]).

LIBERTY

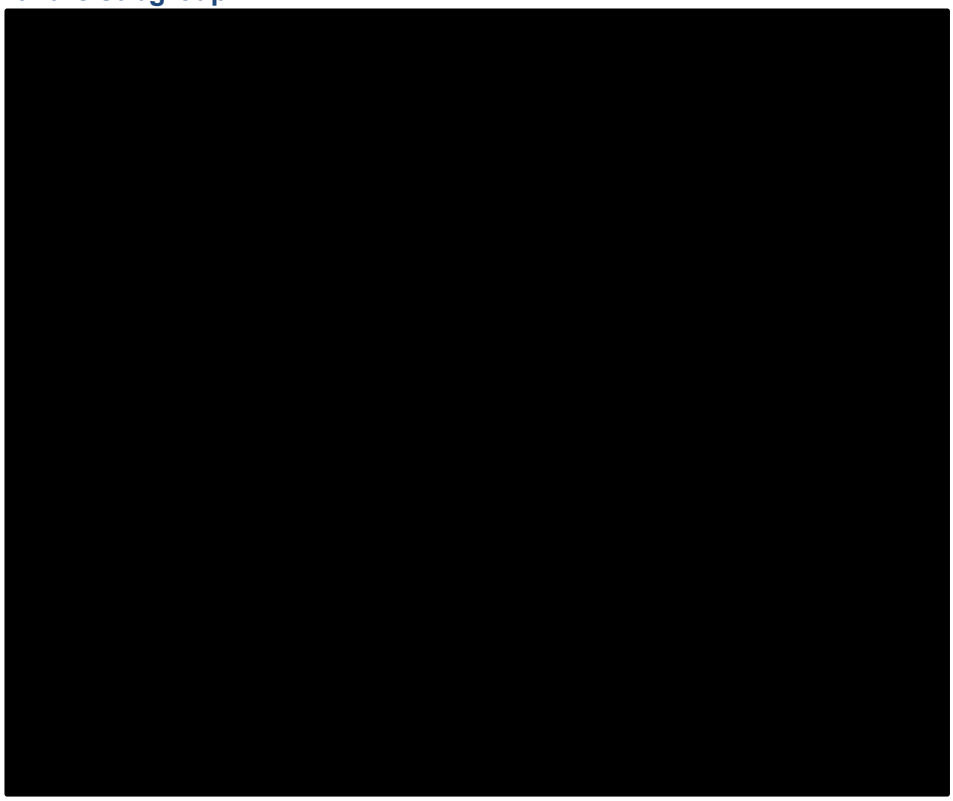
Patients treated with erenumab 140 mg achieved greater reductions in mean MHDs from baseline to Week 12 versus placebo. Patients in the erenumab 140 mg and placebo arms had mean MHDs of [redacted] and [redacted] days at baseline, and mean reductions at Week 12 of [redacted] and [redacted] days, respectively. The adjusted difference in mean MHDs for the erenumab 140 mg arm versus placebo at Week 12 was [redacted] days (95% CI: [redacted]; [redacted]).

≥50% responder rates (MHDs), ≥3 prior prophylactic treatment failure subgroup

Study 295

A significantly higher proportion of patients treated with erenumab 70 mg and 140 mg achieved at least a 50% reduction in MHDs from baseline to Week 12 versus placebo (Figure 17). In total, [redacted] patients ([redacted]) in the erenumab 70 mg arm, and [redacted] patients ([redacted]) in the erenumab 140 mg arm, achieved a reduction in MHDs of ≥50% from baseline, compared to [redacted] patients ([redacted]) in the placebo arm. This corresponded to an odds ratio versus placebo of [redacted] (95% CI: [redacted]; [redacted]) and [redacted] (95% CI: [redacted]; [redacted]) for the erenumab 70 mg and 140 mg arms, respectively. Patients in the erenumab 140 mg arm achieved a markedly greater ≥50% response rate compared to the erenumab 70 mg arm at all assessment timepoints, again showing that the higher dose may be most suitable in this subgroup.

Figure 17: ≥50% responder rate (MHDs) in Study 295, ≥3 prior prophylactic treatment failure subgroup



Source: Study 295 *post-hoc* analysis, data on file (2018)[101]

LIBERTY

A greater proportion of patients treated with erenumab 140 mg achieved a ≥50% reduction in MHDs from baseline versus placebo. In total, [redacted] ([redacted]%) patients in the erenumab 140 mg arm achieved a ≥50% reduction in MHDs from baseline to Week 12, compared to [redacted] ([redacted]%) patients in the placebo arm. This corresponded to an odds ratio versus placebo of [redacted] (95% CI: [redacted]; [redacted]).

Change from baseline in monthly severity of migraine pain, ≥3 prior prophylactic treatment failure subgroup

Study 295

At Week 12, patients treated with erenumab 70 mg and erenumab 140 mg had numerically greater reductions from baseline in monthly average severity of migraine pain, compared with placebo. Patients in the erenumab 70 mg and erenumab 140 mg arms achieved mean reductions versus placebo of [redacted] (95% CI: [redacted]; [redacted]) and [redacted] (95% CI: [redacted]; [redacted]), respectively.

STRIVE

In the last three months of the double-blind treatment phase erenumab 140 mg and placebo arms had mean reductions in monthly average severity of migraine pain of [redacted] and [redacted], respectively, from baseline. This difference was not significant at the 95% confidence level (95% CI: [redacted]; p=[redacted]). In the last three months of the double-blind treatment phase erenumab 70 mg and placebo arms had mean reductions in monthly average severity of migraine pain of [redacted] and [redacted], respectively, from baseline. This difference was not significant at the 95% confidence level (95% CI: [redacted]0; p=[redacted]).

ARISE

At Week 12, patients in the erenumab 70 mg and placebo arms had mean reductions in monthly average severity of migraine pain of [redacted] and [redacted], respectively, from baseline. This difference was not significant at the 95% confidence level ([redacted] [95% CI: [redacted]; p=[redacted]]).

Change from baseline in monthly acute migraine-specific treatment days, ≥3 prior prophylactic treatment failure subgroup

Study 295

At Week 12, patients treated with erenumab 70 mg and erenumab 140 mg had a significantly greater reduction in the monthly acute migraine-specific treatment days from baseline, compared with placebo (Figure 18). Patients achieved a mean reduction of [redacted] and [redacted] days in the erenumab 70 mg and 140 mg arms, respectively, compared to [redacted] days in the placebo arm. This was associated with a LSM difference versus placebo of [redacted] days (95% CI: [redacted]; [redacted]) for the erenumab 70 mg arm, and [redacted] days (95% CI: [redacted]; [redacted]) for the erenumab 140 mg arm. The higher differences observed in the erenumab 140 mg arm compared to the erenumab 70 mg arm indicate that the higher dose is more effective at reducing the acute symptoms of migraine in this patient population.

Figure 18: Change from baseline in monthly acute migraine-specific treatment days in Study 295, ≥3 prior prophylactic treatment failure subgroup

Abbreviations: LSM: least square means
Source: Study 295 *post-hoc* analysis, data on file (2018)[101]

STRIVE

Patients treated with erenumab 70mg and erenumab 140 mg achieved greater reduction in monthly acute migraine-specific treatment days from baseline to the last three months of the double-blind treatment phase compared to placebo. Patients in the erenumab 70 mg and 140 mg arms had a mean reduction of [redacted] and [redacted] days, respectively, compared to [redacted] days for patients in the placebo arm. This was associated with a difference versus placebo of [redacted] (95% CI: [redacted]; [redacted]), and [redacted] (95% CI: [redacted]; [redacted]), respectively. Patients treated with erenumab 140 mg achieved a numerically greater reduction in monthly acute migraine-specific treatment days versus patients treated with erenumab 70 mg, demonstrating that the higher dose may be more suitable in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed.

ARISE

Patients treated with erenumab 70 mg achieved greater reductions in monthly acute headache medication days from baseline than those treated with placebo. At Week 12, patients treated with erenumab 70 mg and placebo achieved mean reductions of [redacted] and [redacted] days, respectively, corresponding to a difference of [redacted] days (95% CI: [redacted]; [redacted]).

LIBERTY

Patients treated with erenumab 140 mg had significantly greater reductions in monthly acute migraine-specific treatment days from baseline versus placebo. At Week 12, patients treated with erenumab 140 mg had a mean change from baseline ([redacted] days) of [redacted] days, compared to [redacted] days in the placebo arm ([redacted] days at baseline), corresponding to a difference of [redacted] days (95% CI: [redacted]; [redacted]). This indicates that treatment with erenumab reduces in the acute symptoms of migraine, and therefore the overall clinical burden.

Number of monthly cumulative hours of migraine, ≥3 prior prophylactic treatment failure subgroup

Study 295

At Week 12, patients treated with erenumab achieved greater reductions in the number of cumulative hours of headache from baseline compared to placebo, with these differences found to be significant for the 140 mg dose. Patients achieved mean reductions from baseline to Week 12 versus placebo of [redacted] (95% CI: [redacted]; [redacted]) and [redacted] (95% CI: [redacted]; [redacted]) in the erenumab 70 mg and 140 mg arms, respectively. Patients treated with erenumab 140 mg achieved considerably greater reductions in the number of cumulative hours of headache compared to patients treated with erenumab 70 mg, suggesting that the higher dose may be more efficacious in minimising the clinical burden of migraine in this patient population.

STRIVE

Patients in the erenumab 140 mg and placebo arms achieved reductions in the last three months of the double-blind treatment phase compared to baseline of [redacted] hours and [redacted] hours, respectively, corresponding to a difference of [redacted] (95% CI: [redacted]; [redacted]). Patients in the erenumab 70 mg and placebo arms achieved reductions in the last three months of the double-blind treatment phase compared to baseline of [redacted] hours and [redacted] hours, respectively, corresponding to a difference of [redacted] (95% CI: [redacted]; [redacted]).

ARISE

Patients treated with erenumab 70 mg achieved greater mean reductions in the monthly cumulative hours of migraine compared to patients treated with placebo. Patients in the erenumab 70 mg and placebo arms achieved reductions from baseline to Week 12 of [redacted] hours and [redacted] hours, respectively, corresponding to a difference of [redacted] (95% CI: [redacted]; [redacted]).

B.2.6.2 Clinical effectiveness results in patients for whom ≥2 prior prophylactic treatments have failed

A summary of the clinical effectiveness results for the key outcomes driving the cost-effectiveness model is presented for the subgroup of patients for whom ≥2 prior prophylactic treatment have failed in Study 295, STRIVE and ARISE in Table 36. This population represents the full trial population in LIBERTY, and therefore these results are presented in Section B.2.5.1. Baseline characteristics are presented in Appendix E.

Table 36: Key clinical effectiveness results for the subgroup of patients for whom ≥2 prior prophylactic treatments have failed in Study 295, STRIVE and ARISE

	Study 295*			STRIVE			ARISE	
	Placebo (n=141)	Erenumab 70 mg (n=90)	Erenumab 140 mg (n=92)	Placebo (n=54)	Erenumab 70 mg (n=49)	Erenumab 140 mg (n=58)	Placebo (n=49)	Erenumab 70 mg (n=56)
Change from baseline in MMDs								
Baseline, mean (SD)	18.2 (4.7)	17.9 (4.4)	17.8 (4.7)	8.12 (2.49)	8.89 (2.04)	8.68 (2.51)	[redacted]	[redacted]
Mean change at Week 12 (SE)**	−2.68	−5.3 (NR)	−6.96 (NR)	−0.24 (0.76)	−1.56 (0.74)	−2.95 (0.73)	[redacted]	[redacted]
Difference (95% CI)	-	−2.71 (−4.20, −1.21)	−4.28 (−5.75, −2.80)	-	−1.32 (−2.64, 0.00)	−2.70 (−3.97, −1.44)	-	[redacted]
p-value	-	<0.05	<0.05	-	0.051	<0.001	-	[redacted]
≥50% responder rate (MMDs)								
n (%)	17 (12.1)	24 (26.7)	32 (34.8)	6 (11.1)	13 (26.5)	21 (36.2)	[redacted]	[redacted]
Odds ratio (95% CI)	-	2.81 (1.39, 5.67)	3.96 (2.01, 7.82)	-	2.89 (1.00, 8.33)	4.54 (1.66, 12.39)	-	[redacted]
p-value	-	0.003	<0.001	-	0.045	0.002	-	[redacted]

*Study 295 mean change from baseline in MMDs is LSM.
**For STRIVE this is mean change in last three months of the double-blind treatment phase
Abbreviations: CI: confidence interval; LSM: least squares mean; MMD: monthly migraine day; NR: not reported; SE: standard error.
Source: Ashina *et al.* (2017)[105]; STRIVE *post-hoc* analysis, data on file[102]; ARISE *post-hoc* analysis, data on file (2018)[103]

B.2.6.3 Clinical effectiveness in patients with high-frequency episodic migraine for whom ≥3 prior prophylactic treatments have failed

HFEM is a recognised subgroup of episodic migraine, who are considered to have a clinical burden similar to those classified as having chronic migraine. However, these patients are unable to access botulinum toxin in line with its NICE recommendation, and therefore face a particularly high unmet need. As such, key clinical effectiveness outcomes in the subgroup of patients with HFEM (8–14 MMDs) for whom ≥3 prior prophylactic treatments have failed are presented below. Analysis in this subgroup was performed for STRIVE, ARISE and LIBERTY, but is not relevant for Study 295 as this study recruited a chronic migraine population (≥15 MMDs at baseline).

Change from baseline in MMDs

STRIVE

Patients had mean MMDs at baseline of [redacted], [redacted] and [redacted] days in the erenumab 70 mg, 140 mg and placebo arms, respectively. At Week 24, patients treated with erenumab 70 mg and 140 mg achieved greater reductions in MMDs versus placebo, with these differences found to be significant for the erenumab 140 mg arm. Patients in the erenumab 140 arm achieved mean reductions in MMDs from baseline to Week 24 versus placebo of [redacted] (95% CI: [redacted]; [redacted]). Patients in the erenumab 70 arm achieved mean reductions in MMDs from baseline to Week 24 versus placebo of [redacted] (95% CI: [redacted]; [redacted]).

ARISE

Patients treated with erenumab 70 mg achieved similar reductions in MMDs from baseline to Week 12 to those treated with placebo. At Week 12, patients in the erenumab 70 mg and placebo arms achieved reductions in MMDs of [redacted] and [redacted], respectively, corresponding to a difference of [redacted] (95% CI: [redacted]; [redacted]).

LIBERTY

Patients treated with erenumab 140 mg achieved numerically greater reductions in MMDs from baseline to Week 12 compared to placebo. Patients in the erenumab 140 mg and placebo arms had mean MMDs at baseline of [redacted] and [redacted], and mean reductions at Week 12 of [redacted] and [redacted] days, respectively. This corresponded to a difference at Week 12 of [redacted] (95% CI: [redacted]; [redacted]).

≥50% responder rates (MMDs)

STRIVE

A greater proportion of patients treated with erenumab 70 mg and 140 mg achieved a ≥50% reduction in mean MMDs from baseline at Week 24 versus placebo. In total, [redacted] ([redacted]%) and [redacted] ([redacted]%) patients in the erenumab 70 mg and 140 mg arms achieved a ≥50% reduction in MMDs from baseline, compared to [redacted] ([redacted]%) patients in the placebo arm. This corresponded to odds

ratios versus placebo of [redacted] (95% CI: [redacted]; [redacted] and [redacted] (95% CI: [redacted]; [redacted]), respectively.

ARISE

At Week 12, [redacted] patients ([redacted]%) treated with erenumab 70 mg, and [redacted] patients ([redacted]%) treated with placebo achieved reductions in MMDs of ≥50% from baseline, corresponding to an odds ratio of [redacted] (95% CI: [redacted]; [redacted]).

LIBERTY

A numerically greater proportion of patients treated with erenumab 140 mg achieved reductions in MMDs from baseline of at least 50% compared to placebo. In total, [redacted] ([redacted]%) patients in the erenumab 140 mg arm, and [redacted] ([redacted]%) patients in the placebo arm, had ≥50% reductions in MMDs from baseline to Week 12. This corresponded to an odds ratio versus placebo of [redacted] (95% CI: [redacted]; [redacted]).

B.2.7 *Meta-analysis*

No meta-analysis of the three erenumab studies presented above was performed. Study 295 used a different definition for a “migraine day” and a “headache day” to that of the studies in episodic migraine (STRIVE, ARISE and LIBERTY), therefore rendering any pooling of these trials inappropriate as outcomes cannot be interpreted as equivalent across trials (see Table 7 for definitions of migraine and headache days across trials). Change from baseline in MMDs and the proportion of patients who achieved ≥50% reduction from baseline MMDs from STRIVE, ARISE and LIBERTY were pooled to inform the economic analysis (see Section B.3.3.2).

B.2.8 *Indirect and mixed treatment comparisons*

B.2.8.1 Overview

As discussed in Section Appendix C: , in UK clinical practice BSC is the key comparator to erenumab for the majority of patients for whom ≥3 prior prophylactic treatments have failed. A small proportion of patients classified as having chronic migraine may also receive botulinum toxin, and therefore this was also considered to be a relevant comparator for the base case considering the chronic migraine population specifically.

For the comparison to BSC, the STRIVE, ARISE, LIBERTY and Study 295 studies provided direct head-to-head evidence against this comparator. Throughout these trials, patients were prescribed any treatments deemed necessary to provide adequate supportive care, meaning that the placebo arms were considered to be representative of BSC. Therefore, no indirect treatment comparison (ITC) was required to determine relative effectiveness estimates for erenumab versus BSC.

For the comparison to botulinum toxin in chronic migraine, the clinical SLR reported in Appendix D identified no studies providing direct head-to-head evidence for erenumab versus this comparator. An ITC was therefore required to generate relative effectiveness estimates for erenumab versus botulinum toxin for patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed. Data for erenumab in chronic migraine patients were available for the subgroup of patients for whom ≥3 prior treatments have failed from Study 295. From the chronic migraine botulinum toxin studies identified in the SLR, only PREEMPT (pooled data from the PREEMPT 1 and PREEMPT 2 trials) reported any data for the subgroup of

patients for whom ≥3 prior prophylactic treatments have failed. Both trials had placebo arms and therefore it was possible to conduct an ITC through the common placebo comparator. For these ITCs, the erenumab 70 mg and 140 mg fixed-doses from Study 295 were compared with the 155 U–195 U botulinum toxin flexible-dose from PREEMPT. The licensed posology for botulinum toxin in chronic migraine is a recommended dose of 155 to 195 units, injected across 31 to 39 sites.[106]

The ITCs were conducted using methodology reported by Bucher *et al.* for change from baseline in mean MMDs, change from baseline in mean MHDs and ≥50% responder rate. For the responder rate analysis for erenumab, Study 295 provided responder rate data when defining response on the basis of percentage reduction in MMDs or percentage reduction in MHDs. In contrast, response data in terms of percentage reduction in MMDs were not reported for the subgroup of patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed in the botulinum toxin studies and data were only available for responder rates defined in terms of percentage reduction in MHDs.[107] As such, one responder rate analysis used responder rates defined in terms of percentage reduction in MHDs from each study; an additional analysis was conducted comparing the ≥50% responder rates for erenumab and botulinum toxin where the responder rates were defined in terms of reductions in MMDs for erenumab and MHDs for botulinum toxin. The above outcomes were analysed as they were the only outcomes for which data were reported for both erenumab and botulinum toxin in the population of chronic migraine patients for whom ≥3 prior prophylactic treatments had failed. Responder rates represent the direct input for relative treatment effect in the cost-effectiveness model, and therefore the results of the responder rate analyses are presented below. Results for the other outcomes are presented in Appendix D. Detailed methods for the ITC can be found in D.1.5 in Appendix D.

Given the limitations in conducting a comparison using data from the subgroup of patients for whom ≥3 prior prophylactic treatments had failed (as outlined in B.2.9.3 below and D.1.4 in Appendix D) two further comparisons using the full trial populations were also conducted. A total of three analyses were therefore performed for each outcome:

- Firstly, the analysis in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed at the primary endpoint (outcomes at 12 weeks for Study 295 and outcomes at 24 weeks for PREEMPT) was conducted. A time point of 24 weeks for assessment of response to botulinum toxin is consistent with the NICE guidance from TA260.[8] For both erenumab and botulinum toxin, the data informing the ITC was for patients who had failed on ≥3 prior treatments (irrespective of treatment category).
- Secondly, a primary endpoint comparison for the full trial populations (outcomes at 12 weeks for Study 295 and outcomes at 24 weeks for PREEMPT). For this comparison, randomisation was maintained and baseline characteristics for both trials could be compared.
- Thirdly, a comparison of the 12-week results for the full trial populations was also conducted. This allowed erenumab and botulinum toxin to be compared at the same time point. It was not possible to conduct a 12-week analysis in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed as outcomes for this subgroup of the PREEMPT studies were reported at 24 weeks only.

A summary of these comparisons is provided in Table 37.

Table 37: Summary of comparisons used in ITC of erenumab versus botulinum toxin

Comparison	Population	Endpoint
1	Subgroup of patients for whom ≥3 prior prophylactic treatments have failed	Erenumab: 12 weeks (primary endpoint) Botulinum toxin: 24 weeks (primary endpoint)

2	Full trial population for Study 295 and PREEMPT	Erenumab: 12 weeks (primary endpoint) Botulinum toxin: 24 weeks (primary endpoint)
3	Full trial population for Study 295 and PREEMPT	Erenumab: 12 weeks (primary endpoint) Botulinum toxin: 12 weeks

The results of the latter two comparisons in the full populations can be used to contextualise the results for the subgroup for whom ≥3 prior prophylactic treatments have failed, which is the subgroup of direct relevance to the decision problem in the submission.

B.2.8.2 ITC results

The two trials (Study 295 and the pooled PREEMPT studies) were judged to be similar in terms of their study design and the patient baseline characteristics were also found to be similar (see Table 18 and Table 19 in Appendix D). The results from each trial that were used as inputs for the ITCs are given in Table 17 in Appendix D.

It should be noted that there was a difference in the time point for the primary endpoint between Study 295 and the PREEMPT study: 12 weeks for Study 295 versus 24 weeks for PREEMPT. Data from the PREEMPT full population showed that the relative effectiveness of botulinum toxin compared to placebo was greater at 24 weeks than at 12 weeks.[108] Assuming this trend was similarly observed in the ≥3 prior prophylactic treatments subgroup of the PREEMPT study (botulinum toxin data are not publicly available to confirm this), then the comparison between erenumab and botulinum toxin using primary endpoint data (i.e. erenumab at 12 weeks, botulinum toxin at 24 weeks) for the ≥3 prior prophylactic treatment subgroup is likely to represent a conservative estimate of the relative effectiveness of erenumab versus botulinum toxin in this subgroup were it possible to consider both treatments at the same time point of 12 weeks. In clinical practice, response to botulinum toxin is assessed at 24 weeks as per the NICE guidance (TA260) for this therapy, whilst response assessment for erenumab is anticipated to occur at 12 weeks. Therefore, although based on different time points for each therapy, the comparison based on the primary endpoint time point for the respective therapies is appropriate for understanding the relative rates of response to therapy (and hence decisions over continuation or not of therapy) that might be expected in clinical practice.

The results of the ITCs for responder rates are presented below, as the relative responder rate is the relative treatment effect input that informs the cost-effectiveness model. The results of ITCs for the other outcomes are presented in Appendix D. [redacted]

ITCs for ≥50% responder rate (defined in terms of MHDs)

The results of the ITC for the ≥50% responder rate (where response is defined in terms of reduction in MHDs) are presented in Table 38 and Table 39 for the comparison with erenumab 70 mg and 140 mg, respectively. The ≥50% responder rate was not reported for the full trial population at 12 weeks in PREEMPT, so the ITC in the full trial population was performed on the primary endpoint results only. For the comparison between erenumab 70 mg and botulinum toxin 155 U–195 U, the odds ratio of [redacted] favours erenumab, [redacted] The odds ratio of [redacted] also favours erenumab 140 mg, suggesting a higher probability of response compared to botulinum toxin 155 U–195 U; [redacted]

Table 38: ITC results for ≥50% responder rate (monthly headache days), erenumab 70 mg vs botulinum toxin 155 U–195 U

Group	Treatment 1	Treatment 2	Odds ratio: erenumab vs botulinum toxin (95% CI)
Subgroup for whom ≥3 prior prophylactic treatments have failed*, primary endpoint comparison	Erenumab 70 mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70 mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70 mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]

Abbreviations: CI: confidence interval; N/A: not applicable.

Table 39: ITC results for ≥50% responder rate (monthly headache days), erenumab 140 mg vs botulinum toxin 155 U–195 U

Group	Treatment 1	Treatment 2	Odds ratio: erenumab vs botulinum toxin (95% CI)
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140 mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 140 mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140 mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]

Abbreviations: CI: confidence interval; N/A: not applicable.

ITCs for ≥50% responder rate (defined in terms of MMDs for erenumab and MHDs for botulinum toxin)

The results of the ITC for the ≥50% responder rate where the definition of response for erenumab is based on reductions in MMDs and for botulinum toxin is based on MHDs is presented in Table 40 and Table 41 below. The odds ratios of [redacted] and [redacted] favour erenumab 70 mg and 140 mg, respectively, suggesting a higher probability of response compared to botulinum toxin 155 U–195 U. [redacted] This ITC was used in the base case of the cost-effectiveness model presented in Section B.3, on the basis that response assessment for botulinum toxin is determined by reductions in MHDs (see NICE TA260), whereas response assessment to erenumab is expected to be based on reductions in MMDs in line with the primary endpoints of the erenumab clinical trials.

Table 40: ITC results for ≥50% responder rate (monthly migraine days and monthly headache days), erenumab 70 mg vs botulinum toxin 155 U–195 U

Group	Treatment 1	Treatment 2	Odds ratio: erenumab vs botulinum toxin (95% CI)
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70 mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70 mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70 mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]

Abbreviations: CI: confidence interval; N/A: not applicable.

Table 41: ITC results for ≥50% responder rate (monthly migraine days and monthly headache days), erenumab 140 mg vs botulinum toxin 155 U–195 U

Group	Treatment 1	Treatment 2	Odds ratio: erenumab vs botulinum toxin (95% CI)
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140 mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 140 mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140 mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]

Abbreviations: CI: confidence interval; N/A: not applicable.

In conclusion, [redacted] These results should be interpreted in the context of the uncertainties in the analysis as described in Section B.2.8.3.

B.2.8.3 Uncertainties in the indirect and mixed treatment comparisons

There were a number of uncertainties when considering the ITCs in the subgroup of patients for whom ≥3 prior prophylactic treatments had failed, which meant that ITC methodological assumptions of comparable patient populations and trial characteristics may not hold for these

analyses. Baseline characteristics were not reported for the subgroup of patients for whom ≥3 prior prophylactic treatments had failed in PREEMPT, although these characteristics were available for erenumab 70 mg and 140 mg (Table 32). However, the baseline characteristics for the full trial populations in Study 295 and PREEMPT were similar. In the absence of appropriate subgroup data from PREEMPT, it therefore seemed reasonable to assume that baseline characteristics in these subgroups were similar, i.e. equivalent to those of the respective full trial populations. This assumption is supported by the consistency between the baseline characteristics of the full trial population and subgroup of patients for whom ≥3 prior prophylactic treatments have failed in Study 295 (Table 8 and Table 32, respectively). Therefore, this assumption should hold and not act as a limitation. In both trials patients were not stratified by previous prophylactic use when randomised. As a result, the analysis for the subgroup comparisons breaks randomisation and patient characteristics may therefore be imbalanced between study subgroup arms (i.e. active intervention versus placebo). Additionally, whilst least squares means were reported for each outcome, the variables adjusted for in PREEMPT are not reported. Finally, the outcomes were reported at different time points with Study 295 reporting outcomes at 12 weeks while PREEMPT reported outcomes at 24 weeks. As explained in Section B.2.8.2, this is likely to represent a conservative estimate of the relative effectiveness of erenumab versus botulinum toxin.

The ITCs comparing the full trial populations overcome some of the uncertainties discussed above. However, these full trial population comparisons are not directly relevant to the positioning of erenumab being targeted in this submission and so should only be used to contextualise the results from the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Despite the limitations associated with the ITCs in this subgroup, the ITC was considered to provide the best available comparison to inform estimates of the relative effectiveness of erenumab and botulinum toxin.

B.2.9 *Adverse reactions*

Summary of safety and tolerability of erenumab

- Overall, erenumab was well-tolerated in clinical trials and demonstrated a safety and tolerability profile comparable to that of placebo.
- As noted in the SmPC, across the erenumab phase II and III clinical trial programme as a whole the most frequently reported adverse drug reactions for 70 mg and 140 mg were injection-site reactions (5.6% and 4.5%), constipation (1.3% and 3.2%), muscle spasms (0.7% and 2.0%) and pruritus (1.0% and 1.8%).
- Across the four large, randomised, placebo-controlled trials presented in this submission (Study 295, STRIVE, ARISE and LIBERTY), the vast majority of AEs experienced by patients in the erenumab treatment arms were of mild or moderate severity and very low numbers of patients experienced any SAEs or AEs of grade 3 or above.
    - SAEs were reported by 1.1%, 1.9% and 1.7% of patients treated with erenumab 140 mg in Study 295, STRIVE and LIBERTY, respectively. SAEs were reported by 3.2%, 2.5% and 1.1% of patients treated with erenumab 70 mg in Study 295, STRIVE and ARISE, respectively. A similar number of SAEs were reported by patients in the placebo arms of the respective trials (2.5%, 2.2%, 1.7% and 0.8% in Study 295, STRIVE, ARISE and LIBERTY).
- AEs leading to discontinuation were very uncommon across all four studies. Of patients treated with erenumab 140 mg, 1.1% (Study 295), 2.2% (STRIVE) and 0% (LIBERTY) of patients experienced AEs leading to discontinuation of erenumab. These results were consistent in patients treated with erenumab 70 mg (0.0%, 2.2% and 1.8% for Study 295, STRIVE and ARISE, respectively).
- Overall, erenumab 70 mg and erenumab 140 mg demonstrated similar safety profiles, with low numbers of AEs, SAEs and AEs leading to treatment discontinuation observed across both doses. This was accepted by a group of six headache expert UK neurologists at a recent advisory board, who cited the similarity of the safety profiles as a key factor underpinning their decision to likely start difficult-to-treat patients on treatment with the 140 mg dose.[67]

B.2.9.1 Overview

Summary of safety from SmPC

The overall safety population in the phase II and III trials of erenumab includes more than 2,500 migraine patients who received at least one dose of erenumab, with more than 1,300 exposed for at least 12 months (more than 2,600 patient-years).[16] A total of 1,613 patients received erenumab during a 12-week placebo-controlled period, of which 507 received the 140 mg dose.[16] The most frequently reported AEs in the 70 mg and 140 mg dose included injection-site reactions (5.6% and 4.5%), constipation (1.3% and 3.2%), muscle spasms (0.7% and 2.0%) and pruritus (1.0% and 1.8%). The majority of these were classified as mild or moderate in severity. Less than 2% of patients in these studies discontinued due to adverse events. The list of adverse reactions as per the SmPC for erenumab is as follows, indicating that there are very few common adverse events associated with this treatment.

Table 42: List of adverse reactions in clinical studies

System organ class	Adverse reaction preferred term	Frequency category[a]
Gastrointestinal disorders	Constipation	Common
Skin and subcutaneous tissue disorders	Pruritus[b]	Common
Musculoskeletal and connective tissue disorders	Muscle spasms	Common
General disorders and administration site conditions	Injection site reactions[c]	Common

[a]The frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); [b]Pruritus includes preferred terms of generalised pruritus, pruritus and pruritic rash. [c]In the integrated 12-week placebo-controlled phase of the studies, injection site reactions were mild and mostly transient. There were no cases of discontinuation due to injection site reactions. The most frequent injection site reactions were localised pain, erythema and pruritus. Injection site pain typically subsided within 1 hour after administration.
Source: SmPC (2018)[16]

Safety results from the studies informing the decision problem (Study 295, STRIVE, ARISE, LIBERTY)

The safety and tolerability of erenumab for migraine patients was evaluated within Study 295, STRIVE, ARISE and LIBERTY. The safety data from all three studies are presented in the following sections of the submission.

In Study 295, the safety analysis set (n=660) included all randomly assigned patients who received at least one dose of investigational product (either erenumab or placebo). Safety was analysed through the incidence of deaths, AEs, serious AEs (SAEs), AEs leading to treatment discontinuation, anti-erenumab antibodies, vital signs, laboratory values and electrocardiogram (ECG) findings. Numbers of patients reporting any suicidal ideation or behaviour were also recorded.

In STRIVE, the safety analysis set (n=952) similarly included all randomised patients who received at least one dose of investigational product. The safety analysis set was used for all safety endpoints, including mean exposure to investigational product, incidence of deaths, AEs, treatment-emergent AEs, SAEs, clinical laboratory values, vital signs and anti-erenumab antibodies.

In ARISE, the safety analysis set (n=572) included all randomised patients who received at least one dose of the investigational product. The safety analysis set was used for all safety endpoints, including the incidence of AEs, clinical laboratory values, vital signs, ECG findings, Columbia-Suicide Severity Rating Scale (C-SSRS) and anti-erenumab antibodies.

In LIBERTY, the safety analysis set (n=243) include all randomised patients who received at least one dose of investigational product. The safety analysis set was used for all safety endpoints including incidence of deaths, AEs, treatment-emergent AEs and SAEs.

B.2.9.2 Treatment-emergent adverse events

Safety was assessed across the phase II and phase III clinical trials for erenumab (including Study 295, STRIVE, ARISE and LIBERTY).

Key safety results for the safety analysis sets in Study 295, STRIVE, ARISE and LIBERTY are presented in Table 43. The most frequently occurring AEs are detailed in Table 44, which were reported in more than 2% of patients, and AEs leading to treatment discontinuation and serious AEs are provided in

Table 45 and

Table 46, respectively.

Study 295

During the treatment phase of Study 295, 281 patients reported experiencing at least one AE, comprising 39.0% (110/282), 43.7% (83/190) and 46.8% (88/188) of patients in each of the placebo, erenumab 70 mg and 140 mg arms, respectively. The overall incidence of SAEs was very low, occurring in 2.5% (7/282), 3.2% (6/190) and 1.1% (2/188) of patients, respectively. The most commonly reported AEs included nasopharyngitis, upper respiratory tract infection, nausea and injection site pain. For all patients, these AEs were reported as mild to moderate, i.e., grade 1 or 2 on the Common Terminology Criteria for Adverse Events (CTCAE) scale.[68]

There were no deaths resulting from the administration of erenumab or placebo across any of the arms of the trial; two patients in each of the placebo and erenumab 140 mg arms experienced AEs which led to discontinuation. No AEs were reported by more than 5% of patients in either the erenumab 70 mg, or the erenumab 140 mg group, or by more than 6% of patients in the placebo group, highlighting the tolerability of erenumab. Moreover, there were no clinically significant abnormalities in vital signs, laboratory values or ECG findings for any patient in this study.[68] Importantly, there were no clinically apparent differences in AEs between the erenumab 140 mg and 70 mg treatment groups.

These results are supported by data from a one-year OLE of Study 295, which demonstrated that long-term treatment with erenumab did not lead to higher exposure-adjusted rates of AEs than those observed in the erenumab or placebo arms during the double-blind treatment phase. SAEs were reported by 14/549 (3.3%) and 10/259 (4.7%) patients in the erenumab 70 mg and 140 mg arms over the duration of the open-label study period.[83]

When taken together with the clinical efficacy outcomes reported in Section B.2.6.1, this indicates that treatment with erenumab 140 mg can lead to numerically superior efficacy outcomes compared to erenumab 70 mg in the subpopulation addressed in this submission, with no measurable difference in safety outcomes.

STRIVE

During the double-blind treatment phase of STRIVE, treatment-emergent AEs were reported by 201/319 (63.0%), 180/314 (57.3%) and 177/319 (55.5%) patients in the placebo, erenumab 70 mg and erenumab 140 mg arms respectively. The most frequently reported AEs were similar to those occurring in Study 295, and included nasopharyngitis, upper respiratory tract infection,

sinusitis, constipation, arthralgia, fatigue and nausea. Across all trial arms, the vast majority of AEs were mild or moderate with only 5.0% (16/319), 4.8% (15/314) and 5.3% (17/319) of patients reporting an AE of grade 3 or 4 on the CTCAE grading scale in the placebo, erenumab 70 mg, and erenumab 140 mg arms respectively. SAEs were reported in 2.2% (7/319), 2.5% (8/314) and 1.9% (6/319) of patients in the placebo, erenumab 70 mg and erenumab 140 mg arms, respectively.[72]

No fatal treatment-emergent AEs had occurred as of the data cut-off on 5th September 2016. There were three events of grade 3 nasopharyngitis and one event of grade 3 nausea within the erenumab 140 mg group, and one event of grade 3 arthralgia in the placebo group.[73] Common AEs were found to be well distributed between the three treatment groups as were discontinuations, with eight (2.5%), seven (2.2%) and seven (2.2%) discontinuations due to AEs in the placebo, 70 mg and 140 mg groups, respectively. This highlights the tolerability of erenumab compared to placebo in patients classified as having episodic migraine.[72]

These results are supported by data from the one-year extension phase of STRIVE, during which SAEs were reported by 3/138 (2.2%), 7/140 (6.0%) and 4/143 (2.8%) patients in the placebo, erenumab 70 mg and erenumab 140 mg arms, respectively.[109]

Again, erenumab 140 mg and 70 mg were shown to have very similar safety profiles, meaning that treatment with erenumab 140 mg leads to improved outcomes in patients for whom ≥3 prior prophylactic therapies have failed, with no effect on safety and tolerability.

ARISE

During the double-blind treatment phase of ARISE, 136 patients (48.1%) in the erenumab 70 mg arm and 158 patients (54.7%) in the placebo arm reported a treatment-emergent AE. The most common AEs were upper respiratory tract infection, injection site pain, influenza, fatigue, nausea, migraine, sinusitis, nasopharyngitis and constipation. The vast majority of AEs were mild or moderate in severity, with only 2.1% (6/283) and 2.8% (8/289) of patients reporting an AE of grade 3 on the CTCAE grading scale in the erenumab 70 mg and placebo arms, respectively, and no patients reporting an AE of grade 4.[100]

Only three patients in the erenumab 70 mg arm (1.1%), and five patients in the placebo arm (1.7%) experienced a SAE, and there were only five (1.8%) and one (0.3%) discontinuations due to AEs in these treatment arms, respectively. No deaths occurred during the double-blind treatment phase. These results are demonstrative of the high tolerability of erenumab 70 mg in patients classified as having episodic migraine.[100]

LIBERTY

During the double-blind treatment phase of LIBERTY, AEs were reported by 67/124 (54.0%) and 65/119 (54.7%) of patients in the placebo and erenumab 140 mg arms, respectively. The most frequently reported AEs were injection site pain, nasopharyngitis, back pain and injection site erythema. SAEs were reported by one patient (0.8%) in the placebo arm and two patients (1.7%) in the erenumab 140 mg arm, and one patient (0.8%) in the placebo arm discontinued due to AEs (due to pregnancy). Overall, a similar frequency of AEs and SAEs were observed across both arms of the trial.[84] Only three patients in total experienced a SAE (one patient [0.8%] in the placebo arm and two patients [1.7%] in the erenumab 140 mg arm), indicating that nearly all of the AEs experienced were mild to moderate in severity.

Table 43: Treatment-emergent adverse events in the safety analysis set of Study 295, STRIVE, ARISE and LIBERTY

Adverse event	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=282)[a]	Erenumab 70 mg (n=190)[a]	Erenumab 140 mg (n=188)[a]	Placebo (n=319)[b]	Erenumab 70 mg (n=314)[b]	Erenumab 140 mg (n=319)[b]	Placebo (n=289)	Erenumab 70 mg (n=283)	Placebo (n=124)	Erenumab 140 mg (n=119)
Total no. of patients (%)	110 (39.0)	83 (43.7)	88 (46.8)	201 (63.0)	180 (57.3)	177 (55.5)	158 (54.7)	136 (48.1)	67 (54.0)	65 (54.3)
With SAEs	7 (2.5)	6 (3.2)	2 (1.1)	7 (2.2)	8 (2.5)	6 (1.9)	5 (1.7)	3 (1.1)	1 (0.8)	2 (1.7)
With Grade ≥2[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥3[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8 (2.8)	6 (2.1)	[redacted]	[redacted]
With Grade ≥4[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With AEs leading to discontinuation of investigational product	2 (0.7)	0 (0.0)	2 (1.1)	8 (2.5)	7 (2.2)	7 (2.2)	1 (0.3)	5 (1.8)	1 (0.8)	0 (0.0)

Footnotes: [a]Number of subjects reporting at least one occurrence of a treatment-emergent adverse event. [b]Number of subjects with non-missing values. [c]Grading categories determined using Common Toxicity Criteria for Adverse Events version 4.03.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: Tepper *et al*. (2017)[68]; Study 295 CSR[69]; Goadsby *et al.* (2017)[72]; STRIVE CSR[73]; Dodick *et al*. (2017)[100]; Dodick *et al*. (2018)[76]; ARISE CSR[77]; LIBERTY data on file (2018)[84]

Table 44: AEs occurring in ≥2% of patients in the safety analysis set of Study 295, STRIVE, ARISE and LIBERTY

Adverse event, no of patients (%)[a]	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=282)	Erenumab 70 mg (n=190)	Erenumab 140 mg (n=188)	Placebo (n=319)	Erenumab 70 mg (n=314)	Erenumab 140 mg (n=319)	Placebo (n=289)	Erenumab 70 mg (n=283)	Placebo (n=124)	Erenumab 140 mg (n=119)
Nasopharyngitis	16 (6)	6 (3)	3 (2)	32 (10.0)	31 (9.9)	35 (11.0)	17 (5.9)	15 (5.3)	12 (9.7)	5 (4.2)

Upper respiratory tract infection	4 (1)	5 (3)	6 (3)	18 (5.6)	21 (6.7)	15 (4.7)	14 (4.8)	18 (6.4)	0	3 (2.5)
Sinusitis	-	-	-	7 (2.2)	7 (2.2)	11 (3.4)	6 (2.1)	6 (2.1)	-	-
Constipation	1 (<1)	0 (0)	8 (4)	4 (1.3)	5 (1.6)	11 (3.4)	6 (2.1)	4 (1.4)	-	-
Arthralgia	-	-	-	6 (1.9)	7 (2.2)	7 (2.2)	-	-	-	-
Fatigue	-	-	-	8 (2.5)	6 (1.9)	7 (2.2)	6 (2.1)	10 (3.5)	2 (1.6)	3 (2.5)
Nausea	7 (2)	4 (2)	6 (3)	6 (1.9)	7 (2.2)	6 (1.9)	13 (4.5)	7 (2.5)	-	-
Influenza	-	-	-	6 (1.9)	4 (1.3)	8 (2.5)	10 (3.5)	11 (3.9)	-	-
Urinary tract infection	-	-	-	7 (2.2)	5 (1.6)	7 (2.2)	-	-	-	-
Back pain	-	-	-	7 (2.2)	6 (1.9)	6 (1.9)	-	-	2 (1.6)	5 (4.2)
Injection-site pain	3 (1)	7 (4)	7 (4)	1 (0.3)	10 (3.2)	1 (0.3)	12 (4.2)	17 (6.0)	7 (5.6)	7 (5.9)
Migraine	3 (1)	3 (2)	5 (3)	10 (3.1)	4 (1.3)	3 (0.9)	8 (2.8)	6 (2.1)	-	-
Hypertension	-	-	-	8 (2.5)	5 (1.6)	0 (0.0)	-	-	-	-
Muscle spasms	4 (1)	1 (<1)	7 (4)	N/A	N/A	N/A	-	-	-	-
Dizziness	-	-	-	-	-	-	-	-	2 (1.6)	3 (2.5)
Injection site erythema	-	-	-	-	-	-	-	-	4 (3.2)	3 (2.5)
Neck pain	-	-	-	-	-	-	-	-	0 (0.0)	3 (2.5)

Footnotes: AEs included in this table if they occurred in ≥2% of patients in at least one trial; recorded as - if they occurred in <2% of patients in specific trial. [a]Number of patients reporting at least one occurrence of an adverse event in that class.
Abbreviations: AE: adverse event.
Source: Tepper *et. al.* (2017)[68]; Goadsby *et al.* (2017)[72]; Dodick *et al*. (2017)[100]; LIBERTY data on file (2018)[84]

Table 45: AEs leading to treatment discontinuation in the safety analysis set in Study 295, STRIVE, ARISE and LIBERTY

Adverse event, no of patients (%)[a]	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=282)	Erenumab 70 mg (n=190)	Erenumab 140 mg (n=188)	Placebo (n=319)	Erenumab 70 mg (n=314)	Erenumab 140 mg (n=319)	Placebo (n=289)	Erenumab 70 mg (n=283)	Placebo (n=124)	Erenumab 140 mg (n=119)
Total no. of patients[b] (%)	2 (<1)	0 (0)	2 (<1)	8 (2.5)	7 (2.2)	7 (2.2)	1 (0.3)	5 (1.8)	–	–
Constipation	0 (0)	0 (0)	1 (<1)	–	–	–	–	–	–	–
Gastro-oesophageal reflux disease	1 (<1)	0 (0)	0 (0)	–	–	–	–	–	–	–
Fatigue	0 (0)	0 (0)	1 (<1)	–	–	–	1 (0.3)	1 (0.4)	–	–
Panic attack	1 (<1)	0 (0)	0 (0)	–	–	–	–	–	–	–
Cough	1 (<1)	0 (0)	0 (0)	–	–	–	–	–	–	–
Dyspnoea	1 (<1)	0 (0)	0 (0)	[redacted]	[redacted]	[redacted]	–	–	–	–
Ventricular extrasystoles	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Tinnitus	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Vertigo positional	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Abdominal pain upper	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Nausea	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Oral pain	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Vomiting	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–

Injection site rash	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Hypersensitivity	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Vestibular neuronitis	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Intentional overdose	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Arthralgia	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Pain in extremity	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Dizziness	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Headache	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Initial insomnia	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Mood swings	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Nervousness	–	–	–	[redacted]	[redacted]	[redacted]	–	–	–	–
Metrorrhagia	0 (0)	0 (0)	1 (<1)	[redacted]	[redacted]	[redacted]	–	–	–	–
Irritable bowel syndrome	–	–	–	–	–	–	–	1 (0.4)	–	–
Allergy to arthropod sting	–	–	–	–	–	–	–	1 (0.4)	–	–
Affect lability	–	–	–	–	–	–	–	1 (0.4)	–	–
Mechanical urticaria	–	–	–	–	–	–	–	1 (0.4)	–	–

Footnotes: [a]Number of subjects reporting at least one occurrence of an adverse event in that class. [b]Number of subjects reporting treatment-emergent adverse events leading to withdrawal of investigational product. '–' indicates that AE not reported in publication/CSR.
Abbreviations: AE: adverse event.
Source: Tepper *et. al.* (2017)[68] ; Goadsby *et al*. (2017)[72]; STRIVE CSR[73]; Dodick *et al*. (2017)[100]; ARISE CSR[77]; LIBERTY data on file (2018)[84]

Table 46: Serious AEs in the safety analysis set in Study 295, STRIVE, ARISE and LIBERTY

Adverse event, no of patients (%)[a]	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=282)	Erenumab 70 mg (n=190)	Erenumab 140 mg (n=188)	Placebo (n=319)	Erenumab 70 mg (n=314)	Erenumab 140 mg (n=319)	Placebo (n=289)	Erenumab 70 mg (n=283)	Placebo (n=124)	Erenumab 140 mg (n=119)
Total no. of patients[b] (%)	7 (2)	6 (3)	2 (1)	7 (2.2)	8 (2.5)	6 (1.9)	5 (1.7)	3 (1.1)	1 (0.8)	2 (1.7)
Abdominal adhesions	0 (0)	0 (0)	1 (<1)	–	–	–	–	–	–	–
Abdominal pain	0 (0)	0 (0)	1 (<1)	–	–	–	–	–	–	–
Cartilage injury	0 (0)	0 (0)	1 (<1)	–	–	–	–	–	–	–
Intervertebral disc protrusion	1 (<1)	1 (<1)	0 (0)	–	–	–	0 (0)	1 (0.4)	–	–
Appendicitis	0 (0)	1 (<1)	0 (0)	–	–	–	–	–	–	–
Costochondritis	0 (0)	1 (<1)	0 (0)	–	–	–	–	–	–	–
Fibroma	0 (0)	1 (<1)	0 (0)	–	–	–	–	–	–	–
Non-cardiac chest pain	0 (0)	1 (<1)	0 (0)	1 (<1)	1 (<1)	1 (<1)	–	–	–	–
Radius fracture	0 (0)	1 (<1)	0 (0)	–	–	–	–	–	–	–
Cholecystitis	1 (<1)	0 (0)	0 (0)	–	–	–	–	–	–	–
Migraine	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (0.3)	1 (0.4)	0	1 (0.8)
Pancreatitis	1 (<1)	0 (0)	0 (0)	–	–	–	–	–	–	–
Parotitis	1 (<1)	0 (0)	0 (0)	–	–	–	–	–	–	–
Urinary tract infection	1 (<1)	0 (0)	0 (0)	–	–	–	0 (0)	1 (0.4)	–	–
Vomiting	1 (<1)	0 (0)	0 (0)	–	–	–	–	–	–	–
Cholelithiasis	–	–	–	0 (0)	2 (<1)	0 (0)	1 (0.3)	0 (0)	–	–
Ankle fracture	–	–	–	0 (0)	0 (0)	1 (<1)	–	–	–	–

Cerebral venous thrombosis[c]	–	–	–	0 (0)	0 (0)	1(<1)	–	–	–	–
***Clostridium difficile* colitis[c]**	–	–	–	0 (0)	0 (0)	1(<1)	–	–	–	–
Viral gastroenteritis	–	–	–	0 (0)	0 (0)	1(<1)	–	–	–	–
Kidney infection[c]	–	–	–	0 (0)	0 (0)	1 (<1)	–	–	–	–
Pyelonephritis[c]	–	–	–	0 (0)	0 (0)	1 (<1)	–	–	–	–
Sepsis[c]	–	–	–	0 (0)	0 (0)	1 (<1)	–	–	–	–
Spinal pain	–	–	–	0 (0)	0 (0)	1 (<1)	–	–	–	–
Vestibular neuronitis	–	–	–	0 (0)	0 (0)	1 (<1)	–	–	–	–
Back pain	–	–	–	0 (0)	1 (<1)	0 (0)	–	–	–	–
Ovarian cyst	–	–	–	0 (0)	1 (<1)	0 (0)	–	–	–	–
Post-traumatic neck syndrome	–	–	–	0 (0)	1 (<1)	0 (0)	–	–	–	–
Acute pyelonephritis	–	–	–	0 (0)	1 (<1)	0 (0)	–	–	–	–
Arthralgia	–	–	–	1 (<1)	0 (0)	0 (0)	–	–	–	–
Endometriosis	–	–	–	1 (<1)	0 (0)	0 (0)	–	–	–	–
Fall	–	–	–	1 (<1)	0 (0)	0 (0)	–	–	–	–
Hypersensitivity	–	–	–	1 (<1)	0 (0)	0 (0)	1 (0.3)	0 (0)	–	–
Intentional overdose	–	–	–	1 (<1)	0 (0)	0 (0)	–	–	–	–
Osteoarthritis	–	–	–	1 (<1)	0 (0)	0 (0)	–	–	–	–
Traumatic fracture	–	–	–	–	–	–	–	–	0	1 (0.8)

GI infection	–	–	–	–	–	–	–	–	1 (0.8)	0
Flank pain	–	–	–	–	–	–	1 (0.3)	0 (0)	–	–
Hyponatremia	–	–	–	–	–	–	1 (0.3)	0 (0)	–	–
Uterine leiomyoma	–	–	–	–	–	–	1 (0.3)	0 (0)	–	–

[a]Number of subjects reporting at least one occurrent of an adverse event in that class. [b]Number of subjects reporting serious treatment-emergent adverse events. [c]All five adverse events (cerebral venous thrombosis, Clostridium difficile colitis, kidney infection, pyelonephritis, and sepsis) were reported in a single patient. '–' indicates that AE not reported in publication/CSR.
Abbreviations: AE: adverse event; GI: gastrointestinal.
Source: Tepper *et al.* (2017)[68], Goadsby *et al.* (2017) Supplementary Appendix[87], Dodick *et al*. (2017)[100], LIBERTY data on file (2018)[84]

B.2.9.3 Safety conclusions

Across all four trials, the vast majority of AEs experienced by patients in the erenumab treatment arms were of mild or moderate severity and very low numbers of patients experienced any SAEs or AEs of grade 3 or above. In Study 295, just 1.1% (two patients) and 3.2% (six patients) experienced an SAE in the erenumab 140 mg and 70 mg arms, respectively. In STRIVE, the proportion of patients experiencing an SAE in the erenumab 70 mg and 140 mg arms was 2.5% (eight patients) and 1.9% (six patients), respectively, and three patients (1.1%) in the erenumab 70 mg arm in ARISE experienced an SAE. Similarly, in LIBERTY, 1.7% (two patients) experienced a SAE in the erenumab 140 mg arm. Across all four studies, the proportion of patients reporting both AEs and SAEs was similar in the erenumab arm to that of the placebo arm, demonstrating the tolerability profile of erenumab to be on par with placebo, i.e. baseline AE rates without treatment. These results are supported by the results of one-year OLE studies for both Study 295 and STRIVE, which demonstrated that long-term treatment with erenumab does not lead to an increase in AEs.[83, 109] Furthermore, erenumab 70 mg and erenumab 140 mg demonstrated similar safety profiles, with low numbers of AEs, SAEs and AEs leading to treatment discontinuation across both arms.

The most commonly observed AEs (of any grade) were consistent across all four studies (nasopharyngitis, nausea, fatigue, upper respiratory tract infection and arthralgia), and the most frequently reported adverse drug reactions for the 70 mg and 140 mg doses were injection site reactions (5.6% and 4.5%), constipation (1.3% and 3.2%), muscle spasms (0.7% and 2.0%) and pruritus (1.0% and 1.8%),[16] demonstrating the reliable tolerability profile of erenumab in patients with both episodic and chronic migraine. In line with this profile, no particular safety monitoring is expected for erenumab.

B.2.10 *Ongoing studies*

There are currently two ongoing OLE studies investigating the efficacy and safety of erenumab in adult migraine patients, as detailed below.

- NCT03333109 (Novartis):[71] a 12-week single-cohort, three-treatment arm, randomised, double-blind study in 880 adults with migraine (classified as 4–14 days per month of migraine symptoms). This study is being conducted in countries not involved in the pivotal trials for erenumab (i.e. beyond the United States and European Union). The primary endpoint is the change in MMDs from baseline to the last four weeks of the double-blind treatment period, and secondary outcomes include the ≥50% responder rate and change in HIT-6 scores from baseline. A final safety follow-up visit will be conducted at Week 24. This study is currently recruiting participants, and the estimated completion date is 7th February 2020.
- NCT01952574 (Amgen):[80] The ongoing part of this study represents the OLE of the 12-week phase II, randomised, double-blind, placebo-controlled, parallel-group, multicentre study of the same NCT number noted in Table 4. This study included 483 adult patients with migraine (classified as having <15 MHDs, and ≥4 and ≤14 MMDs per month in each of the three months prior to screening and during baseline). There were 472 patients enrolled in the parent study, and 383 entered the OLE, with median exposure to erenumab of 575 days (range 28–822 days) at the interim analysis stage of the OLE. At Week 64 mean change from baseline was −5.0 days, with 65% of patients achieving a ≥50% reduction in baseline MMDs.[78] Safety results reported after ≥3 years of open-label treatment demonstrated that erenumab was safe and well-tolerated, with no increase of AEs over time. SAEs were reported by 29/383 (4.4%) and 14/250 (4.9%) patients in the erenumab 70 mg and 140 mg arms, respectively.[110] The estimated completion date for the OLE is 11th November 2019. Further details of this study are presented in Appendix L, as this was a phase II study and does not therefore form part of the key clinical evidence base for the submission.

B.2.11 *Innovation*

Summary of the innovation of erenumab in migraine

- Therapies used currently for prophylaxis of migraine in clinical practice were not developed specifically for treatment of patients with this condition and have been repurposed from other indications. Erenumab represents a major breakthrough as the first targeted therapy for the prophylaxis of migraine.
- Erenumab is a first-in-class fully human CGRP inhibitor and is the only inhibitor in development which specifically targets the CGRP receptor complex, which plays a key role in mediating the pain of migraine. If recommended, erenumab will provide the first targeted migraine therapy recommended for use in the UK in decades.
- The safety and tolerability profile demonstrated by erenumab is similar to that of placebo, with few SAEs reported across the clinical trial programme.
- Erenumab has demonstrated a rapid onset of action, providing significant reductions in monthly migraine frequency from baseline relative to placebo from as early as Week 1.[97, 99]
- Efficacy of erenumab is sustained in the longer-term, with open-label studies demonstrating significant reduction in mean monthly migraine days up to Week 52 in the chronic migraine population,[83] and Week 64 in the episodic migraine population.[78]
- Erenumab is subcutaneously administered, with a formulation that enables patient self-administration; this contrasts with the significant resource requirements associated with administration of botulinum toxin, the only NICE recommended treatment option for migraine prophylaxis. Erenumab has the potential to ease the burden of migraine on NHS resources, both through its lower administrative requirements, and by reducing the need for acute migraine management.
- Erenumab has demonstrated efficacy across the entire spectrum of migraine patients with ≥4 MMDs, including those patients for whom prior prophylactic treatments have failed and therefore have high unmet need. This contrasts to the available oral prophylactic treatments, for which robust data to support the benefit-risk ratio are limited, and to botulinum toxin, the only other recommended treatment for migraine prophylaxis. In several clinical trials, botulinum toxin failed to demonstrate superior efficacy versus placebo in episodic migraine patients, and is therefore licensed only in patients classified as having chronic migraine.[8]
- The prophylaxis of migraine with erenumab has a potential wider societal value, as a reduction in migraine symptoms may mean that patients are able to return to work, reducing productivity loss from migraine. This would also have a positive impact on the UK economy, with absenteeism due to migraine costing the UK economy approximately £4.4 billion per year.[29]
- Given that patients with migraine for whom ≥3 prior prophylactic treatments have failed have a high unmet need, erenumab has the potential to substantially alleviate migraine symptoms for a considerable number of patients in England and Wales for whom existing prophylactic therapies have failed, and to ease the current burden of migraine on NHS resources.

A first-in-class therapy for migraine patients

None of the prophylactic medications currently prescribed in the UK at any line of therapy were developed specifically for use in migraine patients, and were instead repurposed from other indications, meaning that they do not target the underlying biology of the disease. There is very little clinical evidence to support the effectiveness of most treatment options, and they are associated with poor tolerability and variable efficacy profiles, and low levels of adherence.[7, 32, 33,

[61] Erenumab is the only licensed treatment to have been developed specifically for the prophylaxis of migraine, based on an understanding of the underlying pathophysiology of the disease, and represents a major breakthrough as the first targeted therapy for the prophylaxis of migraine. Erenumab is a highly potent and selective antagonist of the CGRP receptor pathway, which plays a key role in mediating the pain of migraine.[14] This novel mechanism of action compared to current therapies is a 'step change' in the management of migraine, and if recommended, erenumab will provide the first targeted prophylactic migraine therapy recommended for use in the UK.[9]

Patients for whom ≥3 prior prophylactic treatments have failed have a particularly high unmet need for treatment options. For the majority of these patients there are no further treatment options available and the patients would therefore receive BSC. The exception to this is the availability of botulinum toxin – the only therapy currently recommended by NICE for chronic migraine prophylaxis. However, botulinum toxin is only available to those patients for whom ≥3 prior prophylactic treatments have failed and who are classified as having chronic migraine, and many of these patients are unable to access botulinum toxin due to it not being available in all NHS Trusts due to its administration needing to be performed by trained expert physicians. Erenumab will be the only treatment option for patients for whom ≥3 prior prophylactic treatments have failed, with a licence for use across the spectrum of patients with ≥4 MMDs rather than for chronic migraine patients only and can be self-administered.

Erenumab has the potential not only to remove the administrative burden of botulinum toxin treatment in this patient population, but also to reduce the burden of acute management across the entire spectrum of migraine. Migraine currently accounts for up to 71,000 emergency admissions in England each year.[43] By reducing both the number of migraine days experienced, and the average severity of migraine pain, treatment with erenumab is expected to lead to reductions in this number, and also in the use of acute pain-relief medication.

Erenumab is well tolerated in patients, with few discontinuations due to AEs

Erenumab was well tolerated in clinical trials, with an overall safety profile comparable to that of placebo. The phase II and III clinical programme for erenumab includes over 2,500 patients (more than 2,600 patient years) who received at least one dose of erenumab. The most frequently reported adverse drug reactions for the 70 mg and 140 mg doses were injection site reactions (5.6% and 4.5%), constipation (1.3% and 3.2%), muscle spasms (0.7% and 2.0%) and pruritus (1.0% and 1.8%).[16] Erenumab was well tolerated across the whole spectrum of migraine patients, with data for AEs consistent across all three studies presented in this submission, including in patients classified as having both chronic and episodic migraine.[68, 72, 78, 100] Clinical experts at an advisory board spoke positively of the beneficial tolerability and safety profile of erenumab across the whole migraine spectrum, with adverse events considered to be similar to expected background rates.[9]

As erenumab does not cross the blood-brain barrier, it is not expected to be associated with CNS-related AEs such as somnolence and cognitive dysfunction. Furthermore, as a monoclonal antibody, erenumab is also not degraded by the liver or the kidneys, reducing the risk of liver or renal toxicity that can be observed with small-molecule therapies.

This tolerability profile contrasts with that of current oral prophylactic treatments used in initial lines of therapy, which are associated with several AEs and co-morbidities and a correspondingly high discontinuation rate.[32] Indeed, BASH guidelines highlight the role that considerations of the

tolerability and safety profiles of existing oral prophylactics play in determining treatment choices currently in UK clinical practice.[7]

Finally, an analysis of 884 patients across four phase II/III clinical trials of erenumab (including Study 295 and STRIVE) found that anti-erenumab antibodies have a low occurrence rate, high reversion rate, and no appreciable clinical impact on the efficacy or safety (including injection-site reactions, hypersensitivity and immune-related disorders) in erenumab-treated subjects. There were three recorded instances of a neutralising antibody (NAb) to erenumab in the 70 mg arms of these trials, of which two patients were NAb-negative by the end of the study, and no recorded instances in the 140 mg arms.[111]

Erenumab provides rapid onset of action, having demonstrated clinical efficacy within four weeks of first administration

In the clinical trial setting, erenumab has been shown to reduce migraine frequency over 12 weeks, with significantly greater reductions in migraine days from baseline relative to placebo observed from as early as Week 1 (see Section B.2.5.1). Given the burdensome nature of migraine on patient HRQoL, patient productivity, and the ability to engage in everyday activities, rapid reductions in migraine frequency are an important feature of the clinical efficacy profile of erenumab. Furthermore, early symptom relief might be expected to engender greater adherence to treatment, with early onset of action potentially providing reassurance to patients that their therapy is working to reduce their migraine symptoms. Importantly, the reduction in mean MMDs observed by Week 1 was sustained over the remainder of the trial period, which suggests that erenumab can deliver a lasting benefit.

Response to erenumab is maintained in the longer-term

The results of an OLE study of erenumab in the chronic migraine population (NCT20130255; an OLE of Study 295) indicate that the response observed in clinical trials is maintained in the long-term. In patients treated with erenumab 70 mg and 140 mg, the mean change in MMDs from baseline (18.1 days) was −7.8 days and −10.0 days at Week 40, and −8.5 and −10.5 days at Week 52, respectively (see Section B.2.5.1 for full results of double-blind treatment phase). In total, 53% and 67% of patients in the erenumab 70 mg and 140 mg arms achieved a ≥50% reduction in MMDs at one year. The favourable safety profile was maintained over the 52-week period, with an overall exposure-adjusted incidence rate for treatment-emergent AEs of 126.3 per 100 patient-years, of which the majority were grade 1 or 2 in severity. A numerically greater benefit was observed with the erenumab 140 mg dose versus the 70 mg dose with respect to the reductions in MMDs, monthly acute migraine-specific medication use, and responder rates.[83]

These results were also echoed in an OLE study of erenumab 70 mg in the episodic migraine patient population (the erenumab 140 mg dose was not investigated in this study). This study (NCT01952574) is summarised in Appendix L. At Week 64, mean change in MMDs from baseline (8.8 days) was –5.0 days (SD: 4.2).[78] At ≥3 years of follow-up, SAEs were reported by by 29/383 (4.4%) and 14/250 (4.9%) patients in the erenumab 70 mg and 140 mg arms, respectively.[110] These results suggest that the efficacy of erenumab will be maintained with extended treatment, and that it can provide a safe and effective therapy for migraine patients in the long-term.

Prophylaxis of migraine with erenumab has potential wider societal value

Migraine is associated with substantial disability and poses an economic burden on society. It affects primarily adults of working and child-bearing age, and in the UK it is estimated that 43 million work days are lost each year to migraine.[29] Therefore, a reduction in migraine symptoms for patients with chronic or episodic migraine may mean that migraineurs are able to return to work, reducing productivity loss from migraine. This would also have a positive impact on the UK economy, with absenteeism costing the UK economy approximately £2.24 billion per year.[47] Erenumab has been observed to improve the QoL of patients across the whole migraine population in Study 295, STRIVE and LIBERTY. Specifically, treatment with erenumab 140 mg led to significantly greater reductions in all three MSQ v2.1 domains in chronic and episodic migraine patients from Study 295 and STRIVE (see Section B.2.5.2).

In patients for whom erenumab is an alternative to botulinum toxin, erenumab provides a more convenient and NHS resource-releasing mode of administration

Botulinum toxin is only recommended for patients classified as having chronic migraine who have not responded to ≥3 prior prophylactic therapies and its use is highly restricted.[10] Where it is available, botulinum toxin requires a trained specialist to perform each administration, requiring patients to visit the hospital and consuming specialist NHS resource. In contrast, erenumab is self-administered by the patient, with only a single nurse-led training session required upon initiation. This means that erenumab is associated with a considerably lower administrative burden for patients and the NHS. Furthermore, it has the potential to widen access to an effective treatment for those patients who are currently unable to access a specialist treatment centre to receive botulinum toxin and hence only receive BSC.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

B.2.12.1 Principal findings from the clinical evidence base

Erenumab provided clinically meaningful responses in terms of the reduction of migraine days in patients for whom prior prophylactic treatments have failed

Studies have shown that treatment with erenumab is associated with significant reductions in MMDs from baseline compared to placebo in patients for whom ≥3 prior prophylactic treatments have failed (See Section B.2.6). In this subgroup in Study 295, treatment with erenumab 70 mg led to mean reductions from baseline to Week 12 of [redacted] days, corresponding to an LSM difference versus placebo of [redacted] days (95% CI: [redacted]; [redacted]). Patients treated with erenumab 140 mg achieved a mean reduction of [redacted] MMDs, which represents a statistically significant difference compared to placebo, of [redacted] days (95% CI: [redacted]; [redacted]). In STRIVE, patients treated with erenumab 70 mg and 140 mg achieved mean reductions in MMDs from baseline to the last three months of the double blind treatment phase versus placebo of [redacted] (95% CI: [redacted]; [redacted]) and [redacted] (95% CI: [redacted]; [redacted]9), respectively. In ARISE, patients treated with erenumab 70 mg achieved reductions of [redacted] days from baseline to Week 12, compared to [redacted] days in the placebo arm, which corresponded to a LSM difference of [redacted] (95% CI: [redacted]; [redacted]). In LIBERTY, patients treated with erenumab 140 mg achieved mean reductions in MMDs from baseline of [redacted] days, compared to [redacted] days for patients treated with placebo (95% CI: [redacted]; [redacted]). The differences in the subgroup of patients for whom ≥3 prior prophylactic treatment categories have failed were

greater than those observed in the full patient population (see Section B.2.5.1), highlighting the efficacy of erenumab in the targeted subgroup.

A significantly greater proportion of patients treated with erenumab achieved ≥50% reduction in MMDs from baseline in patients for whom ≥3 prior prophylactic treatments have failed. In Study 295, [redacted]% and [redacted]% of patients treated with erenumab 70 mg and 140 mg, respectively achieved a ≥50% reduction in MMDs from baseline to Week 12, compared to [redacted]% of those treated with placebo (OR: [redacted] [95% CI: [redacted]; [redacted]] and OR: [redacted] [95% CI: [redacted]; [redacted]], respectively). In STRIVE, similar results were observed, with [redacted]% of patients treated with erenumab 140 mg achieving a ≥50% reduction in MMDs from baseline to the last three months of the double-blind treatment phase versus placebo, compared to [redacted]% of patients in the placebo arm (OR: [redacted] [95% CI: [redacted]; [redacted]]). [redacted] ([redacted]%) patients in the erenumab 70 mg arm achieved a ≥50% reduction in MMDs from baseline to Week 12 (OR versus placebo: [redacted]; 95% CI: [redacted]; [redacted]). In ARISE, [redacted]% of patients in the erenumab 70 mg arm, and [redacted]% of patients in the placebo arm, achieved a ≥50% reduction in MMDs from baseline to Week 12, corresponding to an odds ratio of [redacted] (95% CI: [redacted]; [redacted]). In LIBERTY, [redacted]% of patients in the erenumab 140 mg arm achieved a ≥50% reduction in MMDs from baseline compared to [redacted]% in the placebo arm (OR: [redacted] [95%CI: [redacted]; p=[redacted]). Reductions in MMDs of ≥30% are generally considered to represent clinically meaningful changes for migraine patients, across the spectrum of episodic and chronic migraine patients.[98] The ≥50% responder rate outcomes show erenumab to be effective at reducing baseline MMDs against an even more rigorous endpoint, demonstrating the clinically meaningful benefit of erenumab.

These results suggest that erenumab 140 mg may be more efficacious compared to erenumab 70 mg in the subgroup of patients for whom ≥3 prior treatments have failed. In both Study 295 and STRIVE, patients treated with erenumab 140 mg achieved greater reductions in MMDs and a higher ≥50% response rate compared to patients treated with erenumab 70 mg, with further improvements across a range of additional efficacy outcomes, as outlined in Section B.2.6.1. The higher dose may therefore be most appropriate to minimise the severe burden of disease faced by these patients, given this is a population with a high unmet clinical need. This is supported by feedback from six expert UK neurologists, who considered that for difficult-to-treat patients, the 140 mg dose may be the most efficient treatment approach, citing the trend towards greater efficacy in this population.[67]

Erenumab is effective in patients across the whole spectrum of migraine

Erenumab has shown consistency in providing reductions in mean MMDs from baseline in the entire migraine population of patients with ≥4 MMDs. The results from the ITT populations in trials across episodic and chronic populations demonstrated that treatment with erenumab was associated with significant reductions in terms of several clinically meaningful endpoints compared to placebo, with significant differences observed in the proportion of patients achieving ≥50% reduction from baseline in MMDs between the erenumab 70 mg and 140 mg arms, and the placebo arm in all trials (See Section B.2.5).

Data from HFEM subgroups in STRIVE, ARISE and LIBERTY

In the subgroup of patients with 8–14 MMDs at baseline, treatment with erenumab resulted in greater reductions in MMDs from baseline, and a higher ≥50% responder rate, compared to placebo. In STRIVE, patients in the erenumab 140 mg achieved significantly greater mean reductions in MMDs from baseline to Week 24 versus placebo, of [redacted] days (95% CI:

[redacted]). In the erenumab 140 mg arm, [redacted] ([redacted]%) patients achieved a ≥50% reduction in MMDs, compared to [redacted] ([redacted]%) patients in the placebo arm (OR: [redacted] [95% CI: [redacted]; [redacted]]). In ARISE, patients in the erenumab 70 mg and placebo arms achieved reductions in MMDs of [redacted] and [redacted], respectively, at Week 12, corresponding to a difference of [redacted] (95% CI: [redacted], [redacted]; [redacted]). In total, [redacted] patients ([redacted]%) treated with erenumab 70 mg, and [redacted] patients ([redacted]%) treated with placebo achieved reductions in MMDs of ≥50% from baseline, corresponding to an odds ratio of [redacted] (95% CI: [redacted]; [redacted]). In LIBERTY, the difference in the reduction in MMDs from baseline to Week 12 between the erenumab 140 mg and placebo arms was [redacted] (95% CI: [redacted]; [redacted]). In total, [redacted] ([redacted]%) patients in the erenumab 140 mg arm, and [redacted] ([redacted]%) patients in the placebo arm, had ≥50% reductions in MMDs from baseline to Week 12 (OR: [redacted] [95% CI: [redacted]; [redacted]]).

Comparative evidence for erenumab versus botulinum toxin in patients classified as having chronic migraine

As discussed in Section B.1.2.2, the main comparator for migraine patients for whom ≥3 prior prophylactic treatments have failed is BSC. However, botulinum toxin is recommended for patients who have not responded to ≥3 prior prophylactic treatments and who are classified as having chronic migraine, and is therefore a treatment option for a small number of patients meeting these criteria who have access to a neurology centre in which botulinum toxin is available.[8]

In the absence of direct comparative evidence (i.e. a head-to-head trial) of the efficacy of erenumab versus botulinum toxin, an ITC was conducted (see Section B.2.8 for further details). Results from the ITC indicate that erenumab (both the 70 mg and 140 mg dose) is associated with a greater ≥50% responder rate compared to botulinum toxin (155 U–195 U flexible dose), in the population of chronic migraine patients for whom ≥3 prior prophylactic treatments have failed. [redacted]

The clinical effectiveness of erenumab translates to improved health-related quality of life outcomes for migraine patients

Patients treated with erenumab experienced a significant reduction in MSQ scores compared to those treated with placebo. In Study 295, STRIVE and ARISE, patients treated with erenumab achieved greater improvements across all three domains of MSQ scores from baseline to Week 12 versus placebo. MSQ scores measure the impact of migraine across three essential aspects of a patient's HRQoL, including the extent to which daily activities are limited, and the impact on related emotions. This result therefore indicates that erenumab not only reduces the number of migraine days experienced by patients, but also leads to functional improvements. This was accepted by expert clinicians at a UK advisory board.[9] The MSQ scores are supported by the significant reductions in HIT-6 scores observed in migraine patients treated with erenumab, compared to placebo (see Section B.2.5.2). The HIT-6 captures multiple aspects of the impact of migraine on daily life, including severe pain, fatigue and the limitation of daily activity. Significant differences versus placebo were observed from Week 4 onwards in all three trials and maintained over the trial follow-up period (12 weeks in Study 295, ARISE and LIBERTY; 24 weeks in STRIVE), meaning that patients treated with erenumab experienced improvements in the quality of daily living for an extended period of time. Similar to the clinical efficacy results, patients treated with erenumab 140 mg achieved more rapid improvements across several domains of HRQoL compared to patients treated with erenumab 70 mg, meaning that they experienced higher improvements in HRQoL for a longer duration of time.

As outlined in Section B.1.2.1, migraine has a considerable impact on an individual's ability to work and socialise, limiting the daily activities of more than three-quarters of sufferers. The improvements in patient HRQoL demonstrated by erenumab are therefore important in potentially contributing to a return to work and to a less disrupted home life.

Erenumab demonstrates a safety and tolerability profile comparable to that of placebo

As noted in the SmPC, across the erenumab phase II and III clinical trial programme as a whole the most frequently reported adverse drug reactions for the 70 mg and 140 mg were injection-site reactions (5.6%/4.5%), constipation (1.3%/3.2%), muscle spasms (0.7%/2.0%) and pruritus (1.0%/1.8%). Study 295, STRIVE, ARISE and LIBERTY demonstrated the safety profile of erenumab across the spectrum of migraine patients in four large, randomised, placebo-controlled trials.

Across all four trials, the vast majority of AEs experienced by patients in the erenumab treatment arms were of mild or moderate severity and very low numbers of patients experienced any SAEs or AEs of grade 3 or above. Just 1.1% (2 patients) of patients in Study 295 experienced an SAE in the erenumab 140 mg arm, and the proportions of patients experiencing an SAE in the erenumab 140 mg arm were 1.9% (6 patients) in STRIVE and 1.7% (2 patients) in LIBERTY. SAEs were reported by 3.2%, 2.5% and 1.1% of patients treated with erenumab 70 mg in Study 295, STRIVE and ARISE, respectively. AEs experienced amongst patients treated with erenumab were consistent across the three studies. Furthermore, across all three studies, the proportion of patients reporting both AEs and SAEs was similar, if not lower, for patients treated with erenumab than those in the placebo arm, demonstrating the tolerability profile of erenumab to be on par with placebo, i.e. baseline AE rates without treatment. The safety profiles of erenumab 70 mg and 140 mg were similar, which demonstrates that the higher dose of erenumab can lead to improved clinical efficacy outcomes, with no impact on safety. This was accepted by six headache expert UK neurologists at a recent advisory board, who agreed that they may initiate difficult-to-treat patients on the higher 140 mg dose, given the similarity of the safety profile.[67]

B.2.12.2 Strengths and limitations of the clinical evidence base

The clinical evidence base for erenumab in migraine comes primarily from one phase II trial in patients classified as having chronic migraine (Study 295), and three phase III studies in patients classified as having episodic migraine (STRIVE, ARISE and LIBERTY). These studies provide randomised, placebo-controlled evidence for the efficacy and safety of erenumab for the treatment of migraine prophylaxis. The strengths and limitations of Study 295, STRIVE, ARISE and LIBERTY with regards to internal and external validity are discussed below. The results of full quality assessments for each of these trials are presented in Appendix D.

Overall, the internal and external validity of the trials are supported by the following:

- Adequate randomisation, treatment allocation concealment and blinding, as outlined in Section B.2.4.2. All patients enrolled were randomised following appropriate double-blind procedures.
- Large sample sizes in each of the trials, with 667 patients in Study 295, 955 in STRIVE, 577 in ARISE and 246 in LIBERTY.
- The populations included patients from [redacted] UK sites ([redacted] patients) in Study 295, [redacted] ([redacted] patients) in STRIVE and [redacted] ([redacted] patients) in LIBERTY. The study populations were deemed

generalisable to the UK migraine population, as validated by expert clinicians at a UK advisory board.[9]

- Patients were prescribed any treatments deemed necessary to provide adequate supportive care for the duration of the studies. This reflects the expected use of erenumab in clinical practice, where erenumab would be expected to be administered in combination with BSC.
- At baseline, average monthly acute headache medication usage aligned with BASH guidelines for the acute treatment of migraine, which recommends limiting the use of triptans to a maximum of 10 days per month.[7] In Study 295, average usage was 8.8, 9.7 and 9.5 days in the erenumab 70 mg, erenumab 140 mg and placebo groups respectively (Table 8), and in STRIVE, average use was 6.6 days in both erenumab arms, and 6.9 days in the placebo arm (Table 9). In ARISE, average use was 3.4 days in the erenumab 70 mg arm, and 3.7 days in the placebo arm (Table 10), and in LIBERTY, average use was 4.8 days in the erenumab 140 mg arm, and 4.4 days in the placebo arm (Table 11).
- Patients' prophylactic medication history was consistent with the UK clinical treatment pathway summarised in Section B.1.2.2, whereby topiramate (an anticonvulsant), amitriptyline (a tricyclic antidepressant) and propranolol (a beta blocker) constitute standard of care for earlier lines of prophylactic treatment. The most frequently used prior prophylactic medications in Study 295, STRIVE and ARISE were topiramate ([redacted]%, [redacted]% and [redacted]% of patients, respectively), beta blockers ([redacted]%, [redacted]% and [redacted]%) and tricyclic antidepressants ([redacted]%, [redacted]% and [redacted]%). Equivalent data are unavailable for LIBERTY at time of submission.
- A wide range of outcomes were investigated, including disease activity over time, migraine severity, QoL and safety. These outcomes are of relevance to patients and clinicians in clinical practice.

Limitations of the evidence

Erenumab was assessed up to 12 weeks in Study 295, ARISE and LIBERTY, and 24 weeks in STRIVE. This presents limitations for understanding the safety, efficacy and adherence to erenumab 140 mg in the long-term; it is expected that patients will remain on erenumab treatment for a longer timeframe in clinical practice. However, open label studies have been conducted for erenumab 70 mg in episodic migraine patients and show that over one year, the effect of erenumab on patients has remained fairly constant, with improvements in reduction of mean MMDs from baseline continuing beyond the double-blind treatment phase.[78]

The trials for the efficacy of erenumab in chronic and episodic migraine provide direct comparative efficacy of erenumab against placebo, which provides a proxy for BSC – the most relevant comparator for UK clinical practice. Direct head-to-head data are not available versus botulinum toxin, which is a comparator for a small subset of patients who are classified as having chronic migraine for whom ≥3 prior prophylactic treatments and are able to access the treatment. Therefore, an ITC was required to provide comparative evidence versus botulinum toxin in chronic migraine and this was associated with some limitations (see Section B.2.8).

The decision problem presented in this submission is erenumab for the prophylaxis of migraine in patients for whom ≥3 prior prophylactic treatments have failed. This represents a subpopulation of each of the studies informing the evidence base, which recruited patients with varying prophylactic medication histories. As such, use of this subgroup data does limit available sample size. Furthermore, since trial randomisation was not stratified by prior prophylactic usage, randomisation does not hold in these trial subgroups. Comparison of baseline characteristics in the subgroups of patients for whom ≥3 prior prophylactic treatments have failed does however demonstrate that patients in the erenumab 70 mg and 140 mg arms, and the placebo arms, were associated with similar baseline characteristics (B.2.6.1), and ultimately this subgroup data is

most relevant to the decision problem and most appropriate to use to inform the economic analysis presented in Section B.3.

Finally, the trial inclusion criteria meant that patients classified as having either chronic or episodic migraine were assessed separately (i.e. Study 295 included patients with ≥15 MHDs of which eight were migraine, and STRIVE, ARISE and LIBERTY included patients who had ≥4 and ≤15 MMDs with <15 MHDs). These inclusion criteria were based on the classifications referenced in clinical guidelines and recruitment of patients to trials using these classifications is consistent with trial design generally in this indication. However, as discussed in Section B.1.2.1, these classifications may be of limited relevance to clinical practice and do not adequately reflect the nature of migraine as a spectrum disorder.[1-4] This submission presents a base case analysis that considers the population of patients with ≥4 MMDs as a whole (the "whole population" base case) in order to reflect erenumab's licence and the view of migraine as a spectrum along which patients are distributed, rather than a condition of two binary classifications. The separation of the trial evidence base into episodic and chronic populations presents a limitation for assessing cost-effectiveness of erenumab in this whole population, due to the differences in definition of headache days and migraine days employed in each trial. However, this submission presents an analysis in the whole migraine population who have ≥4 MMDs. A full description on how this was conducted is presented in Section B.3. Ultimately, the totality of the trial evidence base presented in this submission supports the effectiveness of erenumab across the entire patient population of adults with ≥4 MMDs and is the same evidence base that resulted in erenumab being granted a regulatory label across the entire spectrum of migraine patients.

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

- An economic SLR identified no previous economic evaluations of erenumab for prophylaxis of migraine. Therefore, a *de novo* economic model was developed to evaluate the cost-effectiveness of erenumab versus relevant comparators in this submission.
- The model structure used a decision-tree plus Markov model approach, including two health states of on treatment and discontinuation once patients were classified as responders or non-responders.
- The distribution of patients across MMDs for each treatment and time point was modelled based on the clinical trial data presented in Section B.2, and used to calculate the costs and QoL benefits associated with each therapy.
- Erenumab can be prescribed as a 70 mg or 140 mg dose. In the absence of long-term clinical experience of erenumab dosing in UK NHS clinical practice, it was assumed that 50% of patients are initiated on the 70 mg dose, and 50% on the 140 mg dose (this approach is referred to as the "blended dose"). As the higher dose may be more appropriate for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, results are also presented for an analysis in which all patients start treatment on the 140 mg dose. The proportion of patients starting treatment on each dose was explored further in scenario analyses.
- For the comparison to BSC, effectiveness of BSC was based on data from the placebo arms of relevant clinical trials. Botulinum toxin was included as an additional comparator in a subset of the chronic migraine population only, with relative effectiveness to erenumab derived from an ITC (see Section B.2.8).
- Utilities for each MMD frequency were derived from MSQ v2.1 data collected in three erenumab clinical trials (Study 295, STRIVE and ARISE), mapped onto EQ-5D-3L. Disutilities for AEs and mode of administration were not included in the base case analysis.
- Costs and resource use associated with disease management for each MMD frequency were derived from analysis of data from the National Health and Wellness Survey, a cross-sectional questionnaire administered to migraine patients. This captured migraine-specific costs related to hospitalisation and A&E visits, health care professional visits and use of acute medication.
- Drug acquisition and administration costs were sourced from appropriate UK-relevant sources: the British National Formulary, MIMS, NHS Tariff 2017 and Unit Costs of Health and Social Care 2017.
- The decision problem considered adult migraine patients with ≥4 MMDs for whom ≥3 prior prophylactic treatments have failed, representing an optimised positioning for use of erenumab within the NHS. Results are presented for a "whole population base case" (comparator: BSC) and for separate "chronic migraine" (comparators: BSC, botulinum toxin) and "episodic migraine" (comparator: BSC) populations.

Cost-effectiveness results (all results are with PAS)

- In the base case, erenumab was a cost-effective treatment option at a cost-effectiveness threshold of £30,000 in the whole population for whom ≥3 prior prophylactic treatments have failed versus BSC, with an ICER of £22,446 per QALY gained for the blended dose, and £19,827 per QALY gained for the 140 mg dose.
- The blended dose of erenumab is also a cost-effective treatment in the chronic migraine population versus botulinum toxin, with an ICER of £18,893 per QALY gained, and versus

BSC, with an ICER of £17,212 per QALY gained. Erenumab 140 mg is cost-effective versus both botulinum toxin, with an ICER of £17,832, and BSC, with an ICER of £13,340 per QALY gained.

- ICERs in the episodic migraine population exceed £30,000 per QALY gained but, for the reasons outlined in sections B.1.1 and B.1.2.2, it is anticipated that the ICERs for the whole migraine population are the most relevant for decision making. Notably, the adoption of a societal perspective reduced the ICER to less than £20,000 per QALY gained in the episodic migraine population for both the blended dose and the 140 mg dose.
- Subgroup analysis restricting the episodic migraine population (4–14 MMDs) to the HFEM population (8–14 MMDs) resulted in similar ICERs as for the whole population base case and the episodic migraine analyses, respectively.
- Exploratory analyses in patients for whom ≥2 prior prophylactic treatments have failed and who are unsuitable for further prophylactic treatment found erenumab to be cost-effective at a cost-effectiveness threshold of £30,000 in both whole population and chronic migraine population-specific analyses at either the blended dose or 140 mg dose of erenumab (see Appendix Z).
- Scenario analyses in the whole population base case and the chronic migraine populations demonstrated that the ICERs were robust to changes in key model assumptions and input parameters.
- Finally, whilst the societal perspective is not part of the NICE reference case, it is important to note adoption of this perspective significantly improves erenumab cost-effectiveness given that migraine predominantly affects a working age population and has considerable societal impact.
    - Whole population (versus BSC): £2,947 per QALY gained (blended dose); £328 per QALY gained (140 mg dose)
    - Chronic migraine population (versus botulinum toxin): £3,477 per QALY gained (blended dose); £2,417 per QALY gained (140 mg dose)
    - Chronic migraine population (versus BSC): £1,797 per QALY gained (blended dose); erenumab dominates BSC (140 mg dose)
    - Episodic migraine (versus BSC): £13,071 per QALY gained (blended dose) and £17,946 per QALY gained (140 mg dose).

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify economic evidence to support the development of a cost-effectiveness model for erenumab for the prophylaxis of migraine in patients who experience ≥4 migraine days per month. A single SLR was conducted in July 2017 and subsequently updated in January 2018 to identify all literature published since database inception on any of the following topics:

- Economic evaluations of pharmacological interventions for the treatment of migraine
- Health state utility values for migraine patients
- Cost and resource use data for migraine patients

Full details of the search strategy and results of the economic SLR are presented in Appendix G.

A total of 3,410 unique articles were identified from the electronic database searches in the original SLR and reviewed at the title/abstract review stage. In the 2018 update, a further 187 unique articles were identified from the electronic database searches. After title/abstract review in

the original SLR, 205 articles were reviewed at the full-text stage with 30 articles ultimately meeting the inclusion criteria. In the update, 14 articles were reviewed at the full-text stage with 4 articles meeting the inclusion criteria. An additional 6 articles to those captured through the database searches were identified through congress searching, website searching and through hand searching of bibliographies in the original review. Only 1 extra article was identified through hand searches in the update.

In total, 8 records reporting on 6 published economic evaluations were identified in the SLR. Full details of these economic evaluations including the quality assessments of each study are provided in Appendix G. None of the identified economic evaluations reviewed the cost-effectiveness of erenumab.

B.3.2 *Economic analysis*

Given the findings of the SLR detailed above, a *de novo* economic model was developed to evaluate the cost-effectiveness of erenumab versus relevant comparators for this submission. The model structure was informed by the systematic review of economic evaluations in migraine described in Section B.3.1, by considerations of modelling migraine in a clinically meaningful and scientifically robust manner, and by clinical expert opinion.

IHS clinical guidelines and consultation with eight headache expert UK neurologists indicated that both the change in MMDs and the proportion of responders to treatment are important outcomes in migraine prophylaxis, and the model structure therefore needed to allow for tracking of both of these outcomes.[9, 81] The models previously identified in the systematic review were either state transition models (N=5) which used bands of MMD/MHD frequency when reported, or a decision-tree model (N=1) which only used proportion of responders. The economic model for botulinum toxin in patients with chronic migraine (the only other prophylactic treatment appraised by NICE) was a Markov model (Appendix G, Table 43) consisting of health states defined by bands of MHD frequency. Patients transitioned between these health states and also from being “on treatment” to “off treatment”. None of the models identified in the literature review explicitly captured outcomes of both response status and changes in frequency of MMD/MHD, limiting their relevance to clinical practice.

Furthermore, the use of arbitrarily-defined MMD/MHD frequency bands to define model health states, as seen in previously published economic evaluations identified by the SLR such as that for the botulinum toxin appraisal, was considered to lack scientific robustness. Grouping of patients of differing MMD frequencies into a single health state results in a loss of information regarding potential differences in costs and QoL impacts between individual MMD frequencies and loses faithfulness to trial data. In order to account for the cost and quality of life consequences of various frequencies of MMD, it is important that the distributions of patients by MMD are considered in economic evaluations of migraine prophylaxis, rather than relying on estimates of mean frequency or categorical health states i.e. mean MMD frequency estimates. As the impact of each additional MMD is not constant, an approach only considering the mean MMD is inappropriate. Accounting for these non-linear outcomes is useful in more accurately modelling migraine prophylactics.

As such, the modelling approach chosen was a *de novo* economic model which moved away from the grouping of patients into MMD health states and the use of transition probabilities to attempt to predict patient movement between these health states. Instead, the *de novo* approach reproduced directly from the clinical trial data the patient distributions across individual MMD frequencies for each treatment and time point. These frequencies were defined differentially for

responders and non-responders, allowing both MMD frequency and response status outcomes to be explicitly captured in the model. This model structure is described in detail below, with differences compared to the model used to assess botulinum toxin outlined in Table 48.

B.3.2.1 Patient population

The patient population considered in the *de novo* economic model for this submission was adults aged between 18 and 64 years old for whom ≥3 prior prophylactic treatments have failed.

The population considered in the "whole population base case" was all migraine patients with ≥4 MMDs per month, which is consistent with the population of the NICE scope and the licence for erenumab. This population also reflects the fact that migraine is a spectrum disorder, with migraine patients in practice distributed across a continuum of MMD frequencies as discussed in Section B.1.2.1.[1-4] The optimisation of the population to patients for whom ≥3 prior prophylactic treatments have failed (a restriction not specified in the licence for erenumab) reflects the expected positioning of migraine in UK clinical practice (see Section B.1.2.2). This also takes into account the NICE recommendation for botulinum toxin for the treatment of chronic migraine, where treatment after three prior oral prophylactic therapy failures was considered a pragmatic approach within the NHS.[8]

In addition to the "whole population base case", results are also presented separately in patients for whom ≥3 prior prophylactic treatments have failed and who are classified as having chronic migraine (≥15 headache days a month of which ≥8 are migraine) and episodic migraine (4–14 headache days per month). These are referred to as the "chronic migraine population" and "episodic migraine population", respectively. Whilst an evaluation across the whole population is appropriate for addressing the decision problem, separate analyses of chronic and episodic migraine populations were also considered relevant to explore since some clinical guidelines actively distinguish these populations, and given that botulinum toxin, a scope comparator, is only recommended for use in chronic migraine there is an additional comparator to consider in this specific population.[5, 6, 8] In addition, the clinical trial programme for erenumab studied these populations separately due to regulatory requirements, although it should be noted that data from the separate trials in chronic and episodic migraine populations were submitted to the EMA as part of the marketing authorisation application and resulted in a licence for use of erenumab in all migraine patients who experience ≥4 migraine days per month (i.e. not defined in terms of episodic or chronic migraine).

Evidence for the clinical effectiveness of erenumab was provided by the phase II Study 295 in the chronic migraine population, and the phase III STRIVE, ARISE and LIBERTY trials in the episodic migraine population. As described in Section B.2.7, differences in the definitions of migraine and headache for Study 295 compared to the episodic migraine studies meant that these trials could not be pooled for evaluation of the effectiveness of erenumab in reducing frequency of migraine or headache days. Therefore, the analysis of the "whole population base case" was based upon a weighting of the modelled outcomes in the chronic migraine and episodic migraine patients (see Section B.3.3), using the proportion of the whole population assumed to have chronic migraine versus episodic migraine at baseline (66%CM:34%EM).

As outlined in Section B.1.2.2, whilst the recommended dose for erenumab is 70 mg Q4W, some patients may benefit from treatment with a higher dose of 140 mg Q4W. In clinical trials of erenumab, treatment with erenumab 140 mg led to numerically better clinical outcomes compared to erenumab 70 mg in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, with a very similar safety and tolerability profile. Erenumab 140 mg may

therefore be considered to be the most appropriate dose for this patient population, which represents a group with a particularly high unmet need and lack of treatment options. This is supported by feedback from six expert UK neurologists, who indicated that they may initiate these difficult-to-treat patients on the 140 mg dose.[67] As such, it was assumed in the base case in the economic analysis that a proportion of patients would start treatment on the 140 mg dose, with the remainder initiated on the 70 mg dose (this approach is hereafter referred to as the "blended dose"). In the absence of long-term clinical experience, the ratio of patients starting treatment on erenumab 70 mg and 140 mg was assumed to be 50%:50%, with these values varied in scenario analyses. However, given the optimised benefit-risk balance of erenumab 140 mg in this patient population, and the positive feedback from UK clinicians, it is expected that as clinical experience develops [redacted], a higher proportion of patients would be initiated on the higher dose. Analyses are therefore also presented for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, in which all patients are treated with erenumab 140 mg.

In addition to the base case analyses, this submission presents subgroup analyses in patients with HFEM for whom ≥3 prior prophylactic treatments have failed. For these analyses, HFEM was defined as 8–14 MHDs. It should be noted that this clinical subgroup data presented in Section B.2.6.3 corresponded to a HFEM group defined as patients with 8–14 MMDs as this represented the subgroup data available from the clinical studies. However, in practice the HFEM population is defined in terms of MHDs and the subgroup is therefore defined as such for the purposes of the economic evaluation. The HFEM population is a recognised subgroup of episodic migraine patients who are considered to have a clinical burden similar to patients classified as having chronic migraine. However, unlike chronic migraine patients, patients with HFEM at this line of therapy are unable to access botulinum toxin in line with its NICE recommendation. The subgroup of HFEM patients therefore face a particularly high unmet need.[42]

Finally, exploratory analyses were also conducted to model the population of patients in whom ≥2 prior prophylactic treatments have failed and who are unsuitable for further prophylactic treatment. This was based on discussion with expert clinicians who indicated that, if made available, there would be clinical desire to use erenumab at this earlier point in the clinical pathway for those patients unable to receive an existing third-line therapy due to contraindications, special warnings or precautions. This analysis was informed by the clinical subgroup data for patients for whom ≥2 prior prophylactic treatments have failed, presented in Section B.2.6.2. A summary of the cost-effectiveness results for this subgroup is provided in Appendix Z. This population was explored both for the whole migraine population and for the chronic migraine and episodic migraine populations separately.

The patient populations considered in the base case analysis and in subgroup and exploratory analyses are summarised in Table 47. Please see Figure 1 (Section B.1.2.1) for the classification of migraine.

Table 47: Patient populations considered in this submission

	Whole migraine population – base case	Chronic migraine population	Episodic migraine population
Patient population	"Whole population base case"	"Chronic migraine population"	"Episodic migraine population"

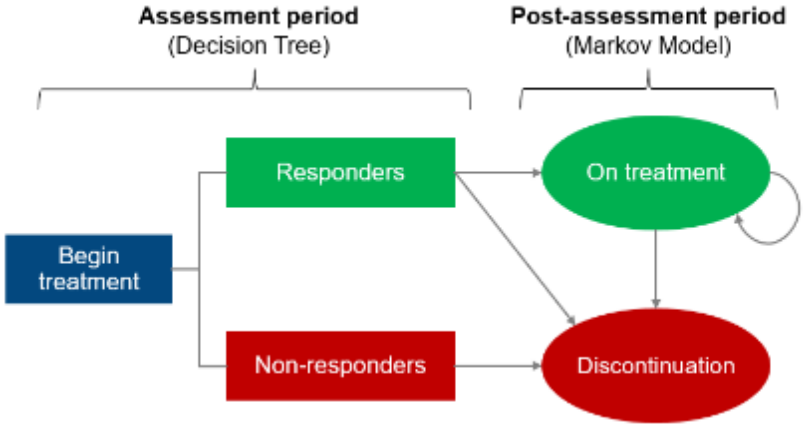
	• ≥4 migraine days per month • Failed ≥3 prior prophylactics • Blended dose and 140 mg dose	• ≥15 headache days per month • ≥8 migraine days per month • Failed ≥3 prior prophylactics • Blended dose and 140 mg dose	• <15 headache days per month • ≥4 to <15 migraine days per month • Failed ≥3 prior prophylactics • Blended dose and 140 mg dose
Subgroup analyses	"HFEM whole population subgroup analysis" • ≥4 migraine days per month • HFEM (≥8 to <15 headache days per month) or chronic migraine (≥15 headache days per month, ≥8 migraine days per month • Failed ≥3 prior prophylactics • Blended dose and 140 mg dose	N/A	"HFEM subgroup analysis" • HFEM (≥8 to <15 headache days per month) • Failed ≥3 prior prophylactics • Blended dose and 140 mg dose
Exploratory ≥2 prior treatment group analyses	"Exploratory whole population analysis 1" • ≥4 migraine days per month • Failed ≥2 prior prophylactics • Blended dose and 140 mg dose	"Exploratory chronic migraine analysis 1" • ≥15 headache days per month • ≥8 migraine days per month • Failed ≥2 prior prophylactics • Blended dose and 140 mg dose	"Exploratory episodic migraine analysis 1" • <15 headache days per month • ≥4 to <15 migraine days per month • Failed ≥2 prior prophylactics • Blended dose and 140 mg dose

Abbreviations: HFEM: high-frequency episodic migraine; N/A: not applicable.

B.3.2.2 Model structure

The model structure employed was a decision-tree plus Markov model. A decision tree was used to represent the assessment period, at the end of which the probability of treatment response was estimated based on the predicted change in MMDs from baseline. The Markov model was used to represent the post-assessment period, during which the responders and non-responders followed distinct pathways. The model structure is presented in Figure 19. The model structure was predicated on the assumption that costs and quality-adjusted life years (QALYs) could be estimated based on MMD frequency, and therefore costs and QALYs within the model were accrued based on the modelled distribution of patients across MMD frequencies in each health state. Patients from all states had an equal risk of transitioning to death, as it was assumed that no excess mortality is associated with migraine.

Figure 19: Cost-effectiveness model structure



Assessment period

The assessment period was modelled as 12 weeks for erenumab and BSC. This was the length of time deemed clinically appropriate to observe a change in MMDs. This also reflects feedback from UK clinicians, the majority of whom reported that they would be likely to assess response after three injections of erenumab (12 weeks).[9] For the analysis of the chronic migraine population, the assessment period for the botulinum toxin comparator was 24 weeks, reflecting the assessment period employed in the economic model from the manufacturer's submission for botulinum toxin for the treatment of chronic migraine (NICE TA260) as reviewed by Royle *et al*, and consistent with the NICE guidance that treatment should be stopped in patients not exhibiting a response after two treatment cycles of botulinum toxin (24 weeks).[8, 112] Differences in the assessment period for erenumab (12 weeks) and botulinum toxin (24 weeks) were incorporated in the model through the use of the ITC that compared erenumab response probability at 12 weeks to botulinum toxin response probability at 24 weeks, as described in Section B.3.3.3. As discussed in Section B.2.8.2, the relative efficacy of botulinum toxin compared to placebo was greater at 24 weeks than at 12 weeks in the full PREEMPT study population; therefore, assuming this trend was similarly observed in the ≥3 prior prophylactic treatments subgroup of the PREEMPT study (botulinum toxin data are not publicly available), the use of this ITC is potentially conservative versus use of a comparison that would have been performed for erenumab versus botulinum toxin at 12 weeks were the data available to consider both therapies at this assessment timepoint.

The model captured the distribution of patients across the frequency of MMDs (0–28 MMDs) at baseline and at the assessment timepoint. The distribution of patients across MMD frequencies was modelled separately for responders and non-responders, with patients assigned to the respective distributions based on the proportion of patients modelled to have a response at the assessment timepoint. In order to determine the proportion of patients classified as responders versus non-responders, it was necessary to define the criteria for meeting the definition of a response (i.e. a response threshold) which was defined as a ≥50% reduction from baseline in MMDs. This was indicated by eight UK expert neurologists who specialise in headache at an Advisory Board to be the most appropriate response criterion for use in clinical practice.[9] This was also the primary endpoint in LIBERTY, and a key secondary endpoint in Study 295, STRIVE and ARISE.

Response status at the assessment timepoint determined not only the subsequent distribution of MMDs, but also the state in which patients entered the Markov model that was used to model the post-assessment period (see below).

Finally, patients were at risk of discontinuation due to adverse events during the assessment period. Patients undergoing discontinuation due to adverse events entered the 'discontinuation' health state and were assumed to rebound to their baseline distribution of MMDs.

Post-assessment period

The post-assessment period was represented by a Markov model structure, with responders and non-responders following distinct treatment pathways.

Patients who did not meet the response threshold (non-responders) discontinued prophylactic treatment at the assessment time point and entered the 'discontinuation' health state, in which they were assumed to receive only BSC (i.e. acute medication only) and to maintain their non-responder MMD improvement at Week 12 for the remainder of the model time horizon.

Responders transitioned to the 'on treatment' state and were assumed to remain on treatment with erenumab or the comparator therapy in this health state until discontinuation. Responders were modelled to maintain the 12-week MMD distribution for responders until discontinuation of therapy.

From Week 24, patients in the 'on treatment' health state were at a continuous per-cycle risk of discontinuation of 2.38%, based on observed all-cause discontinuation data from 383 migraine patients treated with erenumab in an open-label phase II study in patients classified as having episodic migraine.[78] Patients undergoing this negative discontinuation entered the 'discontinuation' health state and were assumed to rebound to the baseline distribution of MMDs.

A scenario analysis considered that patients who were continued responders to treatment were re-evaluated for continuation of treatment (i.e. assessed for positive discontinuation) after a maximum period of 64.5 weeks (based on clinical expert opinion). This scenario aimed to reflect that in practice clinicians may prefer not to keep patients on treatment with erenumab indefinitely. At 64.5 weeks, patients entered a "re-evaluation period" health state, in which they remained for 12 weeks, representing a period of assessment. A proportion of patients were assumed to positively discontinue from this health state and maintain the same improvement in MMDs off treatment until the end of the time horizon, whilst the remaining patients returned to an "on treatment" state, from which they re-entered the "re-evaluation period" health state at a later assessment time point. In this scenario re-evaluations occurred periodically, every 76.5 weeks (64.5 weeks + 12 week re-evaluation period between each re-evaluation). This continued throughout the time horizon, with a decreasing number of patients undergoing re-evaluation each time due to movement of some patients to the positive discontinuation state during each re-evaluation. Details of the model structure in this scenario analysis are provided in Appendix X.

Features of the economic analysis

The cycle length employed in the Markov model was 12 weeks, which is the length of time deemed clinically adequate to observe a change in migraine outcomes.[81] This allowed for the administration of up to three doses of erenumab at four-week intervals, as would be expected in clinical practice. The primary endpoint was assessed at 12 weeks in Study 295, ARISE and LIBERTY, and whilst the primary analysis point for STRIVE was at 24 weeks, outcomes were

also assessed at 12 weeks. Features of the model are presented in Table 48. The rationale for the model structure has been discussed previously in Section B.3.2.

Table 48: Features of the economic analysis

	Previous appraisals	Current appraisal	
Factor	**Botulinum toxin[113]**	**Chosen values**	**Justification**
Model structure	Markov model	Decision tree plus Markov model	This approach was chosen as a review of the IHS clinical guidelines and consultation with clinical experts suggested that change in MMDs as well as percentage response to treatment were important outcomes in migraine prophylaxis.[6, 9] The model structure allows both outcomes to be captured and tracked. In the model produced for TA260, the model structure consisted of health states defined by bands of MHD frequency. The model structure employed for erenumab avoids the use of arbitrarily defined cut-off frequencies by instead reproducing patient distributions across individual MMD frequencies directly from clinical trial data for each treatment and time point, and by response status. This allows the model structure to capture information that is lost by the use of health states defined as bands of MMD/MHD frequency allowing a reflection of costs and QALYs per MMD frequency. See Section B.3.2 for further discussion on rationale for *de novo* model structure
Time horizon	2 years	10 years	A time horizon of 10 years was considered an appropriate duration over which to fully capture the costs and benefits of erenumab. The two-year time horizon used in the botulinum toxin submission was not deemed to be appropriate, as the literature recommends employing a longer time horizon to model chronic conditions like migraine.[114-116] Furthermore, the only available data on long-term outcomes for botulinum toxin suggest that 68% of patients continue to receive treatment after two years, indicating that a two-year time horizon might be inadequate to fully capture all cost and benefits. It is anticipated that some patients might continue treatment with erenumab for longer than two years.[11] A time horizon of 10 years is also consistent with the time horizon used when evaluating biologics for other chronic

			diseases such as severe allergic asthma, chronic spontaneous urticaria and plaque psoriasis.[13, 117] Scenario analyses exploring alternative time horizons were conducted
Source of utilities	Patient-level MSQ data from clinical trials	Patient-level MSQ v.21 data from Study 295, STRIVE and ARISE mapped onto EQ-5D utility scores (values ranged from 0.383 to 0.839).	The NICE reference case stipulates that EQ-5D-3L reported directly by patients is preferred and that valuation should be reflective of a sample of the UK population. The NICE methods guide promotes mapping from other HRQoL measures to EQ-5D in the absence of EQ-5D data.[118] EQ-5D data were not collected in Study 295 in chronic migraine and therefore the only way to capture utility values across the whole migraine population, including patients classified as chronic migraine, was to map patient-level MSQ data from Study 295, STRIVE and ARISE onto EQ-5D-3L (LIBERTY did not collect MSQ data). Utilities were therefore derived from MSQ data. In the erenumab clinical trial programme, EQ-5D was only collected in the LIBERTY study in patients classified as having episodic migraine and, within this study, only at treatment appointments. Thus, the majority of patients would not have been experiencing a migraine at the time of EQ-5D measurement since those patients experiencing a migraine are very likely to have postponed their visits to a time they were without migraine. As such, EQ-5D information was not typically collected during a migraine episode and instead LIBERTY EQ-5D data better reflects the health status of patients during the periods between migraines rather than during migraine episiodes. The MSQ questionnaire recall period was the previous four weeks at the point when the questionnaire was administered and MSQ is therefore more likely to capture the impact of migraine on patients' QoL over time. The MSQ questionnaire was considered to be a better source of HRQoL data than the HIT-6, as the MSQ mapping algorithm developed by Gillard *et al.* explains more of the variation in EQ-5D.[119] The Gillard *et al.* mapping algorithm was used to derive

			EQ-5D utilities from MSQ data in the NICE appraisal of botulinum toxin for chronic migraine[8]
Source of drug costs	Based on one 200 U vial of botulinum toxin at £276.40, and an administration cost of £116.00, leading to a total cost of £392.40 per 12-week cycle	Erenumab costs were based on Novartis' price for erenumab in the UK Botulinum toxin costs were taken from the BNF and NHS National Tariff	Established sources of drug costs within the NHS
Source of other costs	International Burden of Migraine study, PSSRU, NHS reference costs, Annual Survey on Hours and Earnings and International Burden of Migraine study (IBMS)	National Tariff, PSSRU 2016, National Health and Wellness Survey (NHWS) survey, BNF	Sources providing the appropriate granularity of costs as required by the model structure, and of relevance to the UK
Resource use	International Burden of Migraine study (IMBS)	NHWS survey	The NHWS survey is similar to the IBMS survey that informed resource use assumptions in TA260 in that it is a cross-sectional questionnaire administered over the internet to migraine patients. The NHWS survey was commissioned by Novartis to inform the inputs to the economic model for erenumab and provides more up-to-date data on resource use compared to the IBMS study (2017 versus 2010)
Health effects measure	QALYs	QALYs	NICE reference case
Discount rate for costs and QALYs	3.5% per year	3.5% per year	NICE reference case
Perspective	NHS	NHS/PSS	NICE reference case
Half cycle correction applied?	Yes	Yes for disease management and indirect costs, no for treatment costs	Half-cycle correction was applied to adjust for the bias of the assumption that transitions occur at the end or beginning of the cycle. Correction was applied only to costs and QALYs relating to MMD status, which change continuously over time, and not to treatment costs which occur over the full cycle length and hence are not at risk of bias.

Abbreviations: BNF: British National Formulary; EQ-5D: EuroQol Five-Dimensions; IBMS: Institute of Biomedical Science; MHD: monthly headache day; MMD, monthly migraine day; MSQ, Migraine-Specific Quality-of-Life Questionnaire; NICE: National Institute for Health and Care Excellence; NHWS: National Health and Wellness Survey; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year.
Source: Manufacturer submission of evidence: Botulinum toxin type A for the prophylaxis of headaches in adults with chronic migraine, 2011[113]

B.3.2.3 Intervention technology and comparators

Intervention

The intervention of interest in all patient populations was erenumab, which is available in two doses: 70 mg and 140 mg, self-administered subcutaneously at four-week intervals. The licensed posology for erenumab is 70 mg Q4W, however some patients may benefit from treatment with a higher dose of 140 mg Q4W. Both doses were studied in the key clinical trials which provided efficacy and safety inputs for erenumab in the economic model: Study 295 (70 mg and 140 mg), STRIVE (70 mg and 140 mg), ARISE (70 mg only) and LIBERTY (140 mg only).

In the base case, it was assumed that 50% of patients would initiate treatment on erenumab 140 mg, with the remaining 50% starting on erenumab 70 mg (referred to hereafter as the "blended dose"). These proportions are applied in the absence of long-term experience of erenumab in NHS clinical practice. It was assumed that patients would remain on the starting dose for the entire duration of their treatment as there is no evidence to support dose escalation. Furthermore, the SmPC does not include any provision for a dose escalation regimen, stating the following with regards to the licensed posology: "The recommended dose is 70 mg erenumab every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks".

However, as discussed in Section B.1.2.2, and as reflected in the licensed posology, starting on the higher dose of 140 mg may be more suitable for patients with more severe disease, including the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, the optimsed population considered in this submission. As shown in Section B.2.6.1, treatment with erenumab 140 mg leads to numerically superior clinical outcomes compared to erenumab 70 mg in this subgroup, with no relevant dose-dependent trend in AEs. Feedback from six expert UK neurologists has indicated that clinicians would be likely to initiate these difficult-to-treat patients on the 140 mg dose, given the trend towards better efficacy with this dose, and a comparable safety profile with erenumab 70 mg.[67] As such, the 140 mg dose is considered to represent an optimised dose for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. The assumption that 50% of patients initiate treatment on the 140 mg dose is therefore a conservative one, and it is anticipated that as clinical experience with erenumab increases, a higher proportion of patients for whom ≥3 prior prophylactic treatments have failed may initiate treatment on the 140 mg dose. Results for each patient population are therefore presented for both the blended dose, and for erenumab 140 mg only (see Table 47). Scenario analyses have also been conducted whereby the proportion of patients on 70 mg and 140 mg has been varied (see Section B.3.8.3). Results for the comparison in which all patients are assumed to receive 70 mg only are presented in Appendix Z. However, this dosing is not anticipated to reflect UK clinical practice for the optimised patient population of this submission in whom ≥3 prior prophylactic treatments have failed. These results have therefore been shown only for completeness.

Erenumab was modelled to be used in combination with BSC, defined as continued treatment with acute medication and healthcare resource use in line with the MMD frequency being experienced. Erenumab in combination with BSC as an intervention will hereafter be referred to simply as erenumab for ease of exposition.

Comparator

As discussed in Section B.1.2.2, the majority of patients for whom ≥3 prior prophylactic treatments have failed receive BSC in current clinical practice. There are no recommended

treatment options for patients classified as having episodic migraine for whom ≥3 prior prophylactic treatments have failed and whilst botulinum toxin is recommended for patients classified as having chronic migraine at this point in the clinical pathway, the availability of this therapy is restricted as administration must be performed by a trained specialist. BSC is therefore the most relevant comparator to erenumab for the patient population specified in the decision problem of this submission. Throughout Study 295, STRIVE, ARISE and LIBERTY, patients were prescribed any treatments deemed necessary to provide adequate supportive care, meaning that the placebo arms in these trials can be considered a reasonable proxy for BSC in UK clinical practice. Study 295, STRIVE, ARISE and LIBERTY therefore provide direct head-to-head evidence for erenumab versus the relevant comparator for migraine patients in whom ≥3 prior prophylactic treatments have failed.

BSC is also the relevant comparator in the subgroup and exploratory analyses in this submission. The subgroup analysis considered patients classified as having HFEM in whom ≥3 prior prophylactic treatments have failed; the exploratory analysis considered the population of patients for whom ≥2 prior prophylactic treatments have failed and are unsuitable for further treatment with a prophylactic therapy. Both of these populations would receive BSC in clinical practice.

As discussed in Section B.1.2.2, botulinum toxin has been recommended in patients classified as having chronic migraine for whom ≥3 prior oral prophylactic treatments have failed.[8] The use of botulinum toxin in this patient group is restricted as administration must be performed by trained expert physicians. Nevertheless, botulinum toxin is also considered a relevant comparator for the population of patients classified as having chronic migraine as it is available to some patients. The clinical trial of erenumab in chronic migraine (Study 295) compared erenumab against placebo and therefore no direct head-to-head comparison versus botulinum toxin was available. Comparative efficacy data versus botulinum toxin used to inform the model were instead derived from the ITC reported in Section B.2.8. In addition to presenting a comparison versus botulinum toxin as a stand-alone comparator in the chronic migraine population analysis, an exploratory analysis was conducted against a combined comparator of BSC/botulinum toxin which was modelled as a weighted combination of the BSC and botulinum toxin comparators. The weighting used was 72%/28%, as research suggests that approximately 28% of chronic migraine patients have access to botulinum toxin in clinical practice.[34] This exploratory analysis therefore aims to reflect the mix of current treatment options for chronic migraine patients in UK clinical practice.

The comparators considered for the base case, subgroup and exploratory analyses conducted for this submission are summarised in Table 49.

Table 49: Comparators for the patient populations considered in this submission

	Whole migraine population	Chronic migraine population	Episodic migraine population
≥3 prior treatments	"Whole population base case" • BSC	"Chronic migraine population" • BSC • Botulinum toxin	"Episodic migraine population" • BSC
Subgroup analyses	"HFEM and CM subgroup analysis" • BSC	N/A	"HFEM subgroup analysis" • BSC

Exploratory ≥2 prior treatment group analyses	"Exploratory whole population analysis" • BSC	"Exploratory chronic migraine analysis" • BSC	"Exploratory episodic migraine analysis" • BSC
Exploratory ≥3 prior treatment group analysis		"Exploratory chronic migraine analysis 2" • Botulinum toxin/BSC	

Abbreviations: BSC: best supportive care; CM: chronic migraine; HFEM: high-frequency episodic migraine; N/A: not applicable.

B.3.3 *Clinical parameters and variables*

Clinical parameters were derived from the subgroup of patients for whom ≥3 prior treatments had failed in Study 295, STRIVE, ARISE and LIBERTY. It was not possible to pool across all of these trials, as the criteria used to define the length of a qualified migraine headache differed between Study 295, and STRIVE, ARISE and LIBERTY (see Section B.2.3.1). Instead, the model employed data from Study 295 separately to pooled data from STRIVE, ARISE and LIBERTY. The analysis in the whole migraine population was performed by weighting the clinical outcomes (i.e. responder rates and MMD distributions) for the chronic migraine population (informed by Study 295) and the episodic migraine population (informed by STRIVE, ARISE and LIBERTY) according to the expected split between chronic migraine and episodic migraine patients in clinical practice amongst the population of patients for whom ≥3 prior prophylactics have failed. In the whole population base case, it was assumed that chronic migraine patients comprise 66% of the total population, and episodic migraine the remainder. This assumption was made based on market research from the UK, which indicated that two-thirds of patients in secondary care for whom ≥3 prior prophylactic treatments have failed are classified as having chronic migraine.[34] This is also supported by the results of a targeted literature review, with patients classified as chronic migraine comprising approximately two thirds of the total population of migraine patients for whom ≥3 prior prophylactic treatments have failed in two studies.[120, 121]

As discussed in Section B.3.2.1, in addition to the whole population base case analysis, analyses considering chronic migraine and episodic migraine populations separately were also conducted. Clinical parameters were derived from the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in Study 295 for the chronic migraine population, and the pooled STRIVE, ARISE and LIBERTY trials for the episodic migraine population (70mg dose: STRIVE and ARISE anf 140mg dose: STRIVE and LIBERTY). Pooling of the episodic migraine studies was based on the assumption that the trials were homogeneous, with no trial-level effect, and that the trials sampled from the same patient population, with the same baseline MMD frequency. Comparative data were also taken from these trials, with placebo assumed to be representative of BSC, as outlined in Section B.3. In the chronic migraine population analysis, comparative data were also derived from the results of an ITC of erenumab versus botulinum toxin (see Section B.2.8 for more details). Detailed descriptions of clinical parameters and variables informing the model are provided in the following sections.

B.3.3.1 Starting patient characteristics

The base case inputs for the model in terms of patient age and sex are detailed in Table 50, alongside their appropriateness in reflecting migraine patients considered in the decision problem. These inputs were based on the average age and proportion of females across all four trials (Study 295, STRIVE, ARISE and LIBERTY). The age and sex of the patient cohort needed

to be defined because it influenced the background mortality rates applied in the model. The same starting age and gender split were used regardless of the analysis chosen.

Table 50: Patient characteristics in the model

Model parameter	Value	Source and appropriateness for modelling UK migraine population
Mean age, years	42.25 years	Average from Study 295, STRIVE, ARISE and LIBERTY. Data from an analysis of migraine patients in the UK indicates an average age of 40 years[92]
Percentage female	84.51%	Average from Study 295, STRIVE, ARISE and LIBERTY. Data from an analysis of migraine patients in the UK indicates that the majority of migraine patients are female[122]

The model also required the baseline MMD distribution for the population to be specified. The MMD distributions for the whole migraine, chronic migraine and episodic migraine analyses are provided in Figure 20, Figure 21 and Figure 22, respectively, with the data presented in Table 51. These baseline distributions reflect the baseline distribution of patients pooled across erenumab and placebo arms in the clinical studies of erenumab relevant to each population definition (i.e. STRIVE, ARISE and LIBERTY for episodic migraine; Study 295 for chronic migraine). Each model treatment arm is therefore associated with the same baseline distribution of MMD frequencies, with the distribution being specific to the population under analysis. The baseline distribution of MMD frequencies for the whole population is bimodal since it was determined as the weighted average of the baseline MMD distributions in the chronic migraine and episodic migraine populations, with a weighting of 66:34 for chronic migraine:episodic migraine (section B.3.3).

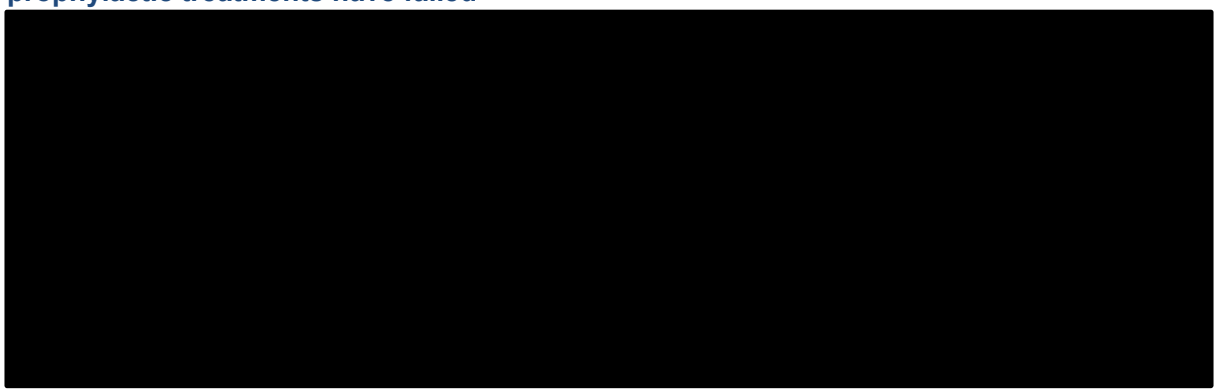
Figure 20: Histogram of baseline MMDs in the whole migraine population for whom ≥3 prior prophylactic treatments have failed

Abbreviations: MMD: monthly migraine day.

Figure 21: Histogram of baseline MMDs in the chronic migraine population for whom ≥3 prior prophylactic treatments have failed

Abbreviations: MMD: monthly migraine day.

Figure 22: Histogram of baseline MMDs in the episodic migraine for whom ≥3 prior prophylactic treatments have failed



Abbreviations: MMD: monthly migraine day.

Table 51: Baseline MMDs in the whole, chronic and episodic migraine patient populations

MMD	Whole migraine population	Chronic migraine	Episodic migraine
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]
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]
Mean MMDs	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.

B.3.3.2 Change in MMDs over the assessment period

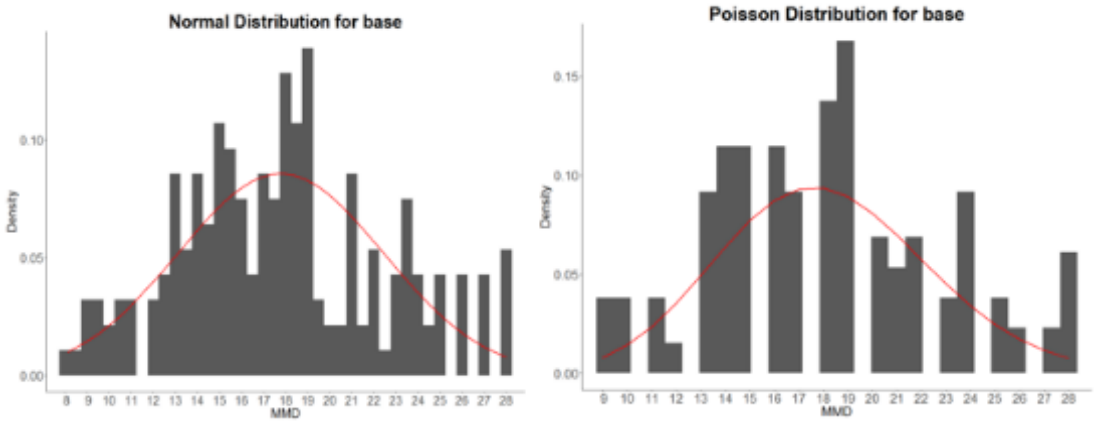
The model captured the distribution of patients across the frequency of MMDs based on patient-level MMD data available from all four studies (Study 295, STRIVE, ARISE and LIBERTY). Analysis of the patient-level trial data allowed the proportion of patients experiencing a given MMD frequency to be captured, by treatment group (erenumab or placebo) and by timepoint. For the cost-effectiveness model, the distribution of MMD frequency was analysed for the below patient categories and timepoints, in both the erenumab and placebo arms. This analysis was performed separately for chronic and episodic migraine populations. These are the patient groups for whom it was possible to calculate the MMD distribution:

- All patients at baseline
- All patients at 12 weeks
- Responders at 12 weeks (responders classed as those obtaining a ≥50% reduction in MMDs from baseline – see Section B.3.3)
- Non-responders at 12 weeks

An exploratory data analysis was conducted to summarise and characterise the features of the patient-level trial data and provide the variables required for statistical analysis of the data. This exploratory data analysis is summarised in Appendix S.

Having analysed the direct trial data, the fitting of statistical distributions to the data was explored to model the predicted proportion of patients associated with each possible frequency of MMDs (see illustrative example of the concept in Figure 23).

Figure 23: Illustrative examples of fitting of statistical distribution to trial data



Abbreviations: MMD: monthly migraine day.

Statistical distributions were fitted separately to the patient-level data for Study 295 in chronic migraine and the pooled patient-level data from STRIVE, ARISE and LIBERTY in episodic migraine. For the analyses in the chronic and episodic migraine populations specifically, the proportion of patients with a given frequency of MMDs was drawn from the appropriate distribution (i.e. Study 295-derived distribution for chronic migraine; STRIVE, ARISE and LIBERTY-derived distribution for episodic migraine). For the base case analysis in the whole population, the proportion of patients with a given frequency of MMDs was drawn as the weighted average of the proportions provided by each of the two statistical distributions, with the weighting of 66:34 for chronic migraine:episodic migraine, as noted previously (Section B.3.3).

A number of statistical distributions were explored for fit to the data: normal, gamma and poisson. Full details of the statistical distribution fitting exercise are provided in Appendix S. The Akaike Information Criterion was used to assess the fit of the statistical model to the data. In the base case the normal distribution was selected based on this model returning the mean MMD values closest to those of the raw trial data. The parameters for the normal statistical distributions used in the base case analysis are provided in Appendix S.

The output of the fitting of the statistical models was the predicted proportions of patients associated with each frequency of MMDs (i.e. the distribution of the cohort across MMD frequencies). The distribution at baseline is provided earlier in the submission in Section B.3.3.1 as a starting patient characteristic. The distributions at 12 weeks for erenumab 70 mg, erenumab 140 mg and BSC are summarised in Figure 24 below for each of the three main analyses (whole population base case, chronic migraine population and episodic migraine population). These figures provide a summary across responders and non-responders at 12 weeks. MMD distributions for responders versus non-responders separately in each population are provided in the cost-effectiveness model.

Patient-level data were not available to fit equivalent distributions for botulinum toxin. Therefore, for the comparison to botulinum toxin in chronic migraine, it was assumed that botulinum toxin was associated with the same MMD distribution for a given category of patients as the selected erenumab intervention (blended dose, 70mg or 140mg) (i.e. it was assumed that a responder or non-responder to botulinum toxin at 24 weeks was associated with the same distribution of MMDs as a responder or non-responder, respectively, to erenumab at 12 weeks). This means that differences in effectiveness of erenumab and botulinum toxin were modelled solely as differences in the proportion of patients classified as responders versus non-responders.

Figure 24: Histograms of MMD frequency distribution at 12 weeks predicted by the statistical model (comprised of responders and non-responders)

Abbreviations: BSC: best supportive care; MMD: monthly migraine day.

B.3.3.3 Response assessment at 12 weeks

As described in Section B.3.2.2, response was defined by a ≥50% reduction from baseline in MMDs. The response rates for erenumab and BSC were taken directly from the trial data analysis of Study 295 for the chronic migraine population. For the episodic population, response rates were based on pooled patient data from STRIVE, ARISE and LIBERTY providing an overall episodic migraine response rate of [redacted] for erenumab 70 mg, [redacted] for erenumab 140mg and [redacted] for placebo (reflecting BSC). The whole population base case consisted of a 66:34 weighting for chronic migraine: episodic migraine distributions as described previously. The response rate for chronic migraine was then applied to the chronic migraine cohort and the response rate for episodic migraine was applied to the episodic cohort. In all cases, the response rates used were those corresponding to the subgroup of patients for whom ≥3 prior prophylactic therapies had failed and for the relevant dose.

The relative efficacy in terms of probability of response for botulinum toxin was based on the odds ratio of response from the comparison to erenumab in the ITC presented in Section B.2.8. Specifically, the odds ratio used was that from the ITCs for the ≥50% responder rate where the definition of response for erenumab was based on reductions in MMDs and for botulinum toxin was based on MHDs (Table 40; an odds ratio of [redacted] for erenumab 70 mg versus botulinum toxin and Table 41; an odds ratio of [redacted] for erenumab 140 mg versus botulinum toxin).

The probabilities of response for each treatment in the relevant populations are provided in Table 52 below. It should be noted that whilst the probabilities of response for erenumab 70 mg, erenumab 140 mg and BSC correspond to response probabilities at 12 weeks, the time point for assessment of response to botulinum toxin is 24 weeks. The odds ratios of [redacted] and [redacted]

derived from the ITCs corresponded to a comparison of the MMDs responder rate for erenumab at 12 weeks with the MHD responder rate for botulinum toxin at 24 weeks. Therefore, the relative response probabilities derived from applying the odds ratios of [redacted] and [redacted] accurately reflect assessment of erenumab at 12 weeks and botulinum toxin at 24 weeks. It should be noted that this is likely conservative with respect to the cost-effectiveness of erenumab, assuming that response rates are likely to increase from Week 12 to Week 24.

As described in Section B.2.6, the population of patients for whom ≥3 prior prophylactic treatments had failed comprised those who had failed on treatments from ≥3 protocol-defined categories. However, in order to most accurately reflect the decision problem, the economic model and ITC utilised data from patients who had failed on ≥3 prior prophylactic treatments irrespective of category. This generated slightly more conservative (lower) probabilities of response but, as mentioned above, most accurately reflects the decision problem, and also fully aligns with the treatment failure definition employed in UK clinical practice and the NICE guidance for botulinum toxin. A comparison of the probabilities of response based on these two definitions is provided in Appendix T for completeness.

Table 52: Probability of response for each treatment

Treatment	Probability of response	
	Chronic migraine	Episodic migraine
Erenumab 70 mg	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Botulinum toxin (chronic migraine only)*	[redacted]	N/A

*Note: probability of response to botulinum toxin was assessed at 24 weeks. The response rates provided in the table are based on application of the odds ratios derived from the ITC to the response rate for the specified erenumab dose
Abbreviations: BSC: best supportive care; N/A: not applicable.

B.3.3.4 Long-term efficacy

It was assumed that those on treatment maintained the improved number of MMDs achieved when response was established, over the full post-assessment period. This assumption is supported by data from an ongoing OLE study of a phase II trial of erenumab in episodic migraine.[78] Of 472 patients enrolled in the initial 12-week RCT, 383 continued into the OLE study, receiving erenumab at a dose of 70 mg for a median duration of 575 days (range: 28–822 days). At Week 64, patients achieved a mean reduction of 5.0 (SD: 4.2) MMDs from a baseline of 8.8 MMDs (SD: 2.6), with 65% of patients achieving a reduction of ≥50% in MMDs from baseline, indicating that reduction in MMD frequency was maintained in the long term. These results were associated with improvements in HIT-6 and MSQ scores, which were maintained through to Week 64. Furthermore, this assumption is also supported by an OLE of Study 295 in patients with chronic migraine. In this study, the mean (95% CI) change from Study 295 baseline in MMDs was –8.36 (95% CI: –8.92, –7.80) days at Week 24 and –9.29 (95% CI: –9.96, –8.62) days at Week 52 for the 549 patients who received either erenumab 70 mg, erenumab 140 mg or a combination of erenumab 70 mg followed by erenumab 140 mg over the course of the OLE

(see Section B.2.10).[123] Finally, this assumption is supported by a targeted literature review assessing the long-term progression of patients treated with prophylactic therapies.[124] Ten studies examining either erenumab, botulinum toxin, beta blockers or topiramate in migraine patients found that the efficacy of these drugs was maintained over the long-term (≥1 year), with prolonged treatment shown to be associated with sustained benefits and improvements in QoL.[125-129]

B.3.3.5 Discontinuation

The base case of the cost-effectiveness model captured three forms of discontinuation:

- Discontinuation due to non-response at the end of the assessment period
- Discontinuation due to adverse events over the assessment period
- Discontinuation in the long-term

Discontinuation due to non-response at the end of the assessment period

As discussed in Section B.3.2.2, all non-responders transitioned into the discontinuation state at the end of the assessment period, and were assumed to continue to receive only BSC and to maintain the non-responder MMD improvement achieved at Week 12 until the end of the time horizon. This was considered an appropriate assumption as it reflects a regression to the mean: in other words, if we assume that at least some patients entered the study whilst experiencing higher than usual disease severity (i.e. baseline frequency of MMDs was above "normal") then the improvements observed in non-responders over the assessment period reflects the regression of the average MMD frequency across patients to the true mean baseline MMD frequency of the group of patients who do not respond to treatment.

Scenario analyses explored different assumptions of non-response being associated with the distribution of MMDs observed for all patients treated with BSC at 12 weeks or rebounding to baseline distribution of MMDs. The former assumption lacks some face validity, as it manifests as an actual improvement in the MMD distribution for non-responders in the post-assessment period relative to the week 12 distribution. Assuming that non-responders in each treatment group revert to baseline MMD distributions after week 12 implies differing overall treatment effect on non-responders in the post-assessment period depending on the treatment received.

Discontinuation due to adverse events over the assessment period

Patients could also discontinue due to treatment-specific AEs over the assessment period (12 weeks for erenumab and BSC, 24 weeks for botulinum toxin). Probabilities of discontinuation for erenumab and BSC were based on data from the Study 295, STRIVE, ARISE and LIBERTY clinical trials. The rates of AEs at 24 weeks in STRIVE were converted to 12-week AE rates from reported risk values using the rate-probability conversion equation reports in Fleurence *et al*. (2007).[130] For botulinum toxin in the chronic migraine analysis, the probability of discontinuation due to AEs was based on a study of Diener *et al.* 2014 (see Table 53).[131] Patients who discontinued due to AEs also transitioned into the discontinuation state and were similarly assumed to receive BSC. Patients discontinuing due to AEs were assumed to rebound to the baseline MMD distribution. Scenario analysis explored a different assumption of patients in the AE discontinuation state instead being associated with the distribution of MMDs observed for patients on BSC at 12 weeks.

Table 53: Probability of discontinuation due to AEs over the assessment period for erenumab, BSC and botulinum toxin

Treatment	Probability of discontinuation due to AEs over assessment period		
	Chronic migraine	Episodic migraine	Whole population
Erenumab 70 mg	0.00%	1.43%	1.08%
Source	*Study 295*	*STRIVE, ARISE & LIBERTY*	*Weighted average of chronic migraine and episodic migraine probabilities*
Erenumab 140 mg	1.06%	0.80%	0.88%
Source	*Study 295*	*STRIVE, ARISE & LIBERTY*	*Weighted average of chronic migraine and episodic migraine probabilities*
BSC	0.71%	0.82%	0.79%
Source	*Study 295*	*STRIVE, ARISE & LIBERTY*	*Weighted average of chronic migraine and episodic migraine probabilities*
Botulinum toxin (chronic migraine only)*	3.40%	N/A	N/A
Source	*Diener et al. (2014)*[131]	*N/A*	*N/A*

*As stated above, botulinum toxin is only a relevant comparator for a subpopulation of chronic migraine patients.
Abbreviations: AE: adverse event; BSC: best supportive care; N/A: not applicable.

Discontinuation in the long-term

Finally, from the assessment period onwards, those remaining on treatment (i.e. responders) were at a constant per-cycle risk of discontinuation, which aimed to capture both patient- and clinician-led discontinuation in the longer-term. This constant per-cycle discontinuation rate was 2.38%, based on the long-term discontinuation observed for patients receiving erenumab 70 mg in the ongoing OLE study of a phase II trial of erenumab.[78] As with other discontinuers, these patients were similarly assumed to receive only BSC. It was assumed that patients discontinuing in this manner reverted to the baseline distribution MMDs. Scenario analysis explored a different assumption of patients in the long-term discontinuation state instead being associated with the distribution of MMDs observed for patients on BSC at 12 weeks.

B.3.3.6 Mortality

The model assumed there to be no excess mortality associated with migraine, and no mortality differentiation between treatments. This assumption was supported by a recent meta-analysis, which showed no association between migraine and all-cause mortality.[132] As such, only general population mortality was included in the model. The rates employed were based on the ONS National Life Tables in England and Wales for the years 2014–2016 which are specific to age and sex.[133]

B.3.3.7 Adverse events

Expert advice from UK clinicians stated that AEs associated with migraine prophylaxis are usually non-severe, consistent with the reported AE profile of erenumab in Section B.2.10. As such, AEs were not explicitly included in the cost-effectiveness model. Adverse events were accounted for in terms of their influence on treatment discontinuation but were not explicitly modelled in terms of events with a cost or HRQoL impact. As discussed in Section B.2.9, the proportion of patients experiencing SAEs when treated with erenumab was found to be low across all three trials (SAEs were reported by 1.1%, 1.9% and 1.7% of patients treated with erenumab 140 mg in Study 295, STRIVE and LIBERTY, and 3.2%, 2.5% and 1.1% of patients treated with erenumab 70 mg in Study 295, STRIVE and ARISE, respectively) and comparable to that seen with placebo. Therefore, it is expected that the cost and HRQoL impact of SAEs would be minimal, and comparable between BSC and erenumab. The approach of not explicitly including specific adverse events is consistent with the approach taken in the NICE appraisal for botulinum toxin in chronic migraine, in which botulinum toxin was considered to be generally well tolerated.[8]

B.3.4 *Measurement and valuation of health effects*

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

Study 295, STRIVE, ARISE and LIBERTY all collected migraine-specific patient-reported outcomes (PROs), with the results of these presented in Section B.2.5.

The NICE reference case stipulates that EQ-5D, reported directly by patients/carers, is the preferred measure of HRQoL in adults, and that valuation of HRQoL should reflect the preferences of a representative sample of the UK population.

EQ-5D data were not collected in Study 295, and therefore the only way to capture utility values across the whole migraine population, including patients classified as chronic migraine, was to map patient-level MSQ v2.1 data from Study 295, STRIVE and ARISE onto EQ-5D-3L (LIBERTY did not collect MSQ data). The MSQ v2.1 represents a migraine-specific PRO that has previously been mapped to EQ-5D-3L.[119] EQ-5D-5L data were available from the LIBERTY study in patients classified as having episodic migraine. However, these data were not considered appropriate to inform utility values in the model, as described previously (See Table 48). The EQ-5D-5L questionnaire reflects a patient's self-assessment at a single point in time as it asks patients to complete the questionnaire based on how they feel "today". In the LIBERTY study EQ-5D data were captured only at treatment appointments. Thus, the majority of patients would not have been experiencing a migraine at the time of EQ-5D measurement since those patients experiencing a migraine are very likely to have postponed their visits to a time they were without migraine. As such, EQ-5D information was not typically collected during a migraine episode and instead LIBERTY EQ-5D data better reflects the health status of patients during the periods between migraines. In contrast to EQ-5D, MSQ has a four-week recall period. Patients in Study 295 and STRIVE were asked to complete the MSQ questionnaire during scheduled visits to the clinic, and recall the last four weeks whilst completing the questionnaire. Therefore, MSQ is more sensitive to changes in the quality of life impact of migraine, and utility values mapped from MSQ v2.1 data collected in Study 295, STRIVE and ARISE were used in the base case of the economic analysis. It should be noted that the NICE appraisal of botulinum toxin in chronic migraine also used MSQ mapped to EQ-5D to inform utility values.[8]

B.3.4.2 Mapping

As described above, MSQ data from Study 295, STRIVE and ARISE were mapped onto EQ-5D-3L to provide the base case utility values across the whole migraine population. MSQ data were not collected in the LIBERTY study.

MSQ data were mapped onto EQ-5D using the framework and algorithms outlined by Gillard *et al.* (2012).[119] This study was identified by the SLR reported in Section B.3.4.3 and is the source used in the NICE appraisal of botulinum toxin in chronic migraine.[8] This provided separate algorithms to map MSQ scores to utility values for chronic and episodic migraine, and for each population provided alternative options of a "simple" algorithm (utility explained only by questionnaire scores) and a "preferred" algorithm (including additional explanatory variables such as co-morbidities). As the trial data did not provide information on employment status or comorbidities that could readily be included in the mapping algorithm, it was considered appropriate to use the "simple" algorithm. The simple algorithms for chronic and episodic migraine are provided below:

Equation 1: MSQ algorithm in chronic migraine

$$EQ5D = -0.0492B_0 + 0.0065MSQ_{RP} + 0.0013MSQ_{RR} + 0.0011MSQ_{EF}$$

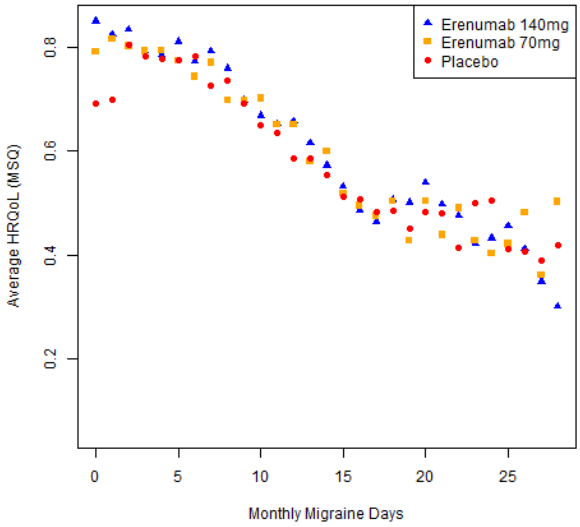
Equation 2: MSQ algorithm in episodic migraine

$$EQ5D = 0.2858B_0 + 0.0029MSQ_{RP} + 0.001MSQ_{RR} + 0.0027MSQ_{EF}$$

Whilst initially it was considered suitable for the choice of mapping algorithm to be based on the trial (with the chronic migraine algorithm used for Study 295 and the episodic migraine algorithm used for STRIVE and ARISE), it was subsequently decided more appropriate to apply the algorithm at an individual patient level based on their baseline number of migraine days and headache days (i.e. the chronic algorithm would be applied if patients had ≥8 MMDs and ≥15 headache days per month at baseline and episodic otherwise. The rationale for applying a utility algorithm based on the current migraine status is provided by (Gillard *et al*. 2012).[119] They stated that, "in developing separate mapping models for chronic and episodic migraine, the potential for over prediction of utility values for individuals in poor health (i.e., individuals with chronic migraine) is reduced". This suggests that using one particular algorithm for each trial would not accurately predict the utilities for patients who had a significant change in MMD frequency. The rationale for combining the MSQ data from Study 295, STRIVE and ARISE was to avoid sparse data which would skew the relationship between monthly migraine day frequency and utility.

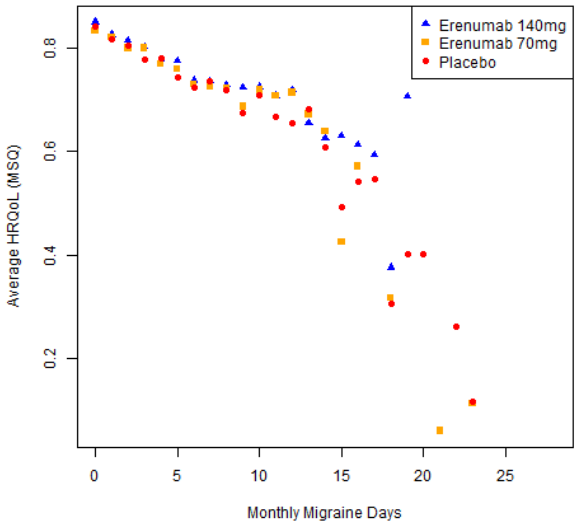
The average MSQ-derived utility values by MMD frequency from Study 295, STRIVE and ARISE datasets individually are provided in Figure 25, Figure 26 and Figure 27, respectively. The equivalent figure for the combined dataset across Study 295, STRIVE and ARISE is provided in Figure 28. A slight treatment effect can be seen, in that patients receiving erenumab 140 mg have a higher utility for a given MMD frequency than those treated with erenumab 70 mg or placebo.

Figure 25: Average MSQ-derived utility for each MMD frequency in Study 295



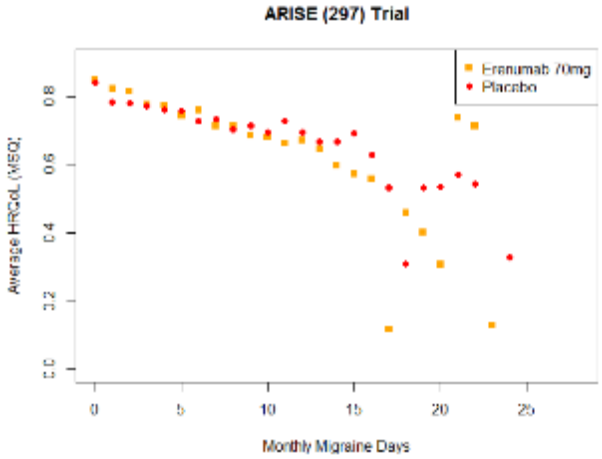
Abbreviations: HRQoL: health-related quality of life; MSQ: Migraine-Specific Quality of Life Questionnaire.

Figure 26: Average MSQ-derived utility for each MMD frequency in STRIVE



Abbreviations: HRQoL: health-related quality of life; MSQ: Migraine-Specific Quality of Life Questionnaire.

Figure 27: Average MSQ-derived utility for each MMD frequency in ARISE



Abbreviations: HRQoL: health-related quality of life; MSQ: Migraine-Specific Quality of Life Questionnaire.

Figure 28: Average MSQ-derived utility values for each MMD frequency in the combined analysis of Study 295, STRIVE (296) and ARISE (297)

Abbreviations: HRQoL: health-related quality of life; MSQ: Migraine-Specific Quality of Life Questionnaire.

Regression analysis

Fitting of statistical distributions to both the combined trial dataset and the individual trial datasets was explored. The derived MSQ utility values were transformed into a disutility by subtracting the utility value from 1, and a statistical model was fitted to predict these disutility values. The disutility predicted by the statistical distributions for each MMD frequency was then retransformed (by subtracting the disutility from 1) to provide utility values for each MMD frequency. Full details of the fitting of statistical regression models are provided in Appendix U.

Although Figure 28 suggests the presence of a treatment effect on utility values it was decided not to include this potential effect in the regression equation, which represents a conservative assumption. The statistical models explored therefore included MMD frequency as the only covariate. Initially, generalised estimating models, which account for the repeated observations for each patient over the duration of the clinical studies, were considered. However, after further exploration of various statistical models, a multilevel model was chosen to account for individual subject level variation and the presence of trial effects when analysing the combined trial data. The multilevel model chosen had a normal link function and was fitted to the combined trial data using a linear mixed effects model (lmer package in R).

The multilevel regression model was fitted separately to Study 295 data, and pooled STRIVE and ARISE data. A multilevel model was also fitted to all three studies combined. These models are summarised in Table 54. The multilevel model across Study 295, STRIVE and ARISE was selected for the base case analysis in all populations. The resultant utility values for each MMD frequency are provided in Appendix U.

Table 54: Multilevel regression models predicting disutility due to MMD frequency for Study 295, STRIVE and ARISE

	Multilevel Model (Combined Study 295, STRIVE and ARISE, Normal)	Multi-Level Model (Study 295, Normal)	Multi-Level Model (STRIVE and ARISE, Normal)
MMD frequency	0.0163 (0.0024)	0.0206 (0.0005)	0.0140 (0.0004)
Constant	0.1614 (0.0157)	0.1353 (0.0062)	0.1768 (0.0034)

Abbreviations: MMD: monthly migraine day.

B.3.4.3 Health-related quality-of-life studies

In line with the NICE guide to the methods of technology appraisal,[118] an SLR to identify relevant utility studies was performed. Full details of the search strategy of the SLR can be found in Appendix H.

The SLR identified 25 publications meeting the eligibility criteria for utilities studies, corresponding to 22 unique studies. Of these, 16 publications (13 studies) reported EQ-5D utility values and the remaining studies reported utility values elicited using an alternative utility measure. Full details of these utility studies are presented in Appendix H. None of the studies identified reported utility values for each MMD frequency, and instead either provided utility values for grouped MMD frequencies, by definition of migraine (chronic or episodic) or did not refer to MMD frequencies at all. The economic model submitted for botulinum toxin also used MSQ-derived utility values via mapping of MSQ to EQ-5D. The algorithm used by the manufacturer was redacted in the submission.

In summary, none of the identified studies in the literature provided utility values to the level of granularity commensurate with the structure of the erenumab cost-effectiveness model. Therefore, in order to provide the utilities required for the model, MSQ values from the erenumab clinical trials mapped onto EQ-5D were used to generate utility values for each MMD frequency, as previously described (See section B.3.4.2).

B.3.4.4 Disutilities associated with adverse events and mode of administration

As discussed in Section B.3.3.7, expert advice from UK clinicians stated that AEs associated with migraine prophylaxis are usually non-severe, and therefore decrements in utility due to AEs were not included in the model. This is supported by the clinical evidence base for erenumab, where SAE rates were seen to be comparable to that of placebo (see Section B.2.9). Scenario analyses were conducted in which disutilities due to mode of administration of treatments were incorporated. These disutilities were based on a vignette-based time trade-off (TTO) study, details of which are presented in Appendix U.

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

As discussed in Section B.3.4.3, the studies found in the SLR did not report utility values for each MMD frequency. Therefore, utility values mapped from MSQ v2.1 data collected in Study 295, STRIVE and ARISE were used in the economic model. The utility values at each MMD frequency (see Appendix U) were used to inform utility values for the population in question based on that population's distribution of MMDs. For example, responders to treatment with erenumab at Week 12 in the chronic migraine population would be associated with utility based on the MMD distribution for erenumab responders in this population. As with efficacy inputs, utilities for the whole migraine population were based on a weighting of the observed MMD distributions (and hence utilities) for the chronic and episodic populations. It should be noted that for modelling of botulinum toxin in chronic migraine patients, the utility values for each health state (i.e. responders, non-responders) are identical to those for erenumab 140 mg, as the same distribution of patients across MMD frequencies is assumed. The calculated mean values for each health state are presented in Table 55 below.

Table 55: Mean utility values for each health state

	Assessment period			Post-assessment period			
	Baseline	Responders	Non-responders	On treatment	Negative disc (non-response)	Negative disc (AE-related)	Negative disc (long-term)
Whole migraine							
Erenumab 70 mg	0.577	0.743	0.601	0.741	0.601	0.577	0.577
Erenumab 140 mg	0.577	0.762	0.603	0.761	0.603	0.577	0.577
Placebo	0.577	0.746	0.592	0.741	0.592	0.577	0.577
Chronic migraine							
Erenumab 70 mg	0.466	0.735	0.491	0.735	0.491	0.466	0.466
Erenumab 140 mg	0.466	0.752	0.512	0.752	0.512	0.466	0.466
Placebo	0.466	0.731	0.495	0.731	0.495	0.466	0.466
Episodic migraine							
Erenumab 70 mg	0.688	0.769	0.695	0.760	0.695	0.688	0.688
Erenumab 140 mg	0.688	0.784	0.686	0.779	0.686	0.688	0.688
Placebo	0.688	0.770	0.685	0.756	0.685	0.688	0.688

Abbreviations: AE: adverse event.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted to identify cost and resource use data for patients with migraine in July 2017, and was updated in January 2018. Full details of the search strategy and results of this SLR are presented in Appendix I.

In total, the SLR identified 22 publications meeting the eligibility criteria for cost and resource studies, corresponding to 19 unique studies. Full details of these studies are presented in Appendix I. Types of resource use reported across the identified studies included healthcare practitioner use (GP visits, neurologist consultations), hospitalisation, emergency department/A&E visits and use of acute migraine medications (e.g. triptans). None of the studies identified reported costs and resource use for each MMD frequency, and instead either grouped resource use by health state, or definition of migraine (chronic or episodic).

B.3.5.1 Intervention and comparators' costs and resource use

Intervention and comparator costs

As discussed in Section B.1.2.2, the most relevant comparator for erenumab in this submission is BSC, across all populations. As noted in Section B.1.2.2, in UK clinical practice BSC is defined as continued treatment with acute medication and healthcare resource use in line with the monthly migraine days experienced. BSC was not considered to be associated with any drug acquisition or administration costs, given that both erenumab and botulinum toxin are used in conjunction with BSC.

The unit cost and resource use associated with the acquisition and administration of erenumab 70 mg, erenumab 140 mg and botulinum toxin are provided in Table 56. The list price of erenumab is £386.50 per 70 mg dose (1 x 70 mg pre-filled pen)), with a patient access scheme (PAS) providing a confidential fixed net price of erenumab at £[redacted] per 70 mg dose and £[redacted] per 140 mg dose. The list price of botulinum toxin is £276.40 per 200 IU vial, as per the dose recommended in the botulinum toxin SmPC for chronic migraine (total dose range of 155 to 195 units).[134, 135] This price was based on the current price listed in the British National Formulary (BNF). Botulinum toxin is not associated with any PAS and it was assumed that there was no vial sharing. Costs for botulinum toxin were applied only for the analysis in the chronic migraine patient population for which botulinum toxin represented a relevant comparator.

In addition to treatment acquisition costs, erenumab was also associated with a one-off cost for self-administration training. This cost was assumed to be £40.04, based on the cost of one hour of working time for a Band 5 hospital nurse,[136] and was only applied once as a single training cost. After receiving this training, patients were assumed to be able to self-inject erenumab. In contrast, botulinum toxin requires a trained specialist to perform each administration, which entails a series of over 30 injections every 12 weeks. As such, this is associated with a considerably greater administrative burden, incurring a cost per dose of £116.00, based on the cost of attending one follow-up appointment.

Table 56: Treatment costs for erenumab and comparators (per cycle)

	Erenumab 70/140 mg		BSC	Botulinum toxin	Source	Description
	70 mg	140 mg				
Drug costs (per dose)	*List price:* £386.50 (1 x 70 mg pre-filled pen) *Price with confidential PAS:* £[redacted] per pack of 1 x 70 mg pre-filled pen	*List price:* £773.00 (two packs of 1 x 70 mg pre-filled pen). [redacted] *Price with confidential PAS:* £[redacted] for two packs of 1 x 70 mg pre-filled pen	£0.00	£276.40 per 200 IU vial	BNF 2017[134]; Novartis data on file	The cost per dose of botulinum toxin assumes there to be no vial sharing, as per TA260[8]
Frequency per cycle	3		N/A	1	SmPC[16]	
Administration costs per cycle	£0.00		£0.00	£116.00	NHS Tariff 2017[137]	Assumed to be the tariff "WF01A Follow Up Attendance - Single Professional (code 400)" in the non-mandatory prices worksheet
Treatment costs per cycle	List price: £1,159.50 Price with confidential PAS: £[redacted] (3 x one monthly injection)	List price: £2,319.00 Price with confidential PAS: £[redacted] (3 x one monthly injection)	£0.00	£392.40		Based on drug costs per cycle plus any administration costs
Initiation costs	£40.04		£0.00	£0.00	PSSRU 2017[136]	One-off cost (for training of the patient on how to use injection) was assumed to be cost of one working hour (not patient contact hour) of a Band 5 hospital nurse as reported in pg. 217, Table 14 (£37) (Hospital-based nurses of the (PSSRU, 2017)) and £3.04 to account for nurse training (Table 19.1, £75,156, per 15.7 years) and (Table 14: Mean annual 1573 working hours)

Abbreviations: BNF: British National Formulary; BSC: best supportive care; N/A: not applicable; NHS: National Health Service; PAS: patient access scheme; PSSRU: Personal Social Services Research Unit.; SmPC: Summary of Product Characteristics.

B.3.5.2 Health-state unit costs and resource use

As previously described, the health states within the model were associated with a given MMD distribution. The extent of background disease management and thus resource utilisation required by patients is dependent on number of MMDs; disease management costs were applied to all patients dependent on MMD frequency, regardless of treatment status. Therefore, the overall mean management costs associated with a particular health state were represented by the weighted average of the costs per MMD, given the distribution of MMDs within that particular health state for erenumab 70mg, erenumab 140mg and BSC. For botulinum toxin we assume the same health states costs and resource use per MMD as erenumab. The components of disease management included in the model were as follows:

- Emergency department (A&E) visits
- Hospitalisations
- General practitioner visits
- Nurse practitioner visits
- Neurologist visits
- Migraine-specific medication (assumed to be represented by triptan use)
- Other medication (assumed to be represented by analgesics)

The unit costs employed in the model for each of these disease management components are presented in Table 57. The methodology for the calculation of the average cost per day of migraine-specific medication and other medication is provided in Appendix V.

Table 57: Disease management costs used in the economic analysis

Unit Costs	Cost (£)	Source	Description
A&E visit	£130.00	NHS Tariff 2017[137]	HRG code "VB08Z" in the A&E worksheet of the 2017/2018 National tariffs
Hospitalisation (per stay)	£574.00	NHS Tariff 2017[137]	Calculated as the non-elective tariff for code AA31E (Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0–6) in worksheet "1 APC & OPROC" of the 2016/2017 tariffs
GP visit	£37.00	PSSRU 2017[136]	Cost of a surgery consultation lasting 9.22 minutes (Table 10.3b General practitioner — unit costs, pg162, PSSRU, 2017). A consultation length of 11.7 minutes was used in the in the NICE costing template (NICE-TA260 2012)

Nurse practitioner visit	£36.00	PSSRU 2017[136]	Assumed be the cost of an hour of a nurse time which is £36.00
Neurologist visit	£125.00	NHS Tariff 2017[137]	Assumed to be the "Follow Up Attendance - Single Professional (WF01A)" for a Neurology outpatient visits (code 400) in the non-mandatory prices of the 2016/2017 NHS tariffs
Triptans per day	£2.55	NHS Tariff 2017[137]	Detailed in Appendix V
Other medication per day	£0.27	NHS Tariff 2017[137]	Detailed in Appendix V

Abbreviations: A&E: Accident and Emergency; GP: General Practitioner; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

Frequency of resource use for disease management components involving healthcare professional resource (i.e. all disease management components other than migraine-specific medication and other medication) were sourced from the National Health and Wellness Survey (NHWS) 2017. This study aimed to characterise the incremental migraine burden from the European patients' perspective according to frequency of migraine. The study included patients from France, Germany, Italy, Spain and the UK. The NHWS study was a cross-sectional questionnaire administered over the internet. Respondents were separately grouped into various categories based on number of headache days per month. Although headache days and migraine days are separate outcomes, it was assumed that resource utilisation per headache day frequency would provide a good approximation for resource utilization per migraine day frequency. [122,138]

Estimates of mean resource utilisation per cycle from the NHWS study are provided in Table 58 below. The NHWS study provided mean utilisation for a six-month period; these were therefore divided by two in order to produce three-monthly utilisation provided in Table 58 to match the model cycle length.

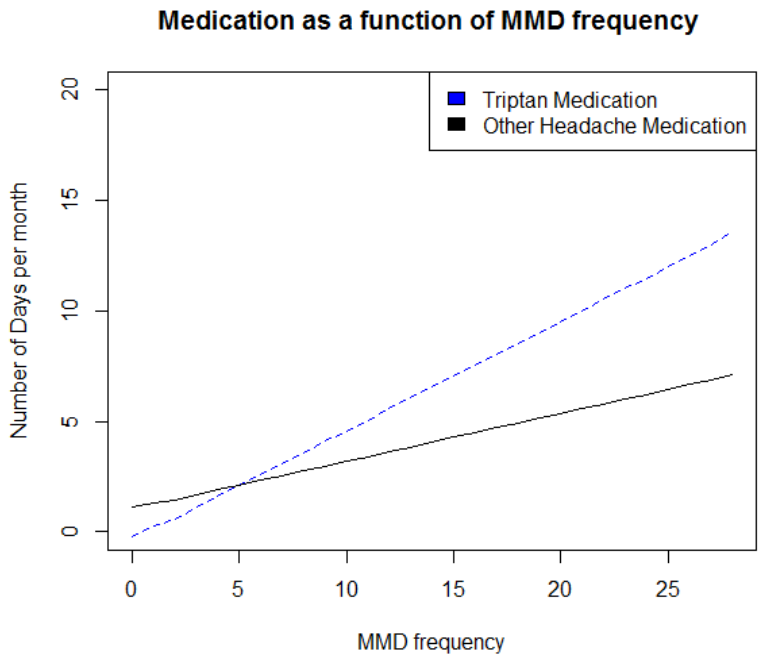
Table 58: Resource utilisation by migraine frequency

Resource utilisation rates per cycle	Not experiencing migraine (0 MMD)		LFEM (1–3 MMD)		Intermediate-frequency episodic (4–7 MMD)		HFEM (8–14 MMD)		Chronic migraine (≥15 MMD)	
Resource Parameter	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Hospitalisations	0.07	0.80	0.13	0.57	0.12	0.68	0.12	0.52	0.16	0.77
A&E Visits	0.09	0.69	0.20	0.76	0.18	0.79	0.28	1.16	0.35	1.41
GP Visits	0.61	1.35	0.87	1.57	1.24	3.91	1.66	3.07	1.76	2.98
Nurse Practitioner Visits	0.19	1.11	0.31	2.33	0.53	3.20	0.15	0.50	0.38	1.34
Neurologist Visits	0.01	0.15	0.05	0.36	0.04	0.24	0.12	0.67	0.22	0.99

Abbreviations: A&E: Accident & Emergency; GP: General Practitioner; HFEM: high-frequency episodic migraine; LFEM: low-frequency episodic migraine; MMD: monthly migraine day; SD: standard deviation.
Source: National Health and Wellness Survey 2018[138]

For the medication-related frequencies of resource utilisation (migraine-specific and other medication), information on medication usage by migraine frequency was derived from Study 295, STRIVE, ARISE and LIBERTY. A simple linear regression with a quadratic term (see Appendix V) was used to predict the number of migraine days with and without migraine-specific medication (assumed to be triptans) and other medication (assumed to be analgesics), providing estimates of average days of medication use for each frequency of MMDs, as presented in Figure 29 below.

Figure 29: Average days of migraine-specific and other medication use predicted by regression model



Abbreviations: MMD: monthly migraine day.

A summary of frequencies of resource use by category and the resultant total management costs by MMD frequency is provided in Table 59.

Table 59: Summary of resource use frequency (per cycle) and total cost by MMD frequency

MMD	Hospital-isations	A&E Visits	GP Visits	Nurse Practitioner Visits	Neurologist Visits	Triptans	Other Medication	Total cost
0	0.070	0.090	0.605	0.190	0.010	0.000	3.323	£83.26
1	0.125	0.200	0.865	0.305	0.045	0.886	3.972	£149.69
2	0.125	0.200	0.865	0.305	0.045	2.368	4.621	£153.65
3	0.125	0.200	0.865	0.305	0.045	3.850	5.270	£157.60
4	0.120	0.175	1.240	0.525	0.040	5.332	5.919	£176.60
5	0.120	0.175	1.240	0.525	0.040	6.814	6.568	£180.55
6	0.120	0.175	1.240	0.525	0.040	8.296	7.216	£184.50
7	0.120	0.175	1.240	0.525	0.040	9.778	7.865	£188.45
8	0.120	0.275	1.660	0.145	0.115	11.260	8.514	£216.64
9	0.120	0.275	1.660	0.145	0.115	12.742	9.163	£220.59
10	0.120	0.275	1.660	0.145	0.115	14.224	9.812	£224.54
11	0.120	0.275	1.660	0.145	0.115	15.706	10.461	£228.49
12	0.120	0.275	1.660	0.145	0.115	17.188	11.109	£232.44
13	0.120	0.275	1.660	0.145	0.115	18.670	11.758	£236.39
14	0.120	0.275	1.660	0.145	0.115	20.152	12.407	£240.34
15	0.155	0.350	1.755	0.380	0.220	21.634	13.056	£299.23
16	0.155	0.350	1.755	0.380	0.220	23.116	13.705	£303.18
17	0.155	0.350	1.755	0.380	0.220	24.598	14.354	£307.13
18	0.155	0.350	1.755	0.380	0.220	26.080	15.003	£311.08
19	0.155	0.350	1.755	0.380	0.220	27.562	15.651	£315.03
20	0.155	0.350	1.755	0.380	0.220	29.044	16.300	£318.98
21	0.155	0.350	1.755	0.380	0.220	30.526	16.949	£322.94
22	0.155	0.350	1.755	0.380	0.220	32.008	17.598	£326.89

23	0.155	0.350	1.755	0.380	0.220	33.490	18.247	£330.84
24	0.155	0.350	1.755	0.380	0.220	34.972	18.896	£334.79
25	0.155	0.350	1.755	0.380	0.220	36.454	19.544	£338.74
26	0.155	0.350	1.755	0.380	0.220	37.935	20.193	£342.69
27	0.155	0.350	1.755	0.380	0.220	39.417	20.842	£346.64
28	0.155	0.350	1.755	0.380	0.220	40.899	21.491	£350.59

Abbreviations: A&E: Accident & Emergency; GP: general practitioner; MMD: monthly migraine day.

B.3.5.3 Adverse reaction unit costs and resource use

As discussed in Section B.3.3.7, adverse events were not included in the cost-effectiveness model following expert advice from UK clinicians that AEs associated with migraine prophylaxis are usually non-severe, consistent with the reported AE profile of erenumab in Section B.2.9.

B.3.5.4 Miscellaneous unit costs and resource use

Whilst A&E visits, hospitalisations and treatment costs are the main drivers of direct costs, migraine also imposes a substantial burden on society. To examine the impact of migraine from a societal perspective, the costs of both absenteeism and presenteeism were incorporated into the model as a scenario analysis. A specific productivity cost was calculated for each MMD, and a weighted cost was derived for each treatment cohort depending on the patient distribution across all potential MMDs. Further details on the indirect costs used in a scenario analysis are presented in Appendix Y.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

A summary of the model parameters of the base case is presented in Table 60.

Table 60: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings			
Time horizon	10 years	N/A	Section B.3.2.2
Discount rate (costs and outcomes)	3.5%	N/A	Section B.3.2.2
Mean age at baseline (years)	42.25 years	N/A	Section B.3.3.1
Percentage female patients	84.51%	N/A	Section B.3.3.1
Clinical inputs			
Baseline MMD distributions	See Section B.3.3.1	N/A	Section B.3.3.1
Responder rate	• Erenumab: direct from Study 295 (chronic migraine) or pooled STRIVE, ARISE and LIBERTY data (episodic migraine)	NA	Section B.3.3.3
Rate of AEs	• Erenumab: combined for Study 295, STRIVE, ARISE and LIBERTY (whole population) direct from Study 295 (chronic migraine) or pooled STRIVE,	N/A	Section B.3.3.5

	ARISE and LIBERTY data (episodic migraine)		
Post-assessment rate of negative discontinuation (per cycle)	2.38%	N/A	Section B.3.3.5
Utility inputs			
Parameters for utility weight regression model in the base case			
295, STRIVE and ARISE: Multilevel (normal)	β0 (intercept): 0.1614; β1 (Reduction per MMD): 0.0163	β0 (se) 0.016 β1 (se) 0.002	Section B.3.4
Drug acquisition and administration			
Acquisition costs (per dose)	• Erenumab 70 mg: [redacted] (with confidential PAS) • Erenumab 140 mg: [redacted] (with confidential PAS) • BSC: £0.00	N/A	Section B.3.5.1
Administration costs (per cycle)	• Erenumab: £0.00 • BSC: £0.00	N/A	Section B.3.5.1
Initiation costs (first dose only)	• Erenumab: £40.04 • BSC: £0.00	N/A	Section B.3.5.1
Number of doses per cycle	• Erenumab: 3 • BSC: N/A	N/A	Section B.3.5.1

Abbreviations: AE: adverse event; BSC: best supportive care; CI: confidence interval; MMD: monthly migraine day; N/A: not applicable; PAS: Patient Access Scheme.

B.3.6.2 Assumptions

The model made several key assumptions, which are outlined in Table 61.

Table 61. Key model assumptions

Model assumption	Justification
The model cycle length is 12 weeks.	This is the length of time deemed clinically adequate to observe a change in migraine outcomes, and was the cycle length employed in the submission for botulinum toxin in chronic migraine.[81, 112, 139] The clinical trials included in this submission also assessed outcomes at 12 weeks.
The MMD distributions of responders and non-responders are derived from the clinical trials of erenumab in migraine patients and are assumed to be generalisable to migraine patients treated with any intervention. Therefore, it is assumed that responders and non-responders to botulinum toxin in the chronic migraine analysis have the same MMD distributions as responders and non-responders to	This assumption reflects the fact that only summary data are available for botulinum toxin, and therefore the MMD distributions of responders and non-responders cannot be directly determined from the botulinum toxin studies.

erenumab in this population. The relative treatment effectiveness of botulinum toxin compared to erenumab is accounted for through different response rates (i.e. a different proportion of patients associated with the responder vs non-responder MMD distribution).	
It is assumed that patients on treatment maintain the reduction in MMDs achieved in the assessment period.	This is supported by data from an open-label phase II extension study of erenumab in migraine patients, in which reductions in MMDs observed during the 12-week initial trial were maintained up to Week 64.[78] Furthermore, an OLE of Study 295 demonstrated maintenance in the improvement versus baseline in MMDs from Week 24 to Week 52.[123] Finally, a targeted literature review investigating the long-term progression of migraine in adults on prophylactic medicines indicated that the efficacy of these drugs is maintained over the long-term, with prolonged treatment associated with sustained benefits and improvements in QoL.[124]
It is assumed that patients who are classified as non-responders at the assessment period will discontinue treatment and receive BSC only. These patients are assumed to maintain the improvement in MMDs they attained over the assessment period.	Migraine is a spectrum disorder and over time patients' disease, including MMDs, may fluctuate. The assumption that non-responders maintain their improvement in MMDs reflects the notion that clinically the improvements in disease observed for non-responders receiving treatment over the response assessment period could have been experienced naturally over time in the absence of any intervention.
Dissipation of the placebo effect is not accounted for in the model, i.e., a proportion of BSC patients will respond to and continue to benefit from treatment.	This is both a simplifying and conservative assumption. Traditionally, it has been believed that the placebo effect lasts for a short time period, and frequency of headache returns afterwards to its prior level, particularly in studies for the prophylactic treatment of migraine. However, Diener *et al.* 2008 provides evidence for the maintenance of this effect over a longer time horizon.[140] Diener references a number of topiramate studies in which the placebo effect was seen after four weeks and maintained for six months while for botulinum toxin the effect was seen for a period of nine months. Given the uncertainty associated with duration and strength of the placebo effect, no adjustment was made to the BSC arm for the assessment period calculations. Effectively, it is assumed that placebo as administered in the trials is also a prophylactic treatment that can be provided to patients (in conjunction with BSC) in order to reduce migraine day frequency. This approach ensures that the treatment effect between erenumab and placebo is accurately captured in the analysis.
It is assumed that there is no migraine-related increased mortality and no differential mortality between arms.	A recent meta-analysis has shown that migraine is not associated with mortality from all causes.[132]
Adverse events are assumed to be non-severe, and as such costs and disutilities associated with these are not included in the base case	Expert advice was to not include disutilities and costs associated with AEs since AEs reported with erenumab are generally non-serious, as shown in Section B.2.9. SAEs were infrequent and comparable between the erenumab and placebo arms across the three trials. Therefore, it was considered appropriate not to

model. Disutilities associated with mode of administration are applied in a scenario analysis.	include costs and disutilities associated with AEs as these would be minimal. This also aligns with the previous submission to NICE for botulinum toxin in chronic migraine.[8]
Placebo is representative of BSC, with acute medications administered as needed and modelled as background disease management.	Patients with migraine are assumed to be referred to a specialist consultant to manage their condition and optimise their background therapy and pain relief. In the clinical trials of erenumab, patients in both arms were administered acute medication as required.
The assessment of response to treatment for botulinum toxin was at 24 weeks, whilst erenumab and BSC were assessed at 12 weeks.	The assessment of botulinum toxin at 24 weeks is in line with the period employed in the manufacturer's submission of botulinum toxin (TA260), and with the recommendation by NICE that response is assessed at 24 weeks. The 12 weeks for erenumab and BSC was the length deemed clinically adequate to observe a change in MMDs and reflects feedback from UK clinicians. The odds ratio of response derived from the ITC accounts for the difference in timepoint of assessment between the two therapies. This is likely to be a conservative assumption for erenumab.
It was assumed that the whole migraine population for patients who have failed ≥3 prior prophylactic treatments would be a weighted proportion of chronic migraine and episodic migraine patients, with chronic migraine patients assumed to be 66% of the population.	It was not possible to pool the erenumab studies as the criteria used to define the length of a qualified migraine headache differed between Study 295, and STRIVE, ARISE and LIBERTY (see Section B.2.3.1). The assumption that 66% of the total population would be classified as chronic migraine was based on market research in the UK and the results of a targeted literature review (see Section B.3.3). Whilst there are some limitations to this approach, it was considered the best available method to enable estimation of the cost-effectiveness of erenumab in the whole migraine population (as per the NICE scope).
It is assumed that 50% of patients start treatment on erenumab 70 mg, and the remaining 50% start treatment on erenumab 140 mg.	The recommended dosage for erenumab is 70 mg Q4W, although some patients may benefit from a dosage of 140 mg Q4W. The higher dose may be more suitable for patients for whom ≥3 prior prophylactic treatments have failed, the population considered in this submission. This is supported by feedback from six expert UK neurologists, who indicated that they would be likely to initiate these patients on the 140 mg dose.[67] The assumption that 50% of patients will initiate treatment on the 140 mg dose is therefore conservative, and reflects the lack of clinical experience with erenumab to provide evidence for the dosing distribution in practice.

Abbreviations: AE: adverse event; BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ITC: indirect treatment comparison; MMD: monthly migraine day; NICE: National Institute for Health and Care Excellence; OLE: open-label extension; QoL: quality of life; SAE: serious adverse event; UK: United Kingdom.

B.3.7 *Base-case results*

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Whole population base case

The summary results for the whole population base case for the blended dose, and for the 140 mg dose of erenumab, are presented in Table 62 and Table 63, respectively. These results show that erenumab has a higher total cost than BSC with a greater QALY gain and reduced MMDs. These results indicate that erenumab is cost-effective at a cost-effectiveness threshold of £30,000 in this population for both doses. Clinical outcomes presented in the model and disaggregated results of the base case incremental cost-effectiveness ratio (ICER) analyses are presented in Appendix J.

Table 62: Summary base case results in the whole migraine population (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£22,446

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 63: Summary base case results in the whole migraine population (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,827

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

Chronic migraine population

The summary results for the chronic migraine population for the blended dose and 140 mg dose of erenumab versus botulinum toxin are presented in Table 64 and Table 65, respectively. The results for the comparison against BSC are presented in Table 66 and Table 67, respectively. For both comparators, and at both doses, erenumab is a cost-effective treatment option at a cost-effectiveness threshold of £20,000 per QALY. Fully incremental analyses in the chronic migraine population are presented in Table 68 and Table 69, for the blended dose and 140 mg dose, respectively.

Table 64: Summary results in the chronic migraine population only versus botulinum toxin (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			

Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,893

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 65: Summary results in the chronic migraine population only versus botulinum toxin (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,832

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

Table 66: Summary results in the chronic migraine population only versus BSC (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,212

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 67: Summary results in the chronic migraine population only versus BSC (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£13,340

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

Table 68: Fully incremental analysis in the chronic migraine population only (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	ICER (£/QALY) – incremental analysis
BSC	[redacted]	[redacted]	
Botulinum toxin	[redacted]	[redacted]	£15,953
Erenumab 70 mg/140 mg	[redacted]	[redacted]	£18,824

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 69: Fully incremental analysis in the chronic migraine population only (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	ICER (£/QALY) – incremental analysis
BSC	[redacted]	[redacted]	
Botulinum toxin	[redacted]	[redacted]	£10,601
Erenumab 140 mg	[redacted]	[redacted]	£17,795

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

Episodic migraine population

The results for the episodic migraine population versus BSC are presented in Table 70 and Table 71. These results indicate that erenumab is associated with an increase in QALYs and costs and has ICERs of greater than £30,000 per QALY gained in this population for both doses.

Table 70: Summary results in the episodic migraine population only (with PAS), blended dose

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£35,787

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

Table 71: Summary results in the episodic migraine population only (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£ 40,662

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

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

The incremental results from the probabilistic sensitivity analyses (1,000 simulations; distributions used to perform the analysis can be found in Appendix W) are presented below for each migraine population. The probabilistic results (which take into account the combined uncertainty across model parameters) are similar to those estimated in the deterministic base case analysis.

Whole population base case

The incremental results from the probabilistic analysis for the whole migraine base case population are presented in Table 72 and Table 73 for the blended and 140 mg dose, respectively. Scatter plots of incremental costs and QALYs for erenumab (with PAS) versus BSC are presented in Figure 30 and Figure 32, and the cost-effectiveness acceptability curve for these analyses is shown in Figure 31 and Figure 33, respectively. When considering a cost-effectiveness threshold of £20,000 per QALY and the PAS price, erenumab has a probability of cost-effectiveness of 35% and 50% against BSC in the whole population base case, for the blended dose and 140 mg dose, respectively. When considering a cost-effectiveness threshold of £30,000 per QALY and the PAS price, erenumab has a probability of cost-effectiveness of 70% and 81% against BSC in the whole population base case, for the blended dose and 140 mg dose, respectively.

Table 72: Probabilistic results for the whole migraine base case population: blended dose[a] of erenumab versus best supportive care

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£22,309

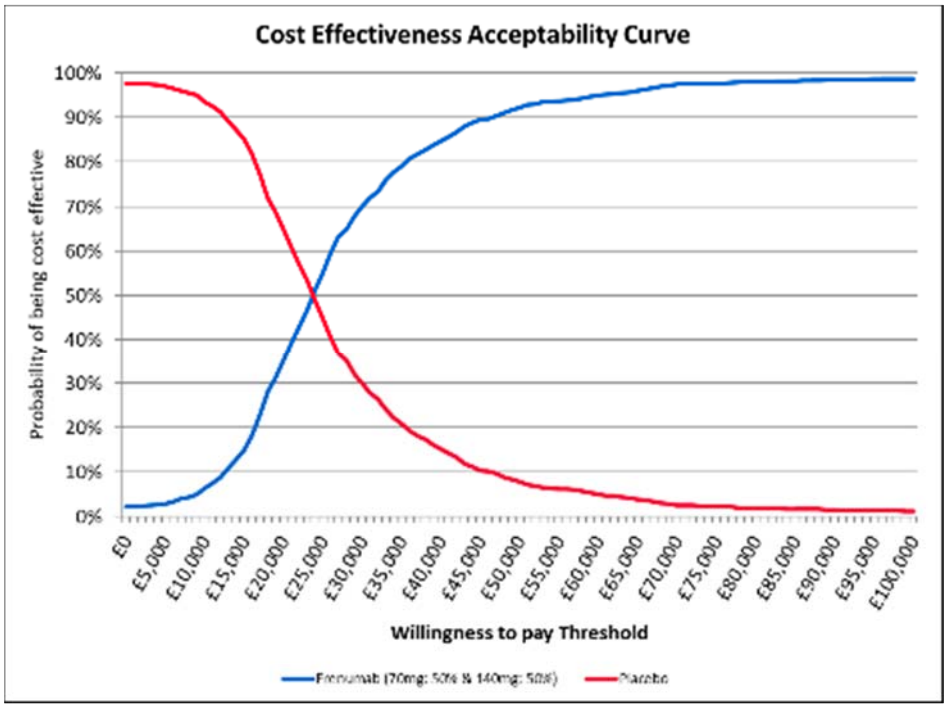
[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 30: Cost-effectiveness plane for blended dose[a] of erenumab (with PAS) versus best supportive care in the whole migraine base case population

[redacted]

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 31: Cost-effectiveness acceptability curve for blended dose[a] of erenumab (with PAS) versus best supportive care in the whole migraine base case population



[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care.

Table 73: Probabilistic results for the whole migraine base case population: erenumab 140 mg versus best supportive care

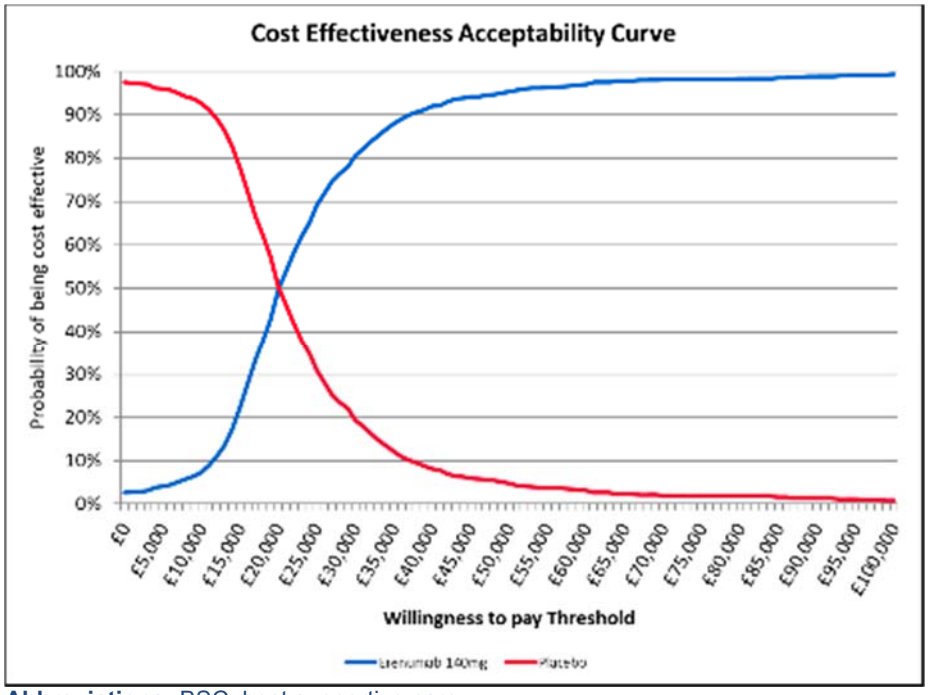
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,472

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

Figure 32: Cost-effectiveness plane for erenumab 140 mg (with PAS) versus best supportive care in the whole migraine base case population

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 33: Cost-effectiveness acceptability curve for erenumab 140 mg (with PAS) versus best supportive care in the whole migraine base case population



Abbreviations: BSC: best supportive care.

Chronic migraine population

The incremental results from the probabilistic analysis for erenumab versus botulinum toxin in chronic migraine are presented in Table 74 and Table 75, for the blended dose and 140 mg dose, respectively. The incremental results from the probabilistic analysis for erenumab versus BSC in chronic migraine are presented in Table 76 and Table 77, for the blended dose and 140 mg dose, respectively. Scatter plots of incremental costs and QALYs, and cost-effectiveness acceptability curves, are presented in Appendix W. When considering a cost-effectiveness threshold of £20,000 per QALY and PAS, erenumab has a probability of cost-effectiveness of 41% and 54% against botulinum toxin, and 62% and 79% against BSC in the chronic migraine population, for the blended dose and 140 mg dose, respectively. When considering a cost-effectiveness threshold of £30,000 per QALY and PAS, erenumab has a probability of cost-effectiveness of 73% and 79% against botulinum toxin, and 84% and 94% against BSC in the chronic migraine population, for the blended dose and 140 mg dose, respectively.

Table 74: Probabilistic results for the chronic migraine population: blended dose[a] of erenumab (with PAS) versus botulinum toxin

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£21,644

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 75: Probabilistic results for the chronic migraine population: erenumab 140 mg (with PAS) versus botulinum toxin

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,655

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 76: Probabilistic results for the chronic migraine population: blended dose[a] of erenumab (with PAS) versus BSC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,553

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 77: Probabilistic results for the chronic migraine population: erenumab 140 mg (with PAS) versus BSC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£12,711

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

Episodic migraine

The incremental results from the probabilistic analysis for erenumab versus BSC in episodic migraine are presented in Table 78 and Table 79, for the blended dose and 140 mg dose, respectively. Scatter plots of incremental costs and QALYs, and cost-effectiveness acceptability curves, are presented in Appendix W. When considering a cost-effectiveness threshold of £20,000 per QALY and PAS, erenumab has a probability of cost-effectiveness of 13% and 10% against BSC in the episodic migraine population, for the blended dose and 140 mg dose, respectively. When considering a cost-effectiveness threshold of £30,000 per QALY and PAS, erenumab has a probability of cost-effectiveness of 37% and 28% against BSC in the episodic migraine population, for the blended dose and 140 mg dose, respectively.

Table 78: Probabilistic results for the episodic migraine: blended dose[a] of erenumab (with PAS) versus best supportive care

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£35,142

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 79: Probabilistic results for the episodic migraine: erenumab 140 mg (with PAS) versus best supportive care

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£38,749

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

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted by varying all parameters at lower and upper bounds. Where possible, statistical distributions were used to inform the lower and upper bounds based on 95% CIs; however, for the majority of inputs such distributions were not available and hence upper and lower bounds were chosen as +/-10% of the base case value or based on a plausible range.

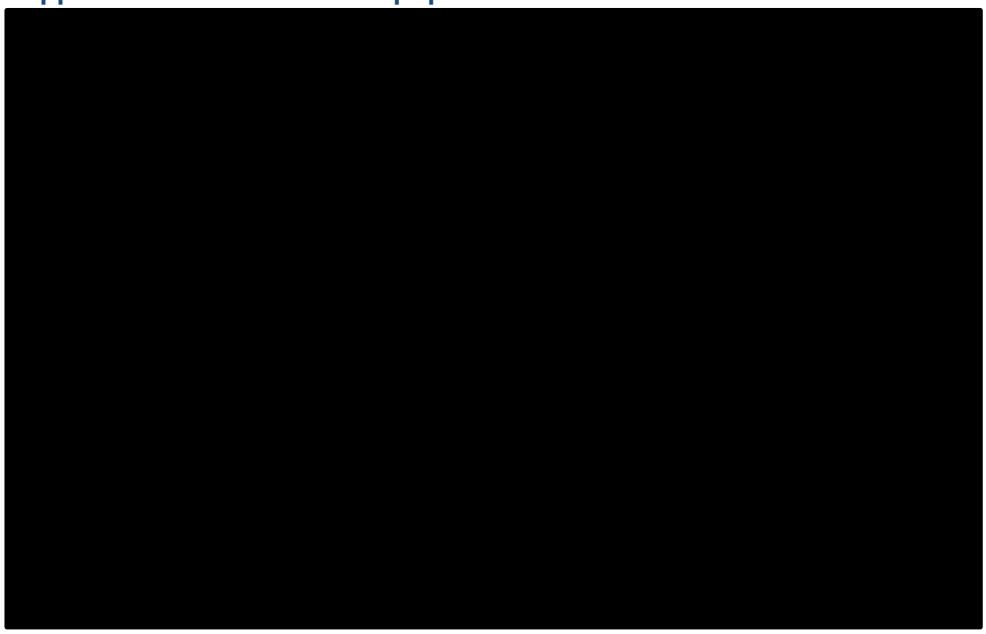
Whole population base case

Tornado diagrams showing the drivers of cost-effectiveness in the comparison of erenumab (with PAS) versus BSC in the whole population base case are presented in Figure 34 and Figure 35, for the blended dose and 140 mg dose, respectively. In both analyses, results were sensitive to varying the mean MMDs for BSC, erenumab 70 mg and erenumab 140 mg non-responders.

Figure 34: Deterministic sensitivity analysis results for the blended dose[a] of erenumab versus best supportive care in the whole population base case

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: CM: chronic migraine; EM: episodic migraine: ICER: incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Figure 35: Deterministic sensitivity analysis results for erenumab 140 mg versus best supportive care in the whole population base case



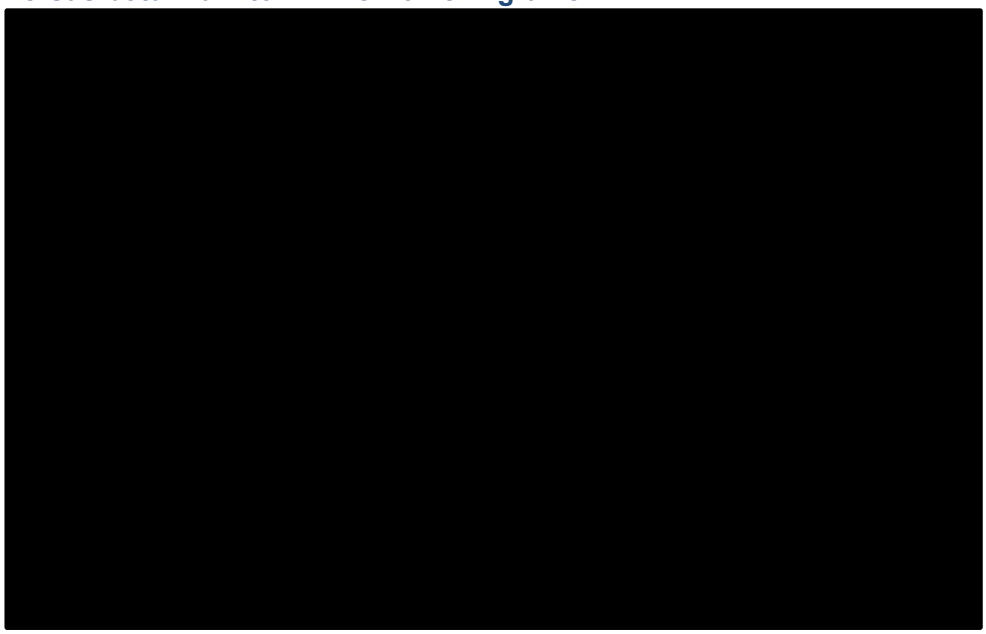
Abbreviations: CM: chronic migraine; EM: episodic migraine: ICER: incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Chronic migraine population

Tornado diagrams showing the top drivers of cost-effectiveness in the comparison of erenumab (with PAS) versus botulinum toxin in the chronic migraine population are presented in Figure 36 and Figure 37, for the blended dose and 140 mg dose, respectively. The top parameters driving the model are erenumab treatment costs and cost discount rate.

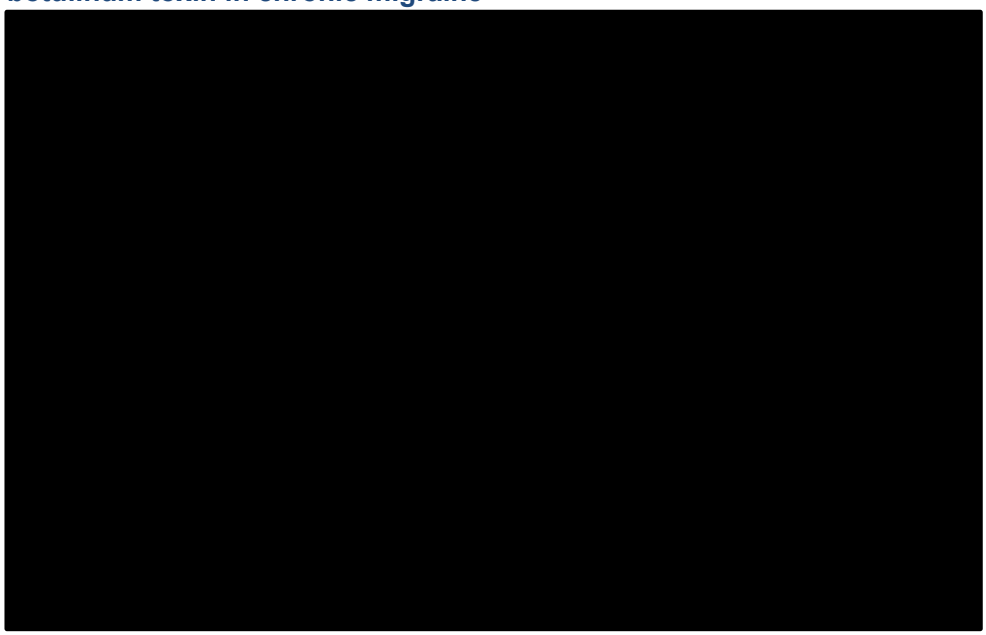
Tornado diagrams showing the drivers of cost-effectiveness in the comparison of erenumab (with PAS) versus BSC in the chronic migraine population are presented in Figure 38 and Figure 39 for the blended dose and 140 mg dose, respectively. The top parameters driving the models are varying the mean MMDs for BSC, erenumab 70 mg and erenumab 140 mg non-responders.

Figure 36: Deterministic sensitivity analysis results for the blended dose[a] of erenumab versus botulinum toxin in chronic migraine



[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: CM: chronic migraine; ICER: incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Figure 37: Deterministic sensitivity analysis results for erenumab 140 mg versus botulinum toxin in chronic migraine



Abbreviations: CM: chronic migraine; ICER: incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Figure 38: Deterministic sensitivity analysis results for the blended dose[a] of erenumab versus BSC in chronic migraine

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: CM: chronic migraine; ICER: incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Figure 39: Deterministic sensitivity analysis results for erenumab 140 mg versus BSC in chronic migraine

Abbreviations: CM: chronic migraine; ICER: incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Episodic migraine

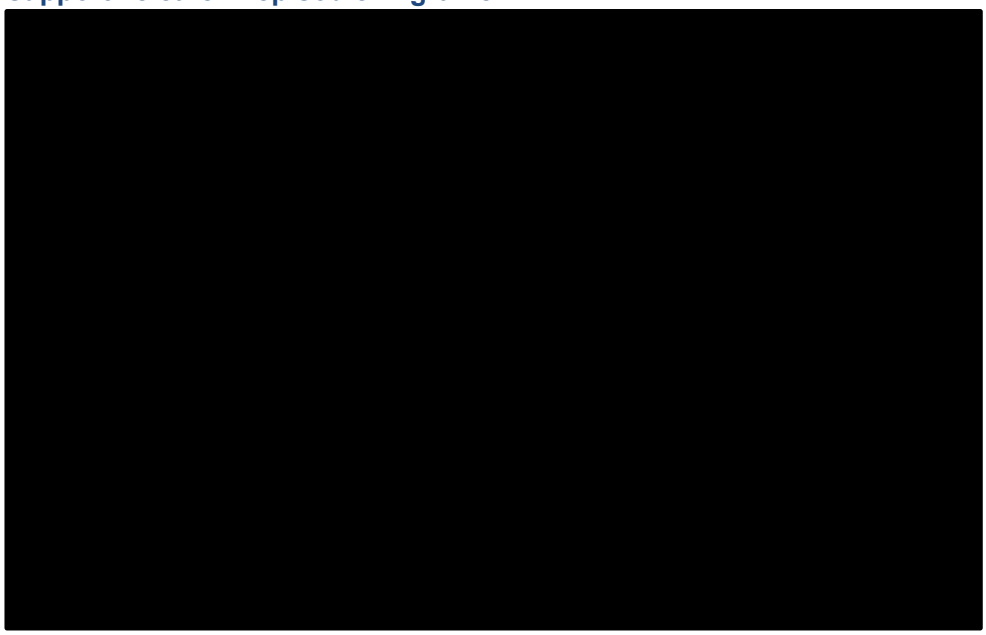
Tornado diagrams showing the key drivers of cost-effectiveness in the comparison of erenumab (with PAS) versus BSC in the episodic migraine population are presented in Figure 40 and Figure 41, for the blended dose and 140 mg dose, respectively. The top parameters driving the model for the blended dose are mean MMDs for erenumab 70 mg, BSC and erenumab 140 mg

non-responders. The top parameters driving the model for the 140 mg dose are erenumab 140 mg and BSC non-responder MMDs.

Figure 40: Deterministic sensitivity analysis results for the blended dose[a] of erenumab versus best supportive care in episodic migraine

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: EM: episodic migraine: ICER: incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Figure 41: Deterministic sensitivity analysis results for erenumab 140 mg versus best supportive care in episodic migraine



Abbreviations: EM: episodic migraine: ICER: incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

B.3.8.3 Scenario analysis

Various scenario analyses were conducted to explore the impact of assumptions that were included in analysis for the base case and different migraine populations. A description of each scenario analysis considered is provided in Table 80 below. Results are presented in below.

Table 80: Description of scenario analyses conducted in each population

#	Scenario analysis	Description of scenario analysis
Whole population base case		
1	Adopt societal perspective	To examine the effect of non-medical expenses and work-related costs
2	Non-response rebound to baseline MMDs	Following the assessment period, non-responders are assumed to lose MMD benefits and return to baseline MMDs
3	Non-response change to 12-week BSC MMDs	Following the assessment period, non-responders are assumed to revert to MMDs as for 12-week placebo
4	AE discontinuation change to 12-week BSC MMDs	Patients who discontinue for AEs are assumed to change to 12-week placebo MMDs
5	Long-term negative discontinuation changed to 12-week BSC MMDs	The MMDs for patient who discontinue treatment due to long-term treatment failure are assumed to change to 12-week placebo MMDs
6	Apply positive discontinuation	Responders are subject to ongoing assessment periodically and a proportion discontinue treatment
7	Apply 30% stopping rule	Change the definition of a response to those achieving a ≥30% reduction in MMDs from baseline (base case definition is a ≥50% reduction in MMDs from baseline)
8	Change time horizon from 10 years to 5 years	The time horizon for the model is changed to 5 years
9	Change time horizon from 10 years to 15 years	The time horizon for the model is changed to 15 years
10	Change proportions of “blended dose” (30%/70% on erenumab 70 mg/140mg)	Change the proportions of the blended dose so 70% of patients start treatment on erenumab 140 mg and 30% on erenumab 70 mg
11	Change proportions of “blended dose” (70%/30% on erenumab 70 mg/140mg)	Change the proportions of the blended dose so 30% of patients start treatment on erenumab 140 mg and 70% on erenumab 70 mg
12	Use pooled utilities model: GEE GLM	Using a GEE GLM specific to whole population to model the utilities associated with MMDs
Chronic migraine population (comparator: botulinum toxin)		
1-11	As per whole population scenarios 1-11	

12	Use indication specific utilities model: GEE GLM	Using a GEE GLM specific to CM population to model the utilities associated with MMDs
13	Apply MoA utility decrement	To assess the application of methods of administration utility decrements for patients who receive botulinum toxin
14	Use ITC headache days for botulinum toxin relative risk	This scenario examines the effect of using the odds ratio using headache days as response outcome
Chronic migraine population (comparator: BSC)		
1-11	As per whole population scenarios 1-11	
12	Use indication specific utilities model: GEE GLM	Using a GEE GLM specific to CM population to model the utilities associated with MMDs
Episodic migraine population		
1-11	As per whole population scenarios 1-11	
12	Use indication specific utilities model: GEE GLM	Using a GEE GLM specific to CM population to model the utilities associated with MMDs
13	Apply utilities from LIBERTY Crosswalk 5L to 3L	MMD utilities are estimated using mapped data from the LIBERTY data for EM patients

Abbreviations: AE: adverse event; CM: chronic migraine; EM: episodic migraine; GEE GLM: generalised estimating equation model; HFEM: high frequency episodic migraine; ITC: indirect treatment comparison; MoA; mode of administration; MMD: monthly migraine day.

Whole population base case

Table 81 and

Table 82 present the scenario analyses for the whole population base case, for the blended dose and 140 mg dose of erenumab, respectively. The results show that for the blended dose, the largest impact is employing a societal impact, which considers indirect costs from absenteeism and presenteeism at work due to migraine in the evaluation. Employing this assumption decreases the ICER by 87% to £2,947 in the blended dose analysis. Changing the proportion of the blended dose so that 70% of patients start treatment on erenumab 140 mg, and the remainder on erenumab 70 mg, decreases the ICER by 5% to £21,256. Only two scenario increases the ICER to above a £30,000 threshold: changing the non-responders to 12-week placebo MMDs and apply a 30% stopping rule. For erenumab 140 mg, adopting a societal perspective decreases the ICER by 98% to £328. Applying a positive discontinuation rule also decreases the ICER by 47% to £10,422. Only two scenario increases the ICER above a £30,000 threshold: changing non-responders to 12-week placebo MMDs and apply a 30% stopping rule.

Table 81: Summary of scenario analyses in the whole population - erenumab (with PAS) compared to BSC, blended dose[a]

#	Scenarios	Erenumab costs	BSC costs	Erenumab QALYs	BSC QALYs	Incremental costs	Incremental QALYs	ICER
	Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,446**
1	Adopt societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,947
2	Non-response rebound to baseline MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,805
3	Non-response change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,102
4	AE discontinuation change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,378
5	Long-term negative discontinuation changed to 12-week BSC MMDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,585
6	Apply positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,105
7	Apply 30% stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,221
8	Change time horizon from 10 years to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,861
9	Change time horizon from 10 years to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,275
10	Change proportions of “blended dose” (30%/70% on erenumab 70 mg/140mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,256
11	Change proportions of “blended dose” (70%/30% on erenumab 70 mg/140mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,899
12	Use pooled utilities model: GEE GLM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,232

[a]The “blended dose” refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: AE: adverse event; BSC: best supportive care; GEE GLM: Generalised estimating equation model: ICER: Incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Table 82: Summary of scenario analyses in the whole population - erenumab (with PAS) compared to BSC, erenumab 140 mg

#	Scenarios	Erenumab costs	BSC costs	Erenumab QALYs	BSC QALYs	Incremental costs	Incremental QALYs	ICER

	Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£19,827**
1	Adopt societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£328
2	Non-response rebound to baseline MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,098
3	Non-response change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,594
4	AE discontinuation change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,777
5	Long-term negative discontinuation changed to 12-week BSC MMDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,176
6	Apply positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,422
7	Apply 30% stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,293
8	Change time horizon from 10 years to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,577
9	Change time horizon from 10 years to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,015
10	Change proportions of “blended dose” (30%/70% on erenumab 70 mg/140mg)	Not applicable to erenumab 140 mg dose analysis						
11	Change proportions of “blended dose” (70%/30% on erenumab 70 mg/140mg)	Not applicable to erenumab 140 mg dose analysis						
12	Use pooled utilities model: GEE GLM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,638

Abbreviations: AE: adverse event; BSC: best supportive care; GEE GLM: Generalised estimating equation model: ICER: Incremental cost-effectiveness ratio; MMD: monthly migraine day; QALY: quality-adjusted life year.

Chronic migraine population

Table 83 and Table 84 present the scenario analyses for the chronic migraine population where the comparator is botulinum toxin, for the blended dose and 140 mg dose, respectively. For the blended dose, adopting a societal perspective resulted in a reduction in the ICER by 82% to £3,477. Selecting a positive discontinuation rule also decreased the ICER to £8,979, a decrease of 52%. Five scenarios increased the ICER to greater than £20,000, and no scenarios increased the ICER over £30,000. Changing the proportions of the blended dose so that 70% of patients start treatment on

erenumab 140 mg, and the rest on erenumab 70 mg, decreased the ICER to £18,432. For the 140 mg dose, adopting a societal perspective resulted in an 89% decrease in the ICER to £2,417.

Table 85 and Table 86 present the scenario analyses for the chronic migraine population where the comparator is BSC. Similar to the analyses in the whole population base case and chronic migraine population with botulinum toxin, the societal perspective decreased the ICER to £1,797 for the blended dose. Changing the proportions of the blended dose so that 70% of patients start treatment on erenumab 140 mg decreased the ICER by 11% to £15,402. For the analysis with erenumab 140 mg, the societal perspective decreased the ICER so that erenumab dominates BSC, and applying positive discontinuation decreased the ICER by 49% to £6,815.

Table 83: Summary of scenario analyses in the chronic migraine population – erenumab (with PAS) compared to botulinum toxin, blended dose[a]

#	Scenarios	Erenumab costs	Botulinum toxin costs	Erenumab QALYs	Botulinum toxin QALYs	Incremental costs	Incremental QALYs	ICER
	Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£18,893**
1	Adopt societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,477
2	Non-response rebound to baseline MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,046
3	Non-response change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,288
4	AE discontinuation change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,484
5	Long-term negative discontinuation change to 12-week BSC MMDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,282
6	Apply positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,979
7	Apply 30% stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,426
8	Change time horizon from 10 years to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,137
9	Change time horizon from 10 years to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,384

10	Change proportions of “blended dose” (30%/70% on erenumab 70 mg/140mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,432
11	Change proportions of “blended dose” (70%/30% on erenumab 70 mg/140mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,414
12	Use indication specific utilities model: GEE GLM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,942
13	Apply MoA utility decrement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,367
14	Use ITC headache days for botulinum toxin relative risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,146

[a]The “blended dose” refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: AE: adverse event; BSC: best supportive care; GEE GLM: Generalised estimating equation model:; ICER: Incremental cost-effectiveness ratio; ITC: indirect treatment comparison; MMDs: monthly migraine days; MoA: mode of administration; QALY: quality-adjusted life year.

Table 84: Summary of scenario analyses in the chronic migraine population – erenumab (with PAS) compared to botulinum toxin, erenumab 140 mg

#	Scenarios	Erenumab costs	Botulinum toxin costs	Erenumab QALYs	Botulinum toxin QALYs	Incremental costs	Incremental QALYs	ICER
	Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,832**
1	Adopt societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,417
2	Non-response rebound to baseline MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,384
3	Non-response change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,618
4	AE discontinuation change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,174
5	Long-term negative discontinuation change to 12-week BSC MMDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,328
6	Apply positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,340

7	Apply 30% stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,582
8	Change time horizon from 10 years to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,119
9	Change time horizon from 10 years to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,468
10	Change proportions of "blended dose" (30%/70% on erenumab 70 mg/140mg)	Not applicable to erenumab 140 mg dose analysis						
11	Change proportions of "blended dose" (70%/30% on erenumab 70 mg/140mg)	Not applicable to erenumab 140 mg dose analysis						
12	Use indication specific utilities model: GEE GLM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,767
13	Apply MoA utility decrement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,593
14	Use ITC headache days for botulinum toxin relative risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,462

Abbreviations: AE: adverse event; BSC: best supportive care; GEE GLM: Generalised estimating equation model:; ICER: Incremental cost-effectiveness ratio; ITC: indirect treatment comparison; MMDs: monthly migraine days; MoA: mode of administration; QALY: quality-adjusted life year.

Table 85: Summary of scenario analyses in the chronic migraine population – erenumab (PAS price) compared to BSC, blended dose[a]

#	Scenario	Erenumab costs	BSC costs	Erenumab QALYs	BSC QALYs	Incremental costs	Incremental QALYs	ICER
	Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,212**
1	Adopt societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,797
2	Non-response rebound to baseline MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,340
3	Non-response change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,335
4	AE discontinuation change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,182
5	Long-term negative discontinuation change to 12-week BSC MMDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,187

6	Apply positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,868
7	Apply 30% stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,803
8	Change time horizon from 10 years to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,011
9	Change time horizon from 10 years to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,123
10	Change proportions of "blended dose" (30%/70% on erenumab 70 mg/140mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,402
11	Change proportions of "blended dose" (70%/30% on erenumab 70 mg/140mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,547
12	Use indication specific utilities model: GEE GLM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,079
13	Apply MoA utility decrement	Not applicable to comparison with BSC						
14	Use ITC headache days for botulinum toxin relative risk	Not applicable to comparison with BSC						

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: AE: adverse event; BSC: best supportive care; GEE GLM: Generalised estimating equation model; ICER: Incremental cost-effectiveness ratio; MMDs: monthly migraine days; MoA: mode of administration; QALY: quality-adjusted life year.

Table 86: Summary of scenario analyses in the chronic migraine population – erenumab (PAS price) compared to BSC, erenumab 140 mg

#	Scenario	Erenumab costs	BSC costs	Erenumab QALYs	BSC QALYs	Incremental costs	Incremental QALYs	ICER
	Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£13,340**
1	Adopt societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Erenumab dominates
2	Non-response rebound to baseline MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,789
3	Non-response change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,555

4	AE discontinuation change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,282
5	Long-term negative discontinuation change to 12-week BSC MMDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,979
6	Apply positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,815
7	Apply 30% stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,017
8	Change time horizon from 10 years to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,354
9	Change time horizon from 10 years to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,908
10	Change proportions of “blended dose” (30%/70% on erenumab 70 mg/140mg)	Not applicable to erenumab 140 mg dose analysis						
11	Change proportions of “blended dose” (70%/30% on erenumab 70 mg/140mg)	Not applicable to erenumab 140 mg dose analysis						
12	Use indication specific utilities model: GEE GLM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,787
13	Apply MoA utility decrement	Not applicable to comparison with BSC						
14	Use ITC headache days for botulinum toxin relative risk	Not applicable to comparison with BSC						

Abbreviations: AE: adverse event; BSC: best supportive care; GEE GLM: Generalised estimating equation model; ICER: Incremental cost-effectiveness ratio; MMDs: monthly migraine days; MoA: mode of administration; QALY: quality-adjusted life year.

Episodic migraine population

Table 87 and Table 88 present the results of scenario analyses in the episodic migraine population, for the blended dose and 140 mg dose of erenumab, respectively. For the blended dose, two scenarios reduced the base case ICER to below a £30,000 cost-effectiveness threshold: employing the societal perspective and including positive discontinuation. Changing the proportions of the blended dose so that 70% of patients started treatment on erenumab 140 mg increased the ICER to £37,902. For the 140 mg dose, two scenarios reduced the base case ICER to below a £30,000 cost-effectiveness threshold: employing the societal perspective and including positive discontinuation.

Table 87: Summary of scenario analyses in the episodic migraine population (with PAS), blended dose[a]

#	Scenarios	Erenumab costs	BSC costs	Erenumab QALYs	BSC QALYs	Incremental costs	Incremental QALYs	ICER
	Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,787**
1	Adopt societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,071
2	Non-response rebound to baseline MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,334
3	Non-response change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,167
4	AE discontinuation change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,760
5	Long-term negative discontinuation change to 12-week BSC MMDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,069
6	Apply positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,994
7	Apply 30% stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£76,735
8	Change time horizon from 10 years to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,498
9	Change time horizon from 10 years to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,308
10	Change proportions of “blended dose” (30%/70% on erenumab 70 mg/140mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,902
11	Change proportions of “blended dose” (70%/30% on erenumab 70 mg/140mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,404
12	Use indication specific utilities model: GEE GLM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,761
13	Apply utilities from LIBERTY Crosswalk 5L to 3L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,080

[a]The “blended dose” refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: AE: adverse event; BSC: best supportive care; GEE GLM: Generalised estimating equation model; ICER: Incremental cost-effectiveness ratio; MMDs: monthly migraine days; QALY: quality-adjusted life year.

Table 88: Summary of scenario analyses in the episodic migraine population (with PAS), erenumab 140 mg

#	Scenarios	Erenumab costs	BSC costs	Erenumab QALYs	BSC QALYs	Incremental costs	Incremental QALYs	ICER
	Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,662**
1	Adopt societal perspective	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,946
2	Non-response rebound to baseline MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,010
3	Non-response change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,003
4	AE discontinuation change to 12-week BSC MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,632
5	Long-term negative discontinuation change to 12-week BSC MMDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,431
6	Apply positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,418
7	Apply 30% stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,077
8	Change time horizon from 10 years to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,091
9	Change time horizon from 10 years to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,268
10	Change proportions of “blended dose” (30%/70% on erenumab 70 mg/140mg)	Not applicable to erenumab 140 mg dose analysis						
11	Change proportions of “blended dose” (70%/30% on erenumab 70 mg/140mg)	Not applicable to erenumab 140 mg dose analysis						
12	Use indication specific utilities model: GEE GLM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,496
13	Apply utilities from LIBERTY Crosswalk 5L to 3L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£77,353

Abbreviations: AE: adverse event; BSC: best supportive care; GEE GLM: Generalised estimating equation model; ICER: Incremental cost-effectiveness ratio; MMDs: monthly migraine days; QALY: quality-adjusted life year.

B.3.8.4 Summary of sensitivity analyses results

Whole population base case – compared to BSC

The probabilistic sensitivity analysis demonstrated that with the PAS price, there is a 36% and 71% probability of erenumab being cost-effective at a £20,000 and £30,000 per QALY ICER threshold, respectively, for the blended dose, and 43% and 83% for the 140 mg dose.

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERs for the blended dose:

- Mean MMDs for BSC non-responders
- Mean MMDs for erenumab 140 mg non-responders
- Mean MMDs for erenumab 70 mg non-responders

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERs for the 140mg dose:

- Mean MMDs for BSC non-responders
- Mean MMDs for erenumab 140mg non-responders

In the scenario analyses, economic results were relatively stable when varying model assumptions, providing consistent ICER estimates. For the blended and 140 mg dose, the only two scenariso associated with ICERs over £30,000 per QALY gained were changing the assumption that following the assessment period, non-responders are assumed to revert to MMDs as for 12-week placebo and changing the assessment of response criteria to 30% reduction in MMDs.

Changing from an NHS/PSS perspective to societal perspective had a considerable impact, decreasing the erenumab ICER to £2,947 and £328 per QALY for the blended dose and 140 mg dose, respectively. This is primarily because migraine affects a working age population and has a significant impact on absenteeism and work impairment. Inclusion of the positive discontinuation rule where responder patients may take breaks from treatment because of positive response decreases the ICER to £12,105 and £10,422, respectively, which may better reflect how erenumab will be used in clinical practice. Changing the proportion of the blended dose so that 70% of patients start treatment on erenumab 140 mg, and the remainder on erenumab 70 mg, decreases the ICER by 5% to £21,256 for the blended dose analysis.

Chronic migraine population – compared to botulinum toxin

In the analysis for erenumab (with PAS) versus botulinum toxin in chronic migraine, the probabilistic sensitivity analysis demonstrated that there is a 47% and 78% probability of erenumab being cost-effective at a £20,000 and £30,000 per QALY ICER threshold, respectively, for the blended dose, and 56% and 82% for the 140 mg dose.

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERs for the blended dose:

- Erenumab 140 mg treatment cost per cycle

- Discount rate applied to costs

For the erenumab 140 mg dose the following had the biggest impact:

- Erenumab 140 mg treatment cost per cycle
- Mean MMDs for erenumab 140mg non-responders

In the scenario analyses, economic model results were relatively stable when varying model assumptions, providing consistent ICER estimates. No scenarios were associated with ICERs over £30,000 per QALY, for either the blended dose or the 140 mg dose. The scenarios which had a significant impact on decreasing the ICER were taking a societal perspective, applying positive discontinuation and the mode of administration utility decrement. Regarding the latter, the ICER reduced to £4,367 and £4,593 per QALY for the blended dose and 140 mg dose, respectively, which may better reflect real world cost-effectiveness as it is likely that in clinical practice there is utility impact given the increased burden for patients from the mode of administration of botulinum toxin. Changing the proportions of the blended dose so that 70% of patients start treatment on erenumab 140 mg, and the rest on erenumab 70 mg, decreased the ICER to £18,432.

Chronic migraine population – compared to BSC

For erenumab (with PAS) versus BSC the probabilistic sensitivity analysis demonstrated a 57% and 84% probability of erenumab being cost-effective at a £20,000 and £30,000 per QALY ICER threshold, respectively, for the blended dose, and 79% and 97% for the 140 mg dose.

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERs for the blended dose:

- Mean MMDs for BSC non-responders
- Mean MMDs for erenumab 70 mg non-responders
- Mean MMDs for erenumab 140 mg non-responders

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERs for the 140 mg dose:

- Mean MMDs for erenumab 140 mg non-responders
- Erenumab 140 mg treatment cost per cycle

In the scenario analyses, economic model results were relatively stable when varying model assumptions, providing consistent ICER estimates. No scenarios were associated with an ICERs over £30,000 per QALY, for either the blended dose or the 140 mg dose. The scenarios which had a significant impact on decreasing the ICER were again adoption of a societal perspective (erenumab dominated BSC) and positive discontinuation. Changing the proportions of the blended dose so that 70% of patients start treatment on erenumab 140 mg decreased the ICER by 11% to £15,402.

Episodic migraine population – compared to BSC

The probabilistic sensitivity analysis demonstrated that with the PAS price, there is a 13% and 36% probability of erenumab being cost-effective with a £20,000 and £30,000 per QALY ICER threshold, respectively for the blended dose and 9% and 34% for the 140 mg.

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERs for the blended dose:

- Mean MMDs for BSC non-responders
- Mean MMDs for erenumab 140 mg non-responders
- Mean MMDs for erenumab 70 mg non-responders

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERs for the 140 mg dose:

- Mean MMDs for erenumab 140mg non-responders
- Mean MMDs for BSC non-responders

Applying utility data from the LIBERTY study increased the ICER to £68,080 and £77,353 for the blended dose and 140 mg dose, respectively. As discussed in Section B.3.4.1, EQ-5D data were only collected in LIBERTY and only at treatment appointments, where it was unlikely patients would have been experiencing a migraine. Mapped utility data was therefore considered to be the most appropriate source of utility data. Notably, the application of a societal perspective reduced the ICER to less than £20,000 per QALY for the blended dose (£13,071 per QALY) and 140 mg dose (£17,946 per QALY), respectively.

B.3.9 *Subgroup and exploratory analysis*

B.3.9.1 HFEM subgroup

The results of the subgroup analyses restricting the episodic population to the HFEM population (8–14 MMDs) in the whole population base case are presented in Table 89 and Table 90 for the blended dose and 140 mg dose, respectively. Results in the episodic migraine population are presented in Table 91 and Table 92, respectively. Restricting to the HFEM population rather than the full episodic migraine population resulted in reductions to the ICERs (i.e. increased cost-effectiveness of erenumab) in both the whole population base case and the episodic migraine population-specific analyses

Table 89: HFEM subgroup analysis results in the whole migraine (HFEM and chronic migraine i.e.≥ 10 MMDs) (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£22,260**

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; HFEM: high-frequency episodic migraine; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 90: HFEM subgroup analysis results in the whole migraine (HFEM and chronic migraine i.e.≥ 10 MMDs) (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£19,239**

Abbreviations: BSC: best supportive care; HFEM: high-frequency episodic migraine; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 91: HFEM subgroup analysis results in the episodic migraine population i.e. 10-14 MMDs (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£37,607

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; HFEM: high frequency episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 92: HFEM subgroup analysis results in the episodic migraine population i.e. 10-14 (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£37,749

Abbreviations: BSC: best supportive care; HFEM: high frequency episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

The overall model structure has been validated through iterative discussions with UK clinical experts and a UK health economics expert, ongoing since September 2016. Additionally, further UK clinical input was sought at Advisory Boards with clinical experts in June 2017 and December 2017.[9, 22]

Further model validation has been performed by two independent health economics experts who provided feedback on technical validity, ensuring that mathematical specifications and logic were applied consistently across sheets in the model.

Comparison of the model outputs and the trial data is provided in the Table 93. These show that the model results are consistent with the clinical trial results.

Table 93: Summary of model result and clinical data results 3+TF population

	Clinical trial data*			Model results		
	Erenumab 70 mg	Erenumab 140mg	Placebo	Erenumab 70 mg	Erenumab 140mg	BSC
	Mean change from baseline in MMDs versus placebo					
Study 295	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STRIVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARISE	[redacted]	[redacted]	[redacted]			
LIBERTY	[redacted]	[redacted]	[redacted]			

*Adjusted mean change. Data for subgroup of patients for whom ≥3 prior prophylactic treatments have failed.
Abbreviations: BSC: best supportive care; MMD: monthly migraine day.

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of economic evidence for erenumab in migraine

The economic analysis demonstrates that erenumab is a cost-effective treatment in the migraine patients with ≥4 MMDs for whom ≥3 prior prophylactic treatments have failed when compared to BSC, with an ICER of £22,446 and £19,827 per QALY for the blended dose and 140 mg dose, respectively. Additionally, the economic analysis demonstrates that erenumab is a cost-effective treatment in chronic migraine patients for whom ≥3 prior prophylactic treatments have failed when compared to botulinum toxin, with ICERs of £18,893 and £17,832 per QALY, or when compared with BSC, with ICERs of £17,212 and £13,340 per QALY, for the blended dose and 140 mg dose, respectively.

Whilst the societal perspective is not part of the NICE reference case, it is important to note that adoption of this perspective significantly improves erenumab cost-effectiveness as migraine is a condition that predominantly affects a working age population. This analysis considered the indirect costs associated with missing work (absenteeism) or reduced productivity at work due to headache or migraine (presenteeism), with data collected from the MIDAS outcome in Study 295 and STRIVE. The ICER for erenumab versus BSC in the whole migraine base case population reduces from £22,446 to £2,947 per QALY for the blended dose, and from £19,827 to £328 for the 140 mg dose, when the societal perspective is included.

Generalisability of the analysis

The economic evaluation is based on patient populations included in the erenumab RCTs for whom ≥3 prior prophylactic treatments have failed. The whole population base case analysis in patients for whom ≥3 prior prophylactic treatments have failed reflects the anticipated population that erenumab will be used for in clinical practice, based on clinical expert opinions. The evaluation is relevant to all groups of patients encompassed in the decision problem, though it should be noted that this is an optimised population versus that defined in the marketing authorisation and the final scope issued by NICE.

Strengths of the economic evaluation

Strengths of the economic evaluation include that the efficacy of treatments within the model is based directly on data from high quality RCTs and that resource use was estimated from UK data. The efficacy profile for both the erenumab arm and the BSC comparator arm are derived from the same trials, which limits issues of heterogeneity and variability in comparator populations and trial design that can arise when drawing data from multiple different data sources.

In addition, the endpoints modelled, change in MMDs and percentage response to treatment, are key outcomes in migraine prophylaxis according to clinical guidelines and clinical expert opinion. The model structure allows for accurate tracking of both of these outcomes during the assessment period. By reproducing the patient distributions across MMDs for each treatment and each time-point, the model retains a strong faithfulness to the trial data. The structure avoids the use of arbitrarily established MMD cut-offs to define model-states and thus captures information that would otherwise be lost through grouping patients into health states. This model structure enables accuracy in the numbers of migraine days incurred or avoided, and thus the costs and

health benefit associated with these days can be quantified. Capturing the full MMD distribution also allows for the possibility that the impact of each additional MMD (in terms of utility loss and increased resource use) may not be constant across the MMD spectrum. The model also seeks to distinguish between responders and non-responders at the end of the assessment period in order to allow for discontinuation of non-responders, which reflects appropriate clinical practice.

Limitations of the economic evaluation

A limitation of the economic evaluation is that no meta-analysis of all four key erenumab studies presented could be performed to inform the whole population base case analysis. Study 295 used a different definition for a “migraine day” and a “headache day” to that of the studies in episodic migraine (STRIVE, ARISE and LIBERTY), therefore rendering any statistical pooling across all four trials inappropriate, as outcomes cannot be interpreted as equivalent across trials (see Table 7 for definitions of migraine and headache days across trials). Therefore, the analysis in the whole population employs data from Study 295 separately to pooled data from STRIVE, ARISE and LIBERTY. The whole population base case was performed by weighting the clinical outcomes for the chronic and episodic migraine populations by the expected split in clinical practice, which was based on market research from the UK (see B.3.3). Whilst there were limitations to this methodology it was considered the best available approach for estimating the cost-effectiveness of erenumab in the whole migraine population based on the available data and the differences in migraine day definitions between chronic migraine and episodic migraine studies.

Patients on treatment are assumed to maintain the reduction in MMD achieved in the assessment period and no future gaining or waning of treatment effect is incorporated. This is a simplifying assumption and in reality some patients will naturally recover whilst others will naturally decline over time. However, the assumption of sustained benefit with erenumab is supported by the open-label data.[75]

The dissipation of placebo effect is not accounted for in model, i.e. a proportion of BSC patients will respond and will continue to benefit. This conservative assumption was made in order to accurately convey the treatment effect observed in the trial data. In reality the placebo benefit may dissipate.

In summary, erenumab (with PAS) is cost-effective versus current standard of care in migraine patients

- Erenumab is a cost-effective treatment in the whole migraine population base case versus BSC at a cost-effectiveness threshold of £30,000, with an ICER of £22,446 per QALY gained for the blended dose (i.e. 50% 70 mg and 50% 140 mg), and £19,827 per QALY gained for the 140 mg dose.
- The blended dose of erenumab is also a cost-effective treatment in the chronic migraine population versus botulinum toxin, with an ICER of £18,893 per QALY gained, and versus BSC, with an ICER of £17,212 per QALY gained. Erenumab 140 mg is cost-effective versus both botulinum toxin, with an ICER of £17,832, and versus BSC, with an ICER of £13,340 per QALY gained.
- ICERs in the episodic migraine population exceeded £30,000 per QALY but, for the reasons outlined in sections B.1.1 and B.1.2.2, it is anticipated that the ICERs for the whole migraine population are the most relevant for decision making.
- Scenario analyses in the whole population and the chronic migraine populations showed that the ICERs were robust to changes in key model assumptions and input parameters.
- Finally, whilst the societal perspective is not part of the NICE reference case, it is important to note adoption of this perspective significantly improves erenumab cost-effectiveness given that migraine predominantly affects a working age population and has considerable societal impact.
    - Whole population (versus BSC): £2,947 per QALY gained (blended dose); £328 per QALY gained (140 mg dose)
    - Chronic migraine population (versus botulinum toxin): £3,477 per QALY gained (blended dose); £2,417 per QALY (140 mg dose)
    - Chronic migraine population (versus BSC): £1,797 per QALY gained (blended dose); erenumab dominates BSC (140 mg dose)
    - Episodic migraine (versus BSC): £13,071 per QALY gained (blended dose) and £17,946 per QALY gained (140 mg dose).

B.4 References

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B.5 Appendices

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: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: 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: Summaries of study NCT01952574, ARIS and completed OLE studies

Appendix M: Eligibility criteria for Study 295, STRIVE and LIBERTY

Appendix N: Definition of outcomes from Study 295, STRIVE and LIBERTY

Appendix O: Full results of outcomes in Study 295

Appendix P: Full results of outcomes in STRIVE

Appendix Q: Full results of outcomes in ARISE

Appendix R: Full results of outcomes in LIBERTY

Appendix S: Regression modelling for estimating change in MMDs

Appendix T: Assessment of response data

Appendix U: Derivation of utility values

Appendix V: Calculation of acute medication costs

Appendix W: Probabilistic sensitivity analysis

Appendix X: Re-evaluation period scenario analysis

Appendix Y: Societal perspective (productivity) scenario analysis

Appendix Z: Subgroup and exploratory analysis

Appendix AA: Results of base case analysis (without PAS)

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Single technology appraisal

Erenumab for preventing migraine [ID1188]

Dear Novartis

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 10 September 2018 from Novartis. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Your response and any supporting documents should be uploaded to NICE Docs

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Anna Brett, Technical Lead (Anna.Brett@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk.

Yours sincerely

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Literature searching

1. With reference to the PRISMA flow diagram for clinical effectiveness (Appendix D, Figure 1), please explain where the numbers for Congress searches come from in the original search (n=727) and the 2018 updated search (n=84), as these do not appear to match Table 4, Appendix D.

2. Please provide details of the source or reference for the filters used in cost-effectiveness searches in Appendix G for Embase and Medline.

3. Please clarify how adverse events were identified. If the searches reported in Appendix D were used, please confirm if results were screened for adverse events. If additional searches were used, please provide full details.

4. Please clarify why the clinical effectiveness searches were updated in July 2018, but cost-effectiveness searches, congress searches, grey literature searches and cost and healthcare resource identification searches were not updated?

Section A: Clarification on effectiveness data

Study selection

A1. Please clarify how many papers / studies were excluded *solely* on the basis of not having an English abstract or full text. Are any relevant studies likely to have been excluded on this basis?

A2. Please clarify why Section B.2.1 reports that the SLR identified 9 studies of erenumab but Table 4 only lists 8 studies. Additionally, please supply the correct reference for study NCT20130255 in Table 4.

A3. Please confirm the status of study reference 128 (NCT02174861) in Table 7 of Appendix D. Is this an ongoing study? If so when is it due to complete?

A4. Please confirm that in the systematic review 'adult' was interpreted to mean people aged over 18 as per the erenumab trials identified.

Included studies (erenumab)

A5. **Priority**: Please provide a table with patient numbers showing all concomitant medication received in the 4 main trials (Study 295, STRIVE, ARISE and LIBERTY) in intervention and placebo groups, for the specified optimised population (≥3 failed prophylactic therapies), whole trial populations and exploratory analysis population (≥2 failed prophylactic therapies).

A6. **Priority**: Please provide more detail on what Best Supportive Care (BSC) in the UK includes. Please elaborate on why the company believes that placebo in the erenumab trials is a good proxy for BSC in the UK.

A7. **Priority:** The submission states in relation to erenumab that: "The recommended dosage is 70 mg Q4W, although some patients may benefit from a dosage of 140 mg Q4W, which is administered as two consecutive injections of 70 mg each." Please

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clarify which patients are expected to benefit from the 140 mg Q4W dose and how these patients can be identified before initiating treatment with erenumab.

A8. **Priority:** The clinical effectiveness data presented in the submission appear to indicate that patients for whom ≥3 prior prophylactic treatments have failed are likely to need the 140 mg Q4W dose of erenumab. Additionally, it is stated in section B.2.6 that "patients for whom ≥3 prior prophylactic treatments have failed may benefit from starting treatment on the higher 140mg dose." It is therefore unclear why the "blended dose" has been used in the company base-case; please clarify.

A9. **Priority:** Please provide adverse events data, by treatment group, for the specified optimised population (failed ≥3 prophylactic therapies), for the 4 main trials.

A10. Please provide details of the previous failed prophylactic treatments (with numbers of patients), by treatment group, for the optimised population (≥3 previous failed prophylactic treatments) in each of the 4 main trials.

A11. Please clarify how many patients in the optimised population had a diagnosis of migraine with aura across the 4 main trials.

A12. Please check Figure 3, Appendix D; the numbers analysed for efficacy in the placebo group do not appear to be correct.

A13. Please clarify whether erenumab is expected to be used in patients under 18 or over 65 years (the main trials excluded these age groups)?

A14. Clinical pathway: Figure 2 in the Company Submission (CS) clearly places erenumab at fourth line only. However, an analysis for patients for whom ≥2 prior prophylactic treatments have failed is also included in the CS and it is stated that this subgroup is relevant as some patients may be unsuitable for a further treatment with a prophylactic therapy as a result of contraindications. If erenumab is expected to be used in some patients for whom fewer than 3 prophylactic treatments have failed, please amend figure 2 appropriately and include an indication of the proportions of patients who may be eligible for treatment with erenumab at each line.

A15. Please provide a justification (references) to support the choice of 50% reduction in monthly migraine days (MMD) to define a responder.

Indirect comparison with botulinum toxin

A16. Please provide details of outcome definition and measurement in PREEMPT for mean monthly headache days (MHD) and >50% responder rate.

A17. Table 15 of the CS provides key clinical effectiveness results from Study 295 at week 12. However, these are different to those from the full trial population at 12 weeks used in the ITC as reported in Table 17, Appendix D. Please clarify the reasons for the discrepancies between these 2 tables. In particular, why are the numbers with a

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50% reduction in mean MHD available for the subgroup but not the full trial population?

Ongoing studies

A18. Are there any further analyses planned or publications in progress for any of the 4 main trials? If so, when will these be available?

Section B: Clarification on cost effectiveness data

Model structure

B1. Treatment response is defined as a ≥50% reduction from baseline in MMDs. However, according to NICE technology appraisal guidance for botulinum toxin in chronic migraine[1], treatment should be stopped in people whose condition: 1) is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or 2) has changed to episodic migraine (defined as fewer than 15 headache days per month) for 3 consecutive months. The committee concluded that a 30% response rate was the most clinically relevant and reasonable negative stopping rule on which to base its decision.

a. Please justify why the economic model adopts a different approach than that recommended by the committee for botulinum toxin.
b. Please provide details regarding the input parameters and assumptions used in scenario analysis 7 (using a 30% response rate for the stopping rule).

Population

B2. For the base-case analysis it is assumed that people with chronic migraine comprise 66% of the total population, and people with episodic migraine the remainder (34%). This is based on Novartis. Data on file: UK Optimisation Research Report, 2018 (document provided). Please provide more detail on how these proportions were calculated and whether the "low-frequency episodic migraine" population is included in the 34%.

B3. The definition of high-frequency episodic migraine (HFEM) is inconsistent throughout the CS. Both 8-14 MHDs and 8-14 MMDs are used to describe this subgroup, and other definitions (for example, 10-14 MHDs) can be found in the literature (Torres-Ferrus et al. 2017[2]).

a. Please clarify what definition should be used to define the HFEM subgroup.
b. Please adopt the definition of 10-14 MHDs for the HFEM subgroup and report on the results

B4. For the subgroup analysis of patients with HFEM, please provide more detail on:

a. How subgroup specific transition probabilities were estimated, and report these.
b. How subgroup specific costs were estimated, and report these (if not the same as the base-case).

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c. How subgroup specific utility values were estimated, and report these (if not the same as the base-case).

B5. In addition to the whole migraine population, patients were split into an episodic (defined as <15 MHDs and ≥4 to <15 MMDs) and chronic migraine population (defined as ≥15 MHDs and ≥8 MMDs). However, these groups are not exhaustive, given that patients might experience ≥15 MHDs, but ≥4 to <8 MMDs.

a. Please provide the number of patients that fall in between the definitions of episodic- and chronic migraine (i.e. patients with ≥15 MHDs, but ≥4 to <8 MMDs).
b. Please explain and justify how this population was dealt with in the model (for the whole population base-case analysis), and amend any analysis if necessary.

Intervention and comparators

B6. **Priority** In appendix Z.2 the results of the scenario analyses for erenumab 70 mg are presented.

a. Please provide more details on which parameters were used in these analyses for erenumab 70 mg.
b. Please provide full incremental analyses, adding both erenumab 70 mg and 140 mg separately (instead of the blended dose) for all populations considered in the base-case (whole migraine population, chronic migraine population and episodic migraine population).

Perspective, time horizon and discounting

B7. Tables 83 and 85 in the CS summarise the scenario analyses in the chronic migraine population, comparing the blended dose erenumab to botulinum toxin and BSC respectively. When extending the time horizon from 10 years to 15 years (scenario 9), please explain why this leads to an increased ICER when comparing erenumab to botulinum toxin, and a decreased ICER when comparing erenumab to BSC (compared to the base-case ICER).

Effectiveness

B8. **Priority:** People with migraine can have stable / persistent migraine, clinical remission, partial remission or progression. Based on the AMPP study (US), after 1 year the proportions would be 84% persistence, 10% clinical remission, 3% partial remission and 3% progression.[3] Accordingly, people can go from low frequency episodic migraine, to chronic migraine (potentially via high frequency episodic migraine) and vice versa.[4] Currently, these aspects of migraine (i.e. its natural progression) are not fully incorporated in the economic model.

a. Please elaborate on the expected impact of not fully incorporating the natural progression of migraine on the estimated cost effectiveness.
b. Please incorporate scenario analyses exploring the impact of different plausible scenarios regarding the natural progression of migraine.

B9. **Priority:** For the extrapolation of treatment effectiveness, it is assumed that reduction in MMD frequency is maintained throughout the time horizon of the model.

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This is justified by referring to open-label, non-randomised extension studies (section B.3.3.4 of the CS):

a. Please justify, based on the data reported from the studies, why it is believed that the reduction in MMD frequency while having erenumab was maintained at 64 weeks, particularly given that the open-label extension did not allow for a comparison with placebo.
    i. For patients having erenumab at the 70 mg dose
    ii. For patients having erenumab at the 140 mg dose
b. Please justify why it is believed that the reduction in MMD frequency while having erenumab at 64 weeks was maintained up to 10 years.
    i. For patients having erenumab at the 70 mg dose
    ii. For patients having erenumab at the 140 mg dose
c. Please justify why the long-term MMD frequency distributions (stratified for responders and non-responders) are assumed to be treatment dependent.
d. Please provide scenarios exploring alternative assumptions about the long-term effectiveness of erenumab/maintenance of MMD frequency. Please also include scenarios where the favourable MMD frequency distribution for responders and erenumab non-responders is linearly altered over time to become identical to the MMD frequency distribution for BSC non-responders.

B10. The nature of treatment discontinuation determines whether patients either rebound to the baseline MMD distribution (discontinuation due to adverse events or long-term discontinuation) or are assumed to maintain the non-responder MMD improvement achieved at week 12 (discontinuation due to non-response at week 12).

a. Please justify why the nature of the discontinuation determines whether patients either rebound to the baseline MMD distribution or maintain the non-responder MMD improvement achieved at week 12.
b. Please provide scenario analyses assuming all patients that discontinue have the week 12 non-responder MMD distribution.

B11. For episodic migraine, data from ARISE, LIBERTY and STRIVE have been pooled to inform clinical effectiveness parameters in the economic model (Sections B.3.3.2 and B.2.7). Please specify how the patient-level data were pooled, and whether the analysis adjusted for differences between studies.

B12. A normal distribution is assumed for the MMD frequency distribution. In Appendix S it is stated “The normal distribution was selected in the base-case for the statistical distribution to fit both the Study 295 data and STRIVE data”.

a. Please justify this choice to assume a normal distribution (e.g. by providing data on the statistical goodness of fit for the different distributions).
b. Please justify why only Study 295 data and STRIVE data were used to inform the selection of the normal distribution (i.e. not ARISE and LIBERTY), and include an analysis where ARISE and / or LIBERTY are used, if considered appropriate.
c. Please elaborate on the potential bias and resulting impact on model outcomes when assuming a normal distribution, given the ceiling effect that appears present in Figure 24 of the CS.

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Adverse events

B13. The impact of adverse events on costs and health-related quality of life is not explicitly considered in the economic model. This is justified by stating that adverse events are usually non-severe. However, adverse events are considered relevant outcomes according to the final scope. Therefore, please provide a scenario analysis explicitly incorporating the impact of adverse events on costs and health-related quality of life, also considering the adverse event profiles of erenumab 70mg and 140mg separately (in the 70mg, 140mg and blended analyses).

Health related quality of life

B14. **Priority:** Utility values used in the model were mapped from the Migraine-Specific Quality of Life Questionnaire (MSQ) collected in Study 295, STRIVE and ARISE. Utility values were then estimated through multilevel models. However, the description of statistical model selection procedures lacks detail.

a. Please provide details on:
    i. how data from STRIVE and ARISE were pooled (episodic migraine) and how data from all 3 trials were pooled (whole population),
    ii. the number of patients and observations included in the analyses (stratified by trial and MMD frequency),
    iii. the number of missing observations and how these were handled,
    iv. the characteristics of patients who were not included in the analysis of health related quality of life data,
    v. the characteristics of patients included in the analyses (stratified by trial, treatment [erenumab or placebo] and MMD frequency),
    vi. a description of the covariates included in the statistical models,
    vii. statistical fit statistics of each fitted model (e.g. Akaike information criterion (AIC), R^2)
    viii. justification for selecting the models used in the base-case analysis.
b. Are the utility values mapped from the MSQ obtained from the subgroup of patients who received either placebo or erenumab (for both 70mg and 140mg) after ≥3 prior prophylactic treatments? If not, please re-estimate the utility values for this subgroup only (provide the details requested under B14a when performing these analyses). Please use these re-estimated utility values in all requested analyses.
c. Please provide a scenario analysis in which health state utility values are directly estimated for each health state instead of estimating utility values for each MMD frequency (provide the details requested under B14a). Please use the mapped MSQ utility data for this analysis.

B15. **Priority:** Despite having access to EQ-5D data (NICE reference case), mapped utilities were used in the company base-case.

a. Please clarify whether utility data applied in scenario 13 for the episodic migraine population were obtained using the preferred cross-walk algorithm according to the NICE position statement[5]. If not, please re-estimate the utility values based on this algorithm.
b. Please provide details on

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i. the number of patients and observations included in the analysis (stratified by MMD frequency),
ii. the number of missing observations and how these were handled,
iii. the characteristics of patients included in and excluded from the analysis
iv. the selection procedure of the statistical models used to estimate these utility values (please provide the details requested under B14a).

c. Please confirm that these utility values were obtained from the subgroup of patients with ≥3 prior prophylactic treatments. If not, please re-estimate these utility values based on this subgroup and provide the details requested in B15b.
d. Please provide a scenario analysis using the utility values estimated in B15c in all populations included in the CS.
e. Multi-level models were used to estimate base-case utility values conditional on MMD frequency. Please provide a scenario analysis in which health state utility values are directly estimated based on the mapped EQ-5D-5L data, instead of estimating utility values for each MMD frequency (provide the details requested under B15b).

B16. Gillard et al. 2012[6] present two algorithms to obtain EQ-5D-3L, one based on the MSQ and one based on the HIT-6.

a. Please provide a scenario analysis using the mapping algorithm based on the HIT-6 instrument (in all populations).

B17. Disutilities for adverse events and mode of administration (used in scenario analysis 13) have been estimated through a vignette-based study described in Appendix U.

a. Please provide the demographic and clinical characteristics of all respondents, stratified by subgroups (i.e. general public respondents and respondents with migraine).
b. Tables 92 and 93 of Appendix U provide relative utility decrements associated with adverse events and mode of administration for each treatment compared to erenumab. Please provide the absolute utility decrements associated with adverse events and mode of administration for each treatment. Please also provide the estimated utility values for each health state and adverse events described in Appendix U, stratified by subgroups (i.e. general public respondents and respondents with migraine).
c. Please provide the source (both reference and digital copy of the source) from which the adverse event rates have been obtained (i.e. the likelihood of being helped or harmed [LHH] study, as mentioned in Appendix U).
    i. Please describe how the study/studies used was/were identified.
d. Please provide details on the expert feedback from UK clinicians who supported the inclusion of mode of administration decrements only in a scenario analysis. Please provide
    i. The number of experts asked.
    ii. The questions asked.
    iii. The answer to each question per expert.

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e. Please provide a scenario analysis in which both mode of administration and AE-related utility decrements are included (provided in response to question B17b).

Resource use and costs

B18. Please comment on the medications listed in Appendix V[7]:

a. Are the listed medications in line with NICE guidelines for acute migraine medication?
b. Are the medications selected comprehensive and representative of resource utilisation for treatment of acute migraine in the UK?
c. On what grounds were the brands and dosage of medications selected?
d. What weights were applied to calculate the weighted average of triptan medication cost per day and where did these weights come from? Please indicate the source and provide an overview of this data.
e. If sumatriptan injections are used for acute migraine treatment in line with guidelines, why were sumatriptan injections excluded from the triptan medication cost?

B19. Please comment on the sources used for resource use and costs (including the National Health and Wellness survey (NHWS) of 2017 and 2018, Study 295, ARISE, LIBERTY and STRIVE):

a. Are all estimates obtained from a UK population with ≥3 prior failed prophylactic treatments?
b. If not, please re-estimate and present adjusted estimates for the population with ≥3 prior failed treatments and provide a scenario analysis using these estimates (in all populations included in the company submission).

B20. For the regression models of migraine drug days and other medication days (Table 97, Appendix V[7]):

a. Please detail the method used, i.e. describe how the data from Study 295, STRIVE and ARISE have been pooled.
b. Describe the methods used to fit the models as well as other relevant information (e.g. proportion missing data, number of patients included in the analyses, number of observations) and provide statistical fit statistics (such as the Akaike Information Criterion, R^2) of each model fitted to the data.
c. Please describe the model selection procedure.

B21. The CS states that in the NHWS study, patients were grouped into categories based on MHDs or number of migraines, the latter grouping being used in the model, assuming number of migraines better approximates MMD.[8] However, Table 58 of the CS[8] presents NHWS by MMD and Table 96 of Appendix V[7] presents NHWS data by MHD.

a. Please clarify which grouping method was used.
b. Please provide a scenario analysis using the alternative assumption of MHD approximating MMD.

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Cost effectiveness results

B22. **Priority:** The NICE reference case requires that uncertainty be explored through appropriate sensitivity analyses. However, not all the parameters are examined for their impact on model outcomes.

a. All relevant parameters should be included in the probabilistic sensitivity analysis (PSA). However, influential parameters associated with treatment and relative effectiveness, such as response rates for erenumab, treatment effect compared with BSC, treatment discontinuation and frequency of MMDs for responders and non-responders, are currently excluded from the PSA. It is important to note that the distributions of frequency of MMDs only reflects first order uncertainty (heterogeneity) and not second order uncertainty, which needs to be incorporated in the PSA. Please provide a model enabling a PSA that incorporates all relevant parameters, including response rates, relative effectiveness compared with BSC, treatment discontinuation and MMD frequency.
b. Please also submit a model file providing fully incremental probabilistic analyses for all interventions (including erenumab 70mg and 140mg as separate interventions instead of using the blended dose) and comparators, such that the CEAC represents all treatments simultaneously. Please enable this for comparisons in all populations considered in the base-case (whole migraine population, chronic migraine population and episodic migraine population).

Validation and transparency

B23. **Priority:** Please provide a cross-validation of the submitted cost effectiveness analysis compared with NICE TA260,[1] including a table overview that considers:

a. Model structure and major assumptions
b. Intervention and comparators
c. Response rates and other influential transition probabilities
d. HRQoL data used
e. Results
f. If applicable, possible explanations for different results compared with NICE TA260.

References

[1] National Institute for Health and Care Excellence. *Botulinum toxin type A for the prevention of headaches in adults with chronic migraine: technology appraisal guidance [Internet]*. London: NICE, 2012 [accessed 23.5.18]. 51p. Available from: nice.org.uk/guidance/ta260

[2] Torres-Ferrus M, Quintana M, Fernandez-Morales J, Alvarez-Sabin J, Pozo-Rosich P. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. *Cephalalgia* 2017;37(2):104-13.

[3] Bigal ME, Lipton RB. Migraine chronification. *Curr Neurol Neurosci Rep* 2011;11(2):139-48.

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[4] Bigal ME, Lipton RB. Concepts and mechanisms of migraine chronification. *Headache* 2008;48(1):7-15.

[5] National Institute for Health and Care Excellence. *Position statement on the use of the EQ-5D-5L valuation set [Internet]*. London: NICE, 2017 [accessed 22.5.18]. 3p. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf

[6] 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 Health* 2012;15(3):485-94.

[7] Novartis Pharmaceuticals UK Ltd. *Single technology appraisal (STA). Erenumab for preventing migraine [ID1188]: company evidence submission appendices. September 2018*. Frimley: Novartis Pharmaceuticals UK Ltd, 2018. 257p.

[8] Novartis Pharmaceuticals UK Ltd. *Single technology appraisal (STA). Erenumab for preventing migraine: company evidence submission to National Institute for Health and Care Excellence [ID1188]. September 2018*. Frimley: Novartis Pharmaceuticals UK Ltd, 2018. 200p.

Single technology appraisal

Erenumab for preventing migraine [ID1188]

Dear Kate,

Thank you for the opportunity to respond to the clarification questions from the Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE. We thank the team for their general comments on the submission and hope that our responses to the individual questions below provide clarity on our approach in the submission and the necessary additional information where this has been possible. The economic analyses provided in response to the questions further reinforce the cost-effectiveness of erenumab in the proposed target population of patients with ≥4 MMDs who have failed on ≥3 prior prophylactic therapies.

As requested, we have uploaded to NICE Docs two versions of this response letter: one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please do not hesitate to get in touch should you have any questions regarding our response.

Kind regards,

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Literature searching

1. With reference to the PRISMA flow diagram for clinical effectiveness (Appendix D, Figure 1), please explain where the numbers for Congress searches come from in the original search (n=727) and the 2018 updated search (n=84), as these do not appear to match Table 4, Appendix D.

The number of included congress abstracts in the company submission is correct. However, the results from the searches were erroneously reported in the original company submission. The following changes have been made to update the reporting of the congress searches:

- The total congress hits from the original systematic literature review (SLR) have been changed from 727 to 719 in the PRISMA flow diagram, as 8 abstracts from 2015 were included erroneously. The PRISMA numbers have been adjusted accordingly
- The total congress hits from the update have been changed from 84 to 91 in the PRISMA flow diagram as these had previously been totalled incorrectly
- Search terms (hits) in the table have been adjusted as they were previously recorded incorrectly so this now adds up to 810 (719 + 91)
- The relevant hits in the table were incorrect (n=28), but have been updated to match the PRISMA flow diagram and the included congress abstracts, listed in Appendix D, Table 7 of the company submission (n=24)

Table 1: Search terms used for congress websites

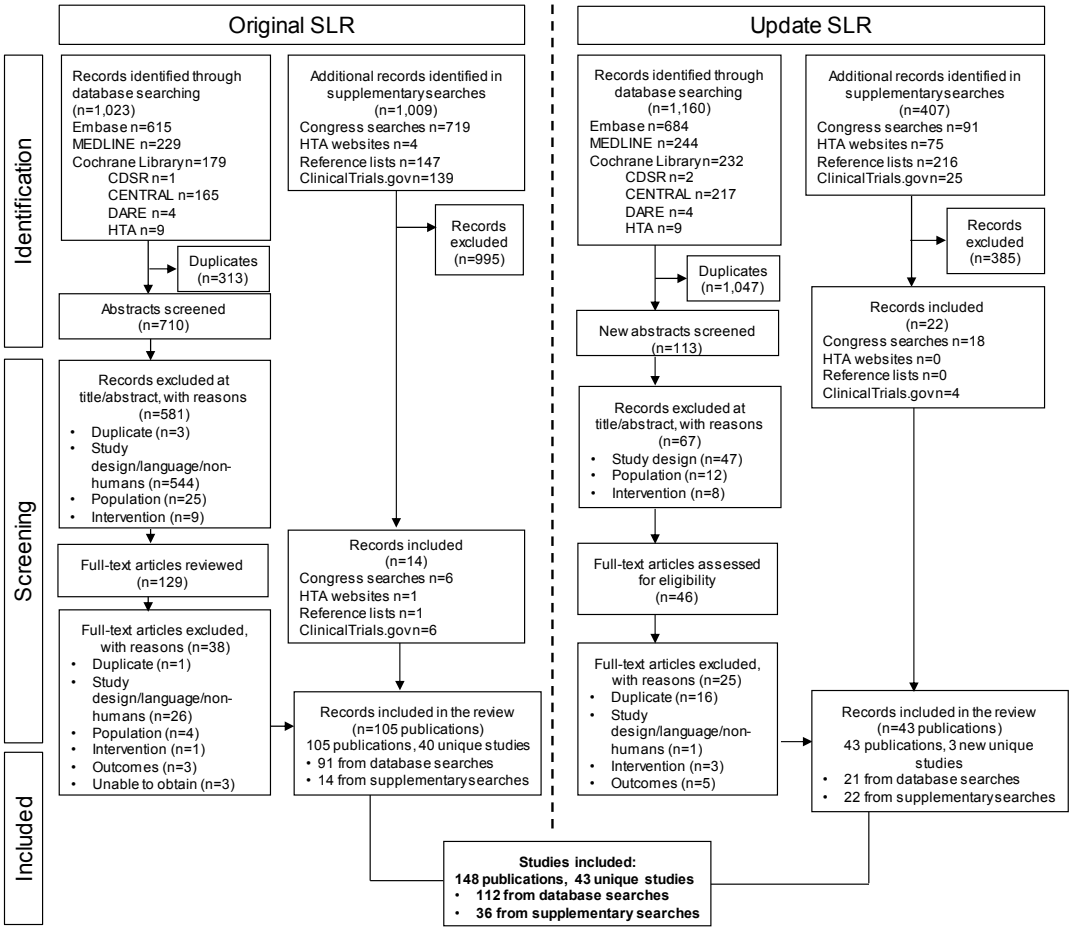
Congress	Link	Search terms (Hits)	Search strategy	Relevant hits
American Academy of Neurology (AAN) 2016, 2017 and 2018	2016: http://www.abstractsonline.com/pp8/#!/4046/ 2017: http://submissions.mirasmart.com/AAN2017/itinerary/SearchResultsProgram.asp 2018: https://submissions.mirasmart.com/AAN2018/itinerary/SearchHome.asp	2016: Migraine (2) 2017: Migraine (40) 2018: Erenumab (10) Botox (6) Botulinum (19)	The term was entered into the 'Search' box. Each abstract was screened for inclusion.	2016: Relevant: 2 After deduplication: 0 2017: Relevant: 2 After deduplication: 0 2018: Relevant (erenumab): 9 Relevant (botox): 0 Relevant (botulinum): 0 After deduplication (erenumab): 0 After deduplication (botox): 0 After deduplication (botulinum): 0

Congress	Link	Search terms (Hits)	Search strategy	Relevant hits
American Headache Society (AHS) 2016, 2017 and 2018	Abstract books were in PDF form	2016: Migraine (4) 2017: Migraine (149) 2018: Erenumab (8) Botox (7) Botulinum (18)	The PDFs were searched using the 'ctrl-f' function for the search term.	2016: Relevant: 1 After deduplication: 0 2017: Relevant: 9 After deduplication: 0 2018: Relevant: 10 After deduplication: 10
American College of Neuropsychopharmacology (ACNP) 2016 and 2017	Abstract books were in PDF form	2016: Migraine (1) 2017: Migraine (5)	The PDFs were searched using the 'ctrl-f' function for the search term.	2016: Relevant: 0 After deduplication: 0 2017: Relevant: 0
Association of British Neurologists (ABN) 2016, 2017 and 2018	2016: http://jnnp.bmj.com/content/87/12#ABNAbstracts2016 2017: https://jnnp.bmj.com/content/88/Suppl_1 2018: Abstract book was in PDF form	2016: Migraine (0) 2017: Erenumab (0) Botox (0) Botulinum (0) 2018: Erenumab (3) Botox (0) Botulinum (3)	Journal supplement searched via the link provided. The search term was then searched for using the 'ctrl-f' function.	2016: Relevant: 0 2017: Relevant: 2018: Relevant: 3 After deduplication: 3
European Academy of Neurology (EAN) 2016, 2017 and 2018	Abstract books were in PDF form	2016: Migraine (2) 2017: Migraine (7) 2018: Erenumab (5) Botox (1) Botulinum (11)	The PDFs were searched using the 'ctrl-f' function for the search term.	2016: Relevant: 1 After deduplication: 0 2017: Relevant: 6 After deduplication: 0 2018: Relevant: 5 After deduplication 5
European Association of Neurosurgical	2016: https://academy.eans.org/eans/#!*search=migraine*browseby=6*listing=3*sortby=1 2017:	2016: Migraine (1) 2017: Migraine (0)	The search term was entered into the 'search' box.	2016: Relevant: 0 2017: Relevant: 0

Congress	Link	Search terms (Hits)	Search strategy	Relevant hits
Societies (EANS) 2016 and 2017	https://academy.eans.org/eans/#!*ce_id=1240*search=migraine*browseby=3*listing=1*sortby=2			
European Headache and Migraine Trust International Congress (EHMTIC) 2016 (not held in 2017)	Abstract book was in PDF form	Migraine (9)	The PDF was searched using the 'ctrl-f' function for the search term.	Relevant: 4 After deduplication: 0
European Headache Federation (EHF) 2017 (not held in 2016)	Abstract book was in PDF form	Migraine (155)	The PDF was searched using the 'ctrl-f' function for the search term.	Relevant: 10 After deduplication: 0
International Headache Society (IHS) 2017 (not held in 2016)	Abstract book was in PDF form	2017: Migraine (336)	The PDF was searched using the 'ctrl-f' function for the search term.	2017: Relevant: 9 After deduplication: 6
PAINWeek 2016 and 2017	Abstract books were in PDF form	2016: Migraine (3) 2017: Migraine (5)	The PDF was searched using the 'ctrl-f' function for the search term.	2016: Relevant: 0 After deduplication: 0 2017: Relevant: 0
World Congress of Neurology (WCN) 2017 (not held in 2016)	2017: http://www.jns-journal.com/issue/S0022-510X(17)X0010-5	Migraine (0)	'Search within issue' was selected, the search term was entered and 'select abstract' was clicked.	2017: Relevant: 0

Abbreviations: AAN: American Academy of Neurology; ABN: Association of British Neurologists; ACNP: American College of Neuropsychopharmacology; AHS: American Headache Society; EAN: European Academy of Neurology; EANS: European Association of Neurosurgical Societies; EHF: European Headache Federation; EHMTIC: European Headache and Migraine Trust International Congress; IHS: International Headache Society; WCN: World Congress of Neurology.

Figure 1: Revised PRISMA flow diagram for the SLR



Abbreviations: CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Controlled Register of Trials; DARE: Database of Abstracts of Reviews of Effects; HTA: Health Technology Assessment; SLR: systematic literature review.

2. Please provide details of the source or reference for the filters used in cost-effectiveness searches in Appendix G for Embase and Medline.

Search terms for cost-effectiveness studies and cost and resource use studies were based on the Scottish Intercollegiate Guidelines Network (SIGN) search filter for economic studies.[1] All of the terms from the filter were used but some extra terms were added to increase the sensitivity of the search. Search terms for health state utility studies were based on those proposed in the NICE Decision Support Unit (DSU)'s Technical Support Document 9.[2]

3. Please clarify how adverse events were identified. If the searches reported in Appendix D were used, please confirm if results were screened for adverse events. If additional searches were used, please provide full details.

Adverse events (AEs) were identified from the results of the database searches detailed in Appendix D of the company submission. Results were screened for AEs including, but not limited to, the AEs reported in Appendix D, Table 6, 'Eligibility criteria for SLR' of the company submission.

4. Please clarify why the clinical effectiveness searches were updated in July 2018, but cost-effectiveness searches, congress searches, grey literature searches and cost and healthcare resource identification searches were not updated?

The searches for the cost-effectiveness searches, congress searches, grey literature searches and cost and healthcare resource identification searches were updated in September 2018. Please find the updated results in Appendix A.

Section A: Clarification on effectiveness data

Study selection

A1. Please clarify how many papers / studies were excluded solely on the basis of not having an English abstract or full text. Are any relevant studies likely to have been excluded on this basis?

At the full-text review stage, one paper was excluded solely on the basis of not having an English full text: *Blumenkron D, Rivera C, Cuevas C. Efficacy of botulinum toxin type A in patients with migraine. Medicina Interna de México. 2006;22(1):25-31*.[3] This paper considered the efficacy of botulinum toxin in patients with migraine. However, the study involved only 30 patients and all patients were recruited from a single hospital in Mexico, limiting generalisability to the UK migraine patient population. In addition, the trial does not specifically state the frequency of migraine attacks, instead characterising patients as mild, moderate, severe and very severe, therefore it is unclear whether results are in patients classified as either chronic or episodic migraine.

A2. Please clarify why Section B.2.1 reports that the SLR identified 9 studies of erenumab but Table 4 only lists 8 studies. Additionally, please supply the correct reference for study NCT20130255 in Table 4.

Document B, Table 4 in the company submission refers to the relevant clinical evidence informing the submission.

Two studies identified in the SLR were omitted in error from Table 4 of the original submission. These are listed below. Neither of these studies informed the clinical evidence base for the economic model.

- NCT02630459[4] – this study is ongoing, specific to Japan, and no results are available. The estimated study completion date is 3rd June 2019.
- NCT03333109[5] – the EMPOWER study – study of safety and efficacy in episodic migraine patients ongoing in countries other than the US, Europe and Japan. The estimated completion date is 7th February 2020.

In addition, study NCT02174861[6] was included – this study was a long-term follow-up of patients enrolled in Study 295. Results are presented in Section B.2.9 (long-term safety data). This study is the same as study NCT20130255 originally listed in Table 4, which refers to the additional study ID number for this trial. This study was incorrectly described as NCT20130255, when the actual study ID is NCT02174861 (20130255 is the Novartis study number for this open-label extension). Results have recently been presented at a congress (Tepper *et al*., Assessment of long-term safety and efficacy of erenumab during open-label treatment of subjects with chronic migraine. Presented at: AHS, San Fransisco, CA, USA, June 28–July 1 2018).[7]

It should be noted that that the total number of studies of erenumab in Table 4 when adding these studies is 10.

A3. Please confirm the status of study reference 128 (NCT02174861) in Table 7 of Appendix D. Is this an ongoing study? If so when is it due to complete?

As discussed in the response to Question A2, NCT02174861 is a long-term follow-up of patients enrolled in Study 295. This study has now been completed.

A4. Please confirm that in the systematic review 'adult' was interpreted to mean people aged over 18 as per the erenumab trials identified.

As per the erenumab trials, the SLR classified adults as people ≥18 years of age.

Included studies (erenumab)

A5. **Priority**: Please provide a table with patient numbers showing all concomitant medication received in the 4 main trials (Study 295, STRIVE, ARISE and LIBERTY) in intervention and placebo groups, for the specified optimised population (≥3 failed prophylactic therapies), whole trial populations and exploratory analysis population (≥2 failed prophylactic therapies).

Study 295

The most common acute headache medications used during baseline or during the double-blind treatment phase were in the categories of triptan-based migraine medications ([redacted]%, [redacted]%, and [redacted]% of subjects in the placebo, erenumab 70 mg, and erenumab 140 mg arms, respectively) and non-opioid acute headache medications ([redacted]%, [redacted]%, and [redacted]%, respectively; see Table 2). Please see Table 14-8.2 on pages 802 and 803 of the clinical study report (CSR) for further details.

Table 2: Concomitant medication usage in Study 295

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Full study population	**n=282**	**n=190**	**n=188**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**

Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥2 prior treatments have failed	**n=141**	**n=92**	**n=92**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

STRIVE

The most frequent (>10%) acute headache medications used during baseline and during the double-blind treatment phase were in the categories of non-opioid acute headache medications ([redacted]%, [redacted]%, and [redacted]% of subjects in the placebo, erenumab 70 mg, and erenumab 140 mg arms, respectively) and triptan-based migraine medications ([redacted]%, [redacted]%, and [redacted]%, respectively; see Table 3). Please see Table 14-8.7.1 on pages 1,159 and 1,160 in the CSR for further details.

Table 3: Concomitant medication usage in STRIVE

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Full study population	**n=319**	**n=314**	**n=319**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]

Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=27**	**n=24**	**n=23**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥2 prior treatments have failed	**n=54**	**n=49**	**n=58**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

ARISE

The most common acute headache medications used during baseline and during the double-blind treatment phase were in the categories of non-opioid acute headache medications ([redacted]% and [redacted]% of subjects in the placebo and erenumab 70 mg arms, respectively) and triptan-based migraine medications ([redacted]% and [redacted]%, respectively; see Table 4). Please see Table 14-8.7.1 on page 659 in the CSR for further details.

Table 4: Concomitant medication usage in ARISE

	Placebo	Erenumab 70 mg
Full study population	**n=289**	**n=283**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥2 prior treatments have failed	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]

LIBERTY

Approximately a third of the total safety analysis set ([redacted]%) received concomitant therapy (any ATC class) during the double-blind treatment phase and the proportion was similar between the

erenumab 140 mg ([redacted]%) and placebo (34.7%) groups. Please see Table 14.3-13 on page 267-276 of the CSR for further details. The majority of patients used acute headache medication during baseline and the double-blind treatment phase. Triptan/ergotamine-based migraine medications and analgesic acute headache medications were the most frequently used headache medications. A similar proportion of patients in the erenumab 140 mg and placebo groups had taken triptans/ergotamines ([redacted]% vs [redacted]%, respectively) as well as analgesics ([redacted]% vs. [redacted]%, respectively). In addition, a small percentage of patients in both treatment groups had taken opioid-containing acute headache medications during baseline and the double-blind treatment phase ([redacted]% vs [redacted]%, respectively; see Table 5). Please see table 14.3-1.4 on page 277 in the CSR for further details.

Table 5: Concomitant medication usage in LIBERTY

	Placebo	Erenumab 140 mg
Full study population	**n=123**	**n=1118**
Triptan/Ergotamine-based migraine medications	[redacted]	[redacted]
Analgesics acute headache medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	n=[redacted]	n=[redacted]
Triptan/Ergotamine-based migraine medications	[redacted]	[redacted]
Analgesics acute headache medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]

A6. **Priority**: Please provide more detail on what Best Supportive Care (BSC) in the UK includes. Please elaborate on why the company believes that placebo in the erenumab trials is a good proxy for BSC in the UK.

As discussed in Document B, Section B.1.2.1, the only option for the majority of patients for whom ≥3 prophylactic treatments have failed is BSC, which consists of continued treatment with acute medication. The relevant NICE guideline (CG150), recommends combination therapy with an oral triptan and a non-steroidal anti-inflammatory drug (NSAID), or an oral triptan and paracetamol, as first-line acute treatment options for patients with migraine.[8] Similarly, the British

Association for the Study of Headache (BASH) guidelines recommend a stepped management programme comprising NSAIDs, including aspirin and ibuprofen, and triptans as required.[9]

Patients in the placebo arms of Study 295, STRIVE, ARISE and LIBERTY were prescribed any treatments deemed necessary to provide adequate supportive care for the duration of the studies (see Question A5). The majority of patients used acute medications during these trials, with triptan-based migraine medications and non-opioid acute headache medications being the most frequent treatment categories used by patients across all arms of these trials. As these treatment categories align with the acute treatment options recommended in clinical guidelines, the placebo arms of these trials are considered to adequately reflect BSC in UK clinical practice.

This is supported by the NICE appraisal for botulinum toxin for chronic migraine (TA260), in which "standard management" (i.e. BSC) was accepted as an appropriate comparator, and was modelled based on the placebo arm of the PREEMPT trials which formed the clinical evidence base for the botulinum toxin appraisal. Similar, to the erenumab studies, patients in both the botulinum toxin and placebo arms were treated with rescue medications such as analgesics and triptans during attacks.

A7. **Priority:** The submission states in relation to erenumab that: "The recommended dosage is 70 mg Q4W, although some patients may benefit from a dosage of 140 mg Q4W, which is administered as two consecutive injections of 70 mg each." Please clarify which patients are expected to benefit from the 140 mg Q4W dose and how these patients can be identified before initiating treatment with erenumab.

The licence for erenumab does not indicate the specific patient population expected to benefit from the 140 mg dose of erenumab.[10] However, as discussed in Document B, Section B.2.6., numerically superior clinical outcomes were observed for patients treated with erenumab 140 mg compared to erenumab 70 mg in the subgroup of patients for whom ≥3 prior treatments have failed. Additionally, there is no difference in the safety profiles of the 70mg and 140mg doses. The 140 mg dose may therefore be most appropriate for the patient population for whom ≥3 prior treatments have failed: the optimised population considered in this submission. This is supported by feedback from six expert UK neurologists, who considered that starting patients on the 140 mg dose may be the most efficient treatment approach for those patients with the greatest unmet need.[11] This patient population can be identified through their usage of prior prophylactic treatments, and it is estimated that overall 19% of patients classified as having chronic migraine and 10% of patients classified as having episodic migraine are in the category of patients for whom ≥3 prior treatments have failed (see Budget Impact Assessment document, Section 3.2).

A8. **Priority:** The clinical effectiveness data presented in the submission appear to indicate that patients for whom ≥3 prior prophylactic treatments have failed are likely to need the 140 mg Q4W dose of erenumab. Additionally, it is stated in section B.2.6 that "patients for whom ≥3 prior prophylactic treatments have failed may benefit from starting treatment on the higher 140mg dose." It is therefore unclear why the "blended dose" has been used in the company base-case; please clarify.

As discussed in Question A7, erenumab 140 mg is anticipated to be most appropriate for the patient population for whom ≥3 prior prophylactic treatments have failed. This is supported by feedback from an advisory board with six expert UK neurologists; overall, advisors considered that starting patients on the 140 mg dose may be the most efficient treatment approach for these patients. However, some advisors noted that they may prefer to initiate patients on erenumab 70 mg instead, given the lack of clinical experience with erenumab.[11] In light of this, and as the 70

mg and 140 mg doses are both licensed, it was considered appropriate to assume that not all patients would initially receive erenumab 140 mg and therefore present cost-effectiveness analyses for a blended dose. This is likely to be a conservative approach with respect to the expected proportion of patients receiving the erenumab 140 mg dose, and it is anticipated that as clinical experience with erenumab increases, a higher proportion of patients for whom ≥3 prior prophylactic treatments have failed may be initiated on the 140 mg dose. Scenario analyses have been presented in which the proportion of patients starting treatment on each dose is varied, to further reflect the inherent uncertainty at the current time with regard to the dosing of erenumab in UK clinical practice (see Document B, Section B.3.8.3). However, we consider 140mg to be the most likely dose for the optimised patient population sought, hence why this dose is reflected in the base case analysis.

A9. **Priority:** Please provide adverse events data, by treatment group, for the specified optimised population (failed ≥3 prophylactic therapies), for the 4 main trials.

Please find below the AE data, by treatment group, for patients for whom ≥3 prior prophylactic treatments have failed in Study 295, STRIVE, ARISE and LIBERTY.

Table 6: Treatment-emergent AEs in patients for whom ≥3 prior prophylactic treatments have failed in Study 295, STRIVE, ARISE and LIBERTY (safety analysis set)

AE	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted]8)	Erenumab 140 mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])	Erenumab 140 mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted]6)
Total no. of patients (%)										
With AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With AEs leading to discontinuation of investigational product	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; SAE: serious adverse event.

A10. Please provide details of the previous failed prophylactic treatments (with numbers of patients), by treatment group, for the optimised population (≥3 previous failed prophylactic treatments) in each of the 4 main trials.

The previous failed prophylactic treatments, by treatment group, in patients for whom ≥3 prior treatments have failed in Study 295, STRIVE and ARISE are presented in Table 7 below. The data for LIBERTY is presented in Table 8. Please see response to question A14 on the NICE recommended prophylactic treatment pathway (see Figure 3).

Table 7: Prior prophylactic treatment failures, by study arm, in patients for whom ≥3 prior treatments have failed in Study 295, STRIVE and ARISE

Treatment	Study 295			STRIVE			ARISE	
	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])	Erenumab 140 mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])	Erenumab 140 mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])
Divalproex sodium, sodium valproate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blockers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tricyclic antidepressants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flunarizine or verapamil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SNRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril or candesartan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8: Prior prophylactic treatment failures, by study arm, in patients for whom ≥3 prior treatments have failed in LIBERTY

Treatment	LIBERTY	
	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Amitriptyline	[redacted]	[redacted]
Candesartan	[redacted]	[redacted]
Flunarizine	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]
Metoprolol	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]
Valproate	[redacted]	[redacted]
Venlafaxine	[redacted]	[redacted]
Other	[redacted]	[redacted]

A11. Please clarify how many patients in the optimised population had a diagnosis of migraine with aura across the 4 main trials.

Please find the number of patients in the population for whom ≥3 prior prophylactic treatments have failed who have been diagnosed with migraine with aura in Study 295, STRIVE, ARISE and LIBERTY summarised in Table 9.

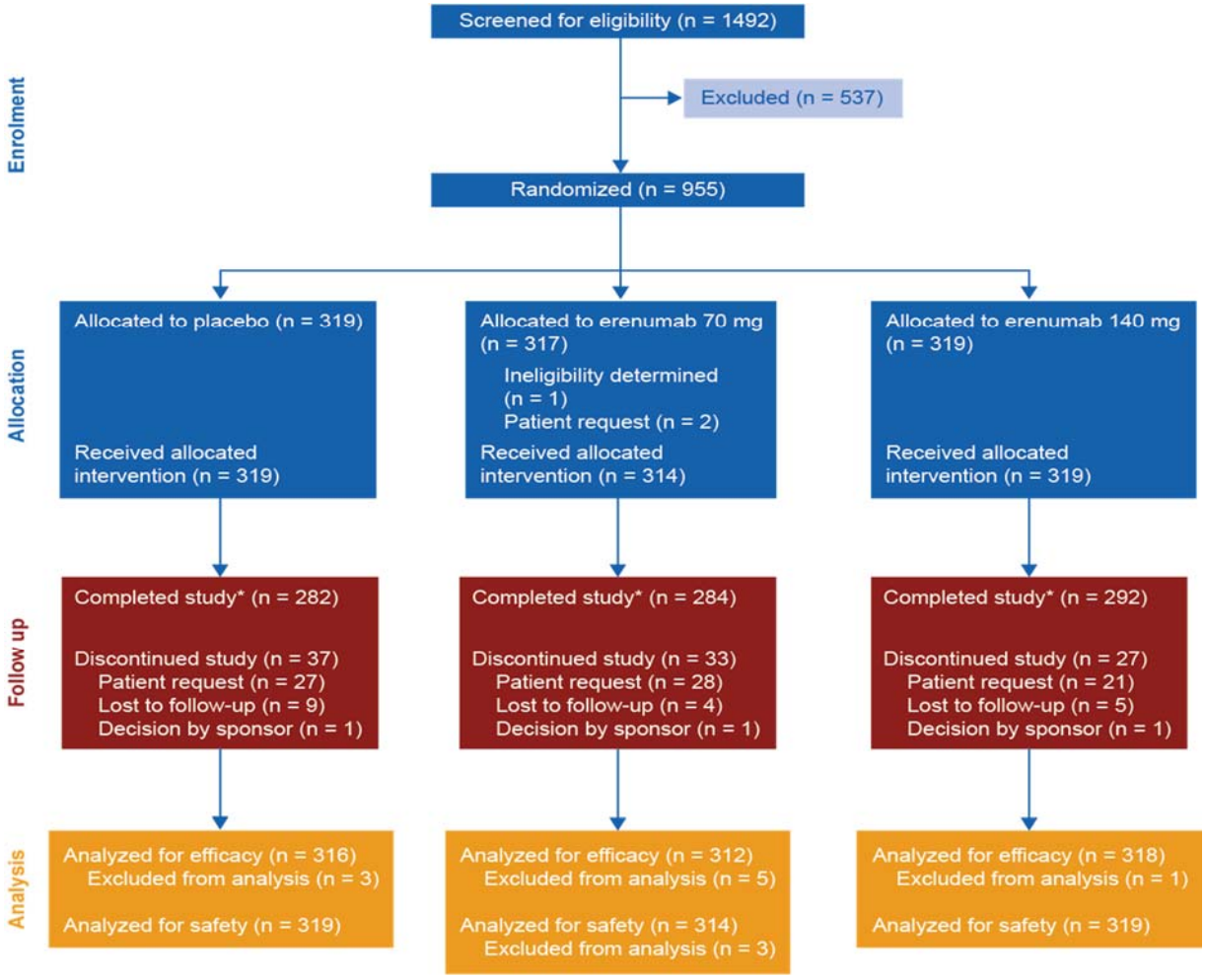
Table 9: Number of patients for whom ≥3 prior prophylactic treatments have failed who have been diagnosed with migraine with aura in Study 295, STRIVE, ARISE and LIBERTY

Study	Diagnosis of migraine with aura at baseline, n (%)
Study 295 (n=[redacted])	[redacted]
STRIVE (n=[redacted])	[redacted]
ARISE (n=[redacted])	[redacted]
LIBERTY (n=[redacted])	[redacted]

A12. Please check Figure 3, Appendix D; the numbers analysed for efficacy in the placebo group do not appear to be correct.

An updated CONSORT diagram of patient disposition in the STRIVE study with the typographical error corrected is provided in Figure 2 below.

Figure 2: CONSORT diagram of patient flow in STRIVE



A13. Please clarify whether erenumab is expected to be used in patients under 18 or over 65 years (the main trials excluded these age groups)?

Erenumab is not expected to be used in patients under 18 years of age as the licence is for the prophylaxis of migraine in adults, classified as ≥18 years. Erenumab is expected to be used in patients over 65 years. Although this age group were not included in the clinical trials reported in the submission, the licence does not provide an upper age restriction. The Summary of Product Characteristics states:[10]

"Aimovig has not been studied in elderly patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age"

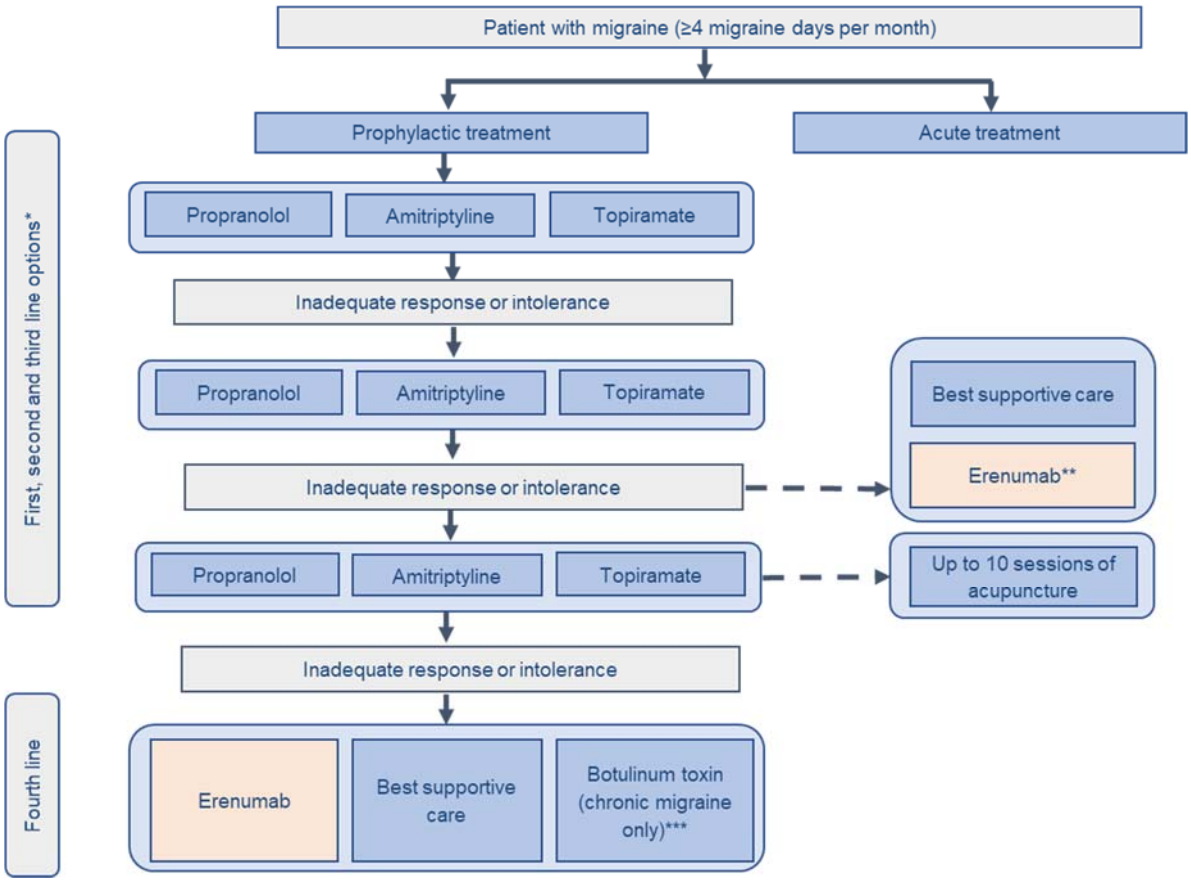
However, as migraine most commonly affects people in their 30s–50s, it is anticipated that few patients over 65 years will be initiated on treatment in clinical practice.

A14. Clinical pathway: Figure 2 in the Company Submission (CS) clearly places erenumab at fourth line only. However, an analysis for patients for whom ≥2 prior prophylactic treatments have failed is also included in the CS and it is stated that this subgroup is relevant as some patients may be unsuitable for a further treatment with a prophylactic therapy as a result of contraindications. If erenumab is expected to be used in some patients for whom fewer than 3 prophylactic treatments have failed, please amend figure 2 appropriately and include an

indication of the proportions of patients who may be eligible for treatment with erenumab at each line.

An amended version of Document B, Figure 2 in the original submission, reflecting the potential use of erenumab in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions, is presented in Figure 3 below.

Figure 3: Clinical pathway of care for migraine patients with ≥4 migraine days per month



*If treatment at its maximum tolerated dose in the first-line is ineffective or poorly tolerated, the other two treatment classes may be considered for second-line. The same applies in moving from second-line to third-line treatment. No treatment should be tried twice in the pathway. **There may be clinical desire to use erenumab at an earlier point in the treatment pathway: in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions. This represents the minority of patients for whom ≥2 prior prophylactic treatments have failed. These patients would otherwise receive BSC in clinical practice. ***Botulinum toxin is recommended only for patients classified as having chronic migraine as per the NICE guidance for this therapy.[13]
Source: based on: NICE clinical guideline CG150: Headaches in over 12: diagnosis and management;[8] BASH Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type Headache, Cluster Headache and Medication-Overuse Headache (3rd Edition);[9] NICE TA260: botulinum toxin type A for the prevention of headaches in adults with chronic migraine;[13] clinical expert opinion from an advisory board.[14]

As discussed in Document B, Section B.1.2.2, there may be clinical desire to use erenumab at an earlier point in the treatment pathway: in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions. The exact proportion of patients who would meet this definition is unclear. However, most patients will receive a third oral

prophylactic therapy before they reach the point at which BSC is their only option, and therefore the population anticipated to receive treatment with erenumab at this point in the pathway is expected to be small.

A15. Please provide a justification (references) to support the choice of 50% reduction in monthly migraine days (MMD) to define a responder.

The definition of a responder as achieving a ≥50% reduction in MMDs from baseline in the company submission was informed by the definition of responder used in the clinical trials for erenumab. The responder rate defined as a ≥50% reduction in MMDs from baseline was the primary endpoint in LIBERTY, and a key secondary endpoint in Study 295, STRIVE and ARISE. This definition of a responder aligns with the International Classification of Headache Disorders (ICHD) guidelines for controlled trials of drugs in migraine, which state that the proportion of patients with a 50% reduction in number of migraine days (i.e. responder rate), as compared to baseline values, is an important efficacy outcome.[15] Whilst it is acknowledged that the choice of a ≥50% reduction is arbitrary, it is considered to be clinically relevant, as most patients with migraine value a ≥50% improvement in headache frequency as the most important attribute of an effective migraine preventive drug.[15] Similarly, International Headache Society (IHS) guidelines for conducting clinical trials in migraine state that responder rates in migraine have traditionally been defined as a ≥50% reduction in MMDs.[16] Whilst these guidelines state that a ≥30% reduction can be clinically meaningful in patients with chronic migraine, the more stringent ≥50% definition was considered to be more appropriate for this submission, where patients across the entire spectrum of migraine patients with ≥4 MMDs are considered, as per the licence for erenumab.[10] Finally, EMA guidelines suggest that the responder rate, where a 'responder' is defined as "*a patient with a 50% or greater reduction in attack frequency during treatment compared to baseline*", is collected as an endpoint in trials of migraine prophylactic therapies.[17]

This is supported further by feedback from six expert UK neurologists, who recommended that clinical trials should capture the percentage responder rates rather than MMD frequencies. The advisors considered it more helpful to tell patients the chance of a therapy working, or how many migraine patients usually respond to a therapy, rather than how many fewer MMDs they could expect to experience..[11]

Indirect comparison with botulinum toxin

A16. Please provide details of outcome definition and measurement in PREEMPT for mean monthly headache days (MHD) and >50% responder rate.

The definitions and measurement in PREEMPT for mean MHD and >50% responder rate are as follows:

- Mean monthly headache days: Mean change from baseline in frequency of headache days for the 28-day period ending with Week 24
- 50% responder rate: Mean change from baseline in frequency of headache days for the 28-day period ending with Week 24[18, 19]

A17. Table 15 of the CS provides key clinical effectiveness results from Study 295 at week 12. However, these are different to those from the full trial population at 12 weeks used in the ITC as reported in Table 17, Appendix D. Please clarify the reasons for the discrepancies

between these 2 tables. In particular, why are the numbers with a 50% reduction in mean MHD available for the subgroup but not the full trial population?

Data on change from baseline in mean MMDs and mean MHDs in Appendix D, Table 17, are the absolute change from baseline at Week 12 for the efficacy analysis set (see Table 10.1 (page 54) and Table 14-4.4.7 (page 281) in the CSR, respectively). The equivalent data presented in Document B, Table 15 of the company submission are taken from an adjusted analysis of the efficacy analysis set, utilising a generalised linear mixed model which included treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure (see study publication (Table 2, page 6), and Table 10.1 (page 54) and Table 14-4.4.7 (page 281) in the CSR, respectively).

A ≥50% reduction in MHDs was not an endpoint in Study 295 (or any other erenumab trial) and is therefore not presented in Document B, Section B.2.5. However, as we identified 50% reduction in MHDs data at 24 weeks for botulinum toxin, we conducted post hoc analysis of the headache day data available from Study 295 for the full population and ≥3 prior prophylactic population at 12 weeks to explore all possible analyses in the ITC. Analyses using the ≥50% reduction in mean MHD were conducted for both the ≥3 prior prophylactic population (comparison 1, Document B, Table 38 and Table 39 of the company submission) and full trial populations (comparison 2, Document B, Table 38 and Table 39 of the company submission). The input data for these analyses in the full populations (comparison 2) were omitted in error from Appendix D, Table 17. Please find below (in Table 7) an updated version of Appendix D, Table 17 with 50% reduction in MHD data included that was omitted previously.

Table 10: Summary of the outcomes and results of the included studies

Study	Treatment	Population	CfB mean monthly migraine days, mean (SE)	CfB mean monthly headache days, mean (SE)	Patients with a 50% reduction in mean monthly headache days, n/N (%)
PREEMPT	Botulinum toxin 155U –195U	Full trial population, 24 weeks	–8.2 (–8.69, –7.70)[a]	–8.4 (–8.90, –7.92)[a]	NR (47.1)
	Botulinum toxin 155U –195U	Full trial population, 12 weeks	–7.09 (0.13)	–7.15 (0.26)	339/688 (49.3)
	Botulinum toxin 155U –195U	≥3 previous prophylaxis treatments, 24 weeks	–7.1[b] (NR)	–7.4[b] (NR)	76/189 (40)
	Placebo	Full trial population, 24 weeks	–6.2 (–6.69, –5.68)[a]	–6.6 (–7.07, –6.08)[a]	NR (35.1)
	Placebo	Full trial population, 12 weeks	–5.59 (0.23)	–5.97 (0.23)	NR
	Placebo	≥3 previous prophylaxis treatments, 24 weeks	–4.3[b] (NR)	–4.7[b] (NR)	51/207 (25)

Study	Treatment	Population	CfB mean monthly migraine days, mean (SE)	CfB mean monthly headache days, mean (SE)	Patients with a 50% reduction in mean monthly headache days, n/N (%)
Study 295 (NCT02066415)	Erenumab 70 mg	Full trial population, 12 weeks	[redacted]	[redacted]	[redacted]
	Erenumab 70 mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Erenumab 140 mg	Full trial population, 12 weeks	[redacted]	[redacted]	[redacted]
	Erenumab 140 mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Placebo	Full trial population, 12 weeks	[redacted]	[redacted]	[redacted]
	Placebo	≥3 previous prophylaxis treatments, 12 weeks	[redacted]	[redacted]	[redacted]

[a]95% confidence intervals are reported instead of standard error; [b]Means reported for these outcomes are least-squares means, not absolute means. [c]Note that the ITC utilised data from patients who had failed on ≥3 prior prophylactic treatments irrespective of category, in order to most accurately reflect the decision problem
Abbreviations: CfB: change from baseline; NR: not reported; SE: standard error.
Source: Aurora *et al.* (2011)[6], Dodick *et al.* (2010)[5], Scottish Medicines Consortium (2017)[4], Study 295 CSR[10], Novartis (2018)[13], Tepper *et al.* (2017)[11]

Ongoing studies

A18. Are there any further analyses planned or publications in progress for any of the 4 main trials? If so, when will these be available?

Please find below a summary of further planned analyses and publications for the four main trials:

- Study 295: Manuscripts on patient reported outcomes and medication overuse have been submitted, publication timelines currently unknown. A manuscript on conversion of chronic migraine to episodic in patients treated with erenumab in Study 295 and the 12 month open-label extension period are also planned, timelines currently unknown.
- STRIVE: Manuscripts on efficacy in treatment failure, responder analysis and 1-year safety and efficacy are currently planned, timings are currently unknown.
- ARISE: No further analyses/publications planned.
- LIBERTY: The publication of the main study is currently under journal review and publication is expected before the end of Q4 2018. Further manuscripts on pre-specified subgroups and patient reported outcomes from LIBERTY are also planned. One year open-label extension data from LIBERTY is planned to be presented at international conferences in 2019 (estimates by Q3 2019).

The open-label extension LIBERTY study is planned for 3 years therefore further publications from this are anticipated. however timelines are currently unknown.

- A manuscript on acute medication use in Study 295 and STRIVE is also planned.

Section B: Clarification on cost effectiveness data

Please note that all analyses in this section incorporate the updated utility data as requested in question B14b, excluding question B16 where other utility data was requested.

Model structure

B1. Treatment response is defined as a ≥50% reduction from baseline in MMDs. However, according to NICE technology appraisal guidance for botulinum toxin in chronic migraine[13], treatment should be stopped in people whose condition: 1) is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or 2) has changed to episodic migraine (defined as fewer than 15 headache days per month) for 3 consecutive months. The committee concluded that a 30% response rate was the most clinically relevant and reasonable negative stopping rule on which to base its decision.

a. Please justify why the economic model adopts a different approach than that recommended by the committee for botulinum toxin.

The primary reason for adopting a different modelling approach than that for botulinum toxin is that the licensed indications for these two treatments are different:

- Botulinum toxin is indicated for the **prophylaxis of headaches** in adults with **chronic migraine** (headaches on at least 15 days per month of which at least 8 days are with migraine)
- Erenumab is indicated for **prophylaxis of migraine** in adults who have **at least 4 migraine days per month.**

Clinical study endpoints investigated in studies differed as summarised below in Table 11 and therefore there was a different evidence base available with which to populate a model.

Table 11: Comparison of primary endpoints investigated in erenumab and botulinum toxin clinical trials

	Botulinum toxin	Erenumab
	PREMEPT	**Study 295**
Chronic Migraine	PREEMPT 1: Mean change from baseline in frequency of **headache episodes** for the **28-day period ending with week 24.** A headache episode was defined as patient-reported headache with a start and stop time indicating that the pain lasted ≥4 continuous hours	Change in **monthly migraine days (MMDs)** from baseline to the **last 4 weeks of the 12-week double-blind treatment phase**.
	PREEMPT2: Mean change from baseline in frequency of **headache days** for the **28-day period ending at week 24** (as reflected in the decision problem). A "headache day" was defined as a day where a patient reported at least 4 continuous hours of a headache episode for any period of time in the	

	24-hour period from midnight (12:00 AM) at the start of the day to 23:59 PM at the end of the day (i.e. a calendar day)	
Episodic Migraine	Botulinum toxin failed to meet primary endpoints in 7 episodic migraine trials	**STRIVE**
		Change from baseline to months 4 through 6 in the mean number of MMDs per month.
		ARISE
		Change from baseline in MMDs in the last month (Month 3)
		LIBERTY
		Proportion of patients with at least 50% reduction from baseline MMDs at Month 3 (Weeks 9–12)

Abbreviations: MMD: monthly migraine day.

A review of the IHS clinical guidelines,[16] as well as consultation with clinical experts intimated that change in MMDs as well as percentage response to treatment were both important outcomes in migraine prophylaxis. The model structure selected allowed for accurate tracking of both of these outcomes (though this simultaneous tracking is limited to the assessment period).

By reproducing the patient distributions across MMDs for each treatment for each time-point, the model retains a strong faithfulness to the trial data. The structure avoids the use of arbitrarily established MMD cut-offs for model-state establishment purposes and thus captures information that would otherwise be lost through grouping patients. This model structure enables accuracy in the numbers of migraine days incurred or avoided, and thus the costs and health benefit associated with these days can be quantified. Capturing the full MMD distribution also allows for the possibility that the impact of each additional MMD (in terms of utility loss and increased resource use) may not be constant across the MMD spectrum. This model structure, which avoided subgrouping patients in health states of migraine frequency or headache frequency (i.e. 4–7 or 8–14 headache day health states as in the botulinum toxin model), is consistent with the erenumab clinical programme and the population submitted for reimbursement which spans across the full spectrum of migraine of more than 4 MMDs. The model developed provides greater granularity with respect to migraine day frequency (i.e. probabilities are specified for each of the 28 days in the month, rather than categories such as 4–7 days) providing results which align more closely to the clinical trials.

b. Please provide details regarding the input parameters and assumptions used in scenario analysis 7 (using a 30% response rate for the stopping rule).

The parameters used in Document B, scenario analysis 7 are the same as those described in Document B, Table 53 in the company submission. The only difference is the response rate for each treatment (≥30% instead of ≥50%, as in the base case); these are provided in Table 12.

Table 12: ≥30% responder rate for each treatment

Treatment	≥30% responder rate	
	Chronic migraine	Episodic migraine

Erenumab 70 mg	47.14%	40.00%
Erenumab 140 mg	52.94%	50.51%
BSC	27.45%	21.80%
Botulinum toxin (chronic migraine only)*	40.70% (vs Erenumab 140 mg) 39.26% (vs Erenumab 70 mg)	N/A

*Note: probability of response to botulinum toxin was assessed at 24 weeks. The response rates provided in the table are based on application of the odds ratios derived from the ITC to the response rate for the specified erenumab dose

Abbreviations: BSC: best supportive care; N/A: not applicable.

Population

B2. For the base-case analysis it is assumed that people with chronic migraine comprise 66% of the total population, and people with episodic migraine the remainder (34%). This is based on Novartis. Data on file: UK Optimisation Research Report, 2018 (document provided). Please provide more detail on how these proportions were calculated and whether the "low-frequency episodic migraine" population is included in the 34%.

The data used to calculate the proportion of people with chronic migraine and the proportion of people with episodic migraine was based on data from slides 4 and 5 in the reference document.

The % of people seen by neurologist with CM, HFEM and IFEM were multiplied by the respective % of people treated by neurologist on ≥4th line treatment in the respective patient population. The % CM and % EM were then expressed as a % of the total migraine population.

Additionally, a targeted literature showed the proportion of CM patient (reported at baseline) who failed prior prophylactic treatment varied from 66.7% to 70%.20

Recent interim data from the BECOME study, investigating the burden of migraine in migraine patients with prophylactic treatment failure, has identified that of [redacted] migraine patients seen by a headache specialist in the UK are [redacted]% are chronic migraine. Information on this study and the interim results and enclosed.[21, 22]

B3. The definition of high-frequency episodic migraine (HFEM) is inconsistent throughout the CS. Both 8-14 MHDs and 8-14 MMDs are used to describe this subgroup, and other definitions (for example, 10-14 MHDs) can be found in the literature (Torres-Ferrus et al. 2017[23]).

a. Please clarify what definition should be used to define the HFEM subgroup.

In the clinical section of the submission (Document B, Section B.2), the data provided was for patients with HFEM defined as 8–14 MMDs. This is because 8–14 MMDs was how randomisation was stratified in the LIBERTY study, which was the only study to define a more severe episodic migraine population subgroup. Therefore, this was the definition for which clinical data were available for all endpoints defined in the final scope at the time of submission. The data used in the economic model defined HFEM patients as 8–14 MHDs. Published literature and clinical trials define HFEM as having 8–14 headache days per month for at least three months or 9–14 headache days per month for at least three months.[24-27] There is no agreed definition of HFEM in clinical guidelines. However, discussions with UK headache specialists identified that experts generally define HFEM as between 8–14 or 10–14 MHDs. Therefore, the

cost-effectiveness results presented in the company submission are for HFEM patients defined as 8–14 MHDs.

For clarity, the following text in the company submission should be corrected as follows:

- **Section B.3, Summary box (pg 123): "**Subgroup analysis restricting the episodic migraine population (4–14 MMDs) to the HFEM population (8–14 ~~MMDs~~ MHDs) resulted in similar ICERs as for the whole population base case and the episodic migraine analyses, respectively."
- **Section B.3.5.2, Table 58 header row (pg 157): "**HFEM (8-14 ~~MMD~~ MHD)"
- **Section B.3.9.1 (pg 191): "**The results of the subgroup analyses restricting the episodic population to the HFEM population (8–14 ~~MMDs~~ MHDs) in the whole population base case are presented in Table 89 and Table 90 for the blended dose and 140 mg dose, respectively."

b. Please adopt the definition of 10-14 MHDs for the HFEM subgroup and report on the results

The model has been updated to include this scenario and this setting can be found in the in the 'Settings and Summary Results' tab (HFEM definition [cell D48]) of the model. Please note that all analyses in this section incorporate the updated utility data requested in question B14b. Results are presented in Table 13 to Table 16.

Table 13: HFEM (10–14 MHDs) subgroup analysis results in the whole migraine (HFEM and chronic migraine i.e. ≥ 10 MMDs) (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,761

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; HFEM: high-frequency episodic migraine; ICER: incremental cost-effectiveness ratio; MHD: migraine headache day; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 14: HFEM (10–14 MHDs) subgroup analysis results in the whole migraine (HFEM and chronic migraine i.e.≥ 10 MMDs) (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,109

Abbreviations: BSC: best supportive care; HFEM: high-frequency episodic migraine; ICER: incremental cost-effectiveness ratio; MHD: migraine headache day; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 15: HFEM subgroup analysis results in the episodic migraine population i.e. 10–14 MHDs (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£31,283

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg

Abbreviations: BSC: best supportive care; HFEM: high frequency episodic migraine; ICER: incremental cost-effectiveness ratio; MHD: migraine headache day; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 16: HFEM subgroup analysis results in the episodic migraine population i.e. 10–14 MHDs (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£30,664**

Abbreviations: BSC: best supportive care; HFEM: high frequency episodic migraine; ICER: incremental cost-effectiveness ratio; MHD: migraine headache day; PAS: patient access scheme; QALY: quality-adjusted life year.

B4. For the subgroup analysis of patients with HFEM, please provide more detail on:

a. How subgroup specific transition probabilities were estimated, and report these.

Analyses in the HFEM subgroup population were conducted in the same way as analyses for other populations in the model. During the assessment period the response rate determining the proportion of patients who move to the responder and non-responder states for each arm is specific to the HFEM population. These response rates were estimated from pooled patient data for the HFEM population (defined as 8–14 MHDs, or 10–14 MHDs for the analyses in Section B3.b of this response) for whom ≥3 prior prophylactic therapies had failed from STRIVE (70 mg, 140 mg and placebo), ARISE (70 mg, and placebo), and LIBERTY (140 mg and placebo). This provides response rates of [redacted]% for erenumab 70 mg, [redacted]% for erenumab 140 mg and [redacted]% for placebo (reflecting BSC) for the 8–14 MHDs subgroup and response rates of [redacted]% for erenumab 70 mg, [redacted]% for erenumab 140 mg and [redacted]% for placebo (reflecting BSC) for the for the 10–14 MHDs subgroup. In the post-assessment period, all other movements between states use the same parameters as for the episodic migraine population. It should be noted however, that the whole population analysis is the most appropriate analysis, as it is reflective of clinical practice rather than individual artificially defined subgroups.

b. How subgroup specific costs were estimated, and report these (if not the same as the base-case).

c. Costs specific to the HFEM subgroup are estimated in the same way as for other populations as described in Document B, Section B.3.5. Health states within the model were associated with a given MMD distribution. The extent of background disease management and thus resource utilisation costs required by patients is dependent on the MMD distribution for the population. Therefore, the overall mean management cost associated with the different health states is represented by the weighted average of the costs per MMD, for the MMD distribution specific to the HFEM population. How subgroup specific utility values were estimated, and report these (if not the same as the base-case).

Utilities specific to the HFEM subgroup are estimated in the same way as for other populations as described in Document B, Section B.3.4.5. Utilities are defined per MMD frequency and then estimated based on the distribution of MMDs for the population in question (e.g. HFEM). For example, responders to treatment with erenumab at Week 12 in the HFEM population would receive the health state utility value based on the MMD distribution for erenumab responders in this population.

For any subgroup, the utility for any health state is a weighted average value given how many patients are estimated to be distributed across MMDs and given utility value per MMD frequency. The estimate of utility value per MMD frequency is based on the whole population and is not assumed to differ between subgroups.

B5. In addition to the whole migraine population, patients were split into an episodic (defined as <15 MHDs and ≥4 to <15 MMDs) and chronic migraine population (defined as ≥15 MHDs and ≥8 MMDs). However, these groups are not exhaustive, given that patients might experience ≥15 MHDs, but ≥4 to <8 MMDs.

a. Please provide the number of patients that fall in between the definitions of episodic- and chronic migraine (i.e. patients with ≥15 MHDs, but ≥4 to <8 MMDs).

Given the definitions of chronic and episodic migraine used in the clinical trial programme, which were based on clinical guidelines, patients falling outside of these definitions were not included in the clinical trials. However, the licence for erenumab covers all patients that have ≥4 MMDs, therefore under the terms of this licence, erenumab could be used in patients with ≥15 MHDs, and ≥4 to <8 MMDs.

b. Please explain and justify how this population was dealt with in the model (for the whole population base-case analysis), and amend any analysis if necessary.

The EMA's interpretation of the clinical trial evidence for erenumab has resulted in a licence for the prophylaxis of migraine in patients with ≥4 MMDs per month. The licence does not specify or restrict based on episodic or chronic migraine, and allows use of erenumab in patients who may fall between the eligibility criteria of the two trials in terms of frequency of migraine and headache days. As such, the economic model, which uses this clinical trial evidence, is considered generalisable to the whole migraine population.

Intervention and comparators

B6. **Priority** In appendix Z.2 the results of the scenario analyses for erenumab 70 mg are presented.

a. Please provide more details on which parameters were used in these analyses for erenumab 70 mg.

The parameters used in the analyses for erenumab 70 mg are the same as those described in Document B, Table 53 in the company submission. The only differences are as follows:

- Response rates were specific to erenumab 70 mg, based on the response rates observed for this dose of erenumab in the relevant clinical trials (Study 295, STRIVE and ARISE). Where botulinum toxin was a relevant comparator, the response rate for botulinum toxin was based on the results of the ITC versus erenumab 70 mg.
- The distribution of MMDs for responders and non-responders at 12 weeks was specific to the dose of erenumab, and therefore different for erenumab 70 mg and erenumab 140 mg. Baseline MMD distributions were the same across all treatment arms and therefore did not differ between the analysis of erenumab 70 mg and the analysis of erenumab 140 mg.

Please note the responses provided to questions A7 and A8, in which we note it is anticipated that 140mg is likely to be the dose used more frequently in clinical practice.

b. Please provide full incremental analyses, adding both erenumab 70 mg and 140 mg separately (instead of the blended dose) for all populations considered in the base-

case (whole migraine population, chronic migraine population and episodic migraine population).

Fully incremental analyses in the whole migraine population, chronic migraine population and episodic migraine population, respectively, are presented in Table 17, Table 18 and Table 19. These analyses use the updated utility data as requested in Question B14.b. It should be noted that both doses are cost-effective compared to BSC.

Table 17: Fully incremental analysis in the whole migraine population (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) – versus BSC	ICER (£/QALY) – incremental analysis
BSC	[redacted]	[redacted]				
Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	£23,030	Extendedly dominated
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,037	£8,011

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 18: Fully incremental analysis in the chronic migraine population only (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) – versus BSC	ICER (£/QALY) – incremental analysis
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£11,530	£11,530
Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	£26,811	Dominated
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£14,499	£19,831

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 19: Fully incremental analysis in the episodic migraine population only (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) – versus BSC	ICER (£/QALY) – incremental analysis
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£21,537	£21,537
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£29,991	£54,050

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

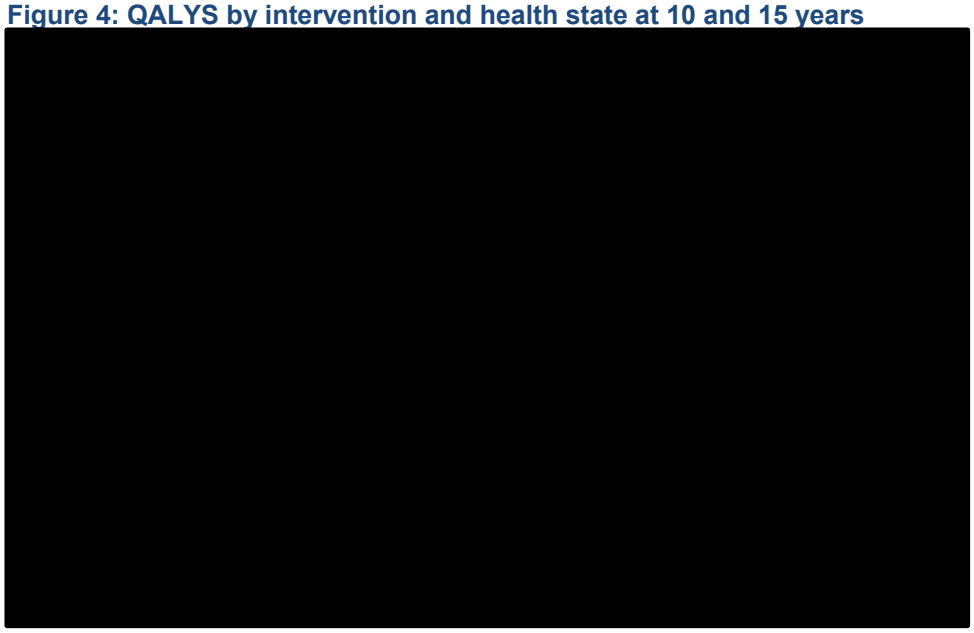
Perspective, time horizon and discounting

B7. Tables 83 and 85 in the CS summarise the scenario analyses in the chronic migraine population, comparing the blended dose erenumab to botulinum toxin and BSC respectively. When extending the time horizon from 10 years to 15 years (scenario 9), please explain why this leads to an increased ICER when comparing erenumab to botulinum toxin, and a decreased ICER when comparing erenumab to BSC (compared to the base-case ICER).

Comparison with BSC

With the shift to the longer time horizon there is a proportionately greater relative increase in the cost of BSC than erenumab. Throughout the modelled time horizon the vast majority of BSC patients have discontinued due to non-response (see Figure 4) and costs are incurred comparatively linearly (see Figure 5). In contrast, with erenumab a greater proportion of the costs is incurred during early cycles when more patients are receiving treatment, at a higher cost i.e. cumulative costs of erenumab are increasing at a decreasing rate. Although erenumab generates greater quality-adjusted life years (QALYs) than BSC throughout the time horizon, the additional QALY gains are declining for both treatments over time and erenumab QALY gains converge towards those of BSC in later years of the model (see Figure 6). With the increasing difference in costs of erenumab versus BSC, and declining differences in QALYs over time, the ICER gradually decreases as the time horizon is extended.

Figure 4: QALYS by intervention and health state at 10 and 15 years



Abbreviations: BSC: best supportive care; QALY: quality-adjusted life year.

Figure 5: Cumulative costs by intervention over time

Abbreviations: BSC: best supportive care.

Figure 6: QALYs gained annually by intervention over time

N.B. Botulinum toxin generates more QALYs than erenumab during the first year, due to the different time points for response assessment; all patients continue on botulinum toxin for 24 weeks whereas erenumab non-responders discontinue at 12 weeks.
Abbreviations: BSC: best supportive care; QALY: quality-adjusted life year.

Comparison with Botulinum toxin

The higher ICER versus botulinum toxin over a longer time horizon is due to greater incremental costs of erenumab, rather than decreased incremental QALYs. Costs of erenumab increase more than botulinum toxin since more patients remain on erenumab (due to higher initial response rate with erenumab and the same long-term discontinuation assumption, see Figure 4), and erenumab drug costs per patient are higher. In later years of the model, the majority of QALY gains with both erenumab and botulinum toxin result from non-responding patients who

have discontinued treatment. The additional QALY gains with erenumab as a result of more patients staying on treatment are relatively small. Hence the longer time horizon results in an increase in cumulative costs of erenumab with comparatively smaller increase in QALYs, and the ICER increases. The relative increases in costs for erenumab and BSC and erenumab and botulinum toxin are quite similar.

Effectiveness

B8. **Priority:** People with migraine can have stable / persistent migraine, clinical remission, partial remission or progression. Based on the AMPP study (US), after 1 year the proportions would be 84% persistence, 10% clinical remission, 3% partial remission and 3% progression.[28] Accordingly, people can go from low frequency episodic migraine, to chronic migraine (potentially via high frequency episodic migraine) and vice versa.[29] Currently, these aspects of migraine (i.e. its natural progression) are not fully incorporated in the economic model.

a. Please elaborate on the expected impact of not fully incorporating the natural progression of migraine on the estimated cost effectiveness.

As discussed during the technical TC, a simplifying assumption of the economic model is that natural history of progression has not been explicitly incorporated. The natural history of migraine was considered in discussions with experts in the model development. However, it was felt that including this would add significant complexity to the model.

Furthermore, Evidence available on the natural history of migraine is limited and not specific to the UK or Europe. Therefore, it was considered that inclusion would add considerable uncertainty to the cost-effectiveness analysis.

A simplifying model assumption was therefore made as, in practice, some patients will naturally recover, and some patients will naturally decline over relatively short time periods (e.g. month-to-month fluctuations). It is very unlikely that including these individual level fluctuations would have a significant impact on the estimated cost-effectiveness at a population level over a time horizon relevant to decision making.

Elements such as potential remission for successfully treated patients are explored in the re-evaluation/positive discontinuation scenario, where patients may take a treatment holiday, which is how UK experts suggest they will use erenumab. Only a certain proportion of these patients return to treatment with erenumab and the others could be considered to be in remission (please see scenario 6 in section B.3.8.3 in the main company submission).

Finally, no data are available on how erenumab treatment may impact the natural disease progression and therefore populating a model with these elements would rely heavily on assumptions rather than data and be subject to significant uncertainty. If there is any disease modification with erenumab, the cost-effectiveness of erenumab will have been underestimated.

Additionally, it should be noted that the model approach does not incorporate the dissipation of placebo effect over time (i.e. a “waning” of placebo effect) which is likely to be conservative with regard to the cost-effectiveness of erenumab.

b. Please incorporate scenario analyses exploring the impact of different plausible scenarios regarding the natural progression of migraine.

Please note that all analyses in this section incorporate the updated utility data as requested in question B14b. Results are presented for the whole population base case population for the blended and 140mg dose.

Three different scenarios exploring the natural progression of migraine have been incorporated into the economic model and are described below. In all scenarios, there is limited impact on the cost-effectiveness results.

- Scenario 1: To reflect disease progression, utility health state values for responders on treatment, for all arms, were decreased by 1% per year for the full-time horizon to reflect decreasing disease status and utility. This setting can be applied using Cell D50 on the 'Settings & Summary Results' tab in the CE model. Results are presented in Table 20 and Table 21.

Table 20: Summary results for decreasing utility values annually to reflect a disease progression scenario in the whole migraine population (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,259

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 21: Summary results for decreasing utility values annually to reflect disease progression scenario in the whole migraine population (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,015

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

- Scenario 2: To reflect disease remission, the long-term discontinuation rate was doubled (cell I28 in the 'long term transitions' tab in the economic model was manually changed from 2.38 to 4.76%). Results are presented in Table 22 and Table 23.

Table 22: Summary results for increasing long-term discontinuation to reflect a disease remission scenario in the whole migraine population (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,909

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 23: Summary results for increasing long-term discontinuation to reflect a disease remission scenario in the whole migraine population (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)

BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£16,964**

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

- Scenario 3: Another method of reflecting disease remission has been explored in the positive discontinuation scenario by increasing the percentage of people that do not return to treatment has been increased from 20% to 30%. (Cell D30 in the 'long term transitions' tab in the economic model was manually changed from 20% to 30%). Results are presented in Table 24 and Table 25.

Table 24: Summary results for increasing long-term discontinuation to reflect a disease remission scenario in the whole migraine population (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£8,256**

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 25: Summary results for increasing long-term discontinuation to reflect a disease remission scenario in the whole migraine population (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£7,014**

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Cost-effectiveness results when applying scenario 1 and 2, described above, in combination are presented in Table 26 and Table 27.

Table 26: Summary results for decreasing utility values annually to reflect a disease progression and increasing the long-term discontinuation rate to reflect a disease remission scenario in the whole migraine population (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£18,671**

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 27: Summary results for decreasing utility values annually to reflect a disease progression and increasing the long-term discontinuation rate to reflect a disease remission scenario in the whole migraine population (with PAS), erenumab 140mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£16,748**

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

B9. **Priority:** For the extrapolation of treatment effectiveness, it is assumed that reduction in MMD frequency is maintained throughout the time horizon of the model. This is justified by referring to open-label, non-randomised extension studies (section B.3.3.4 of the CS):

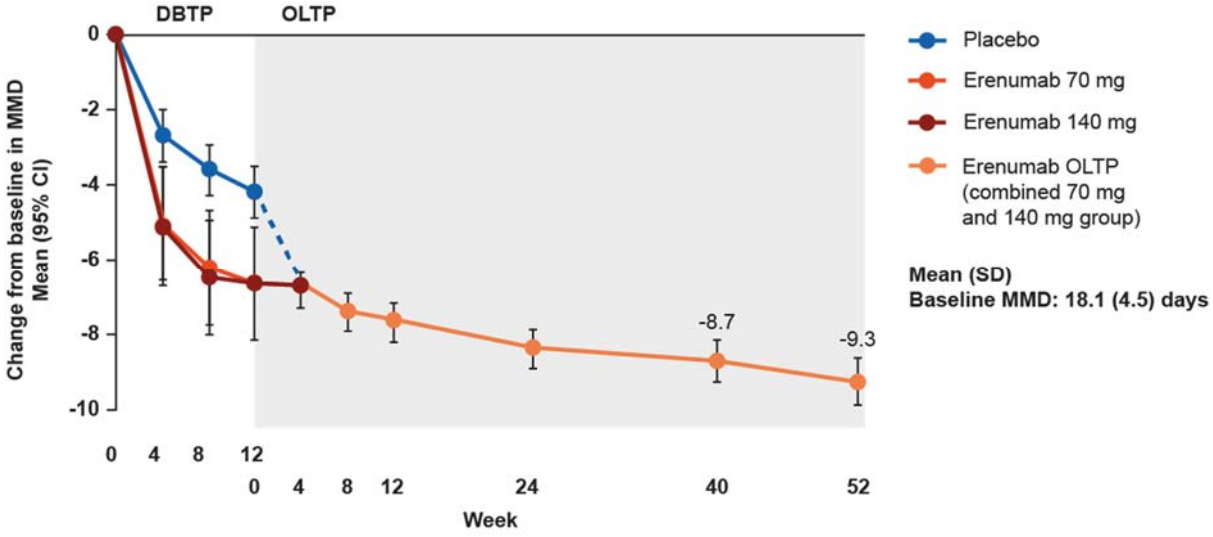
a. Please justify, based on the data reported from the studies, why it is believed that the reduction in MMD frequency while having erenumab was maintained at 64 weeks, particularly given that the open-label extension did not allow for a comparison with placebo.

i. For patients having erenumab at the 70 mg dose

ii. For patients having erenumab at the 140 mg dose

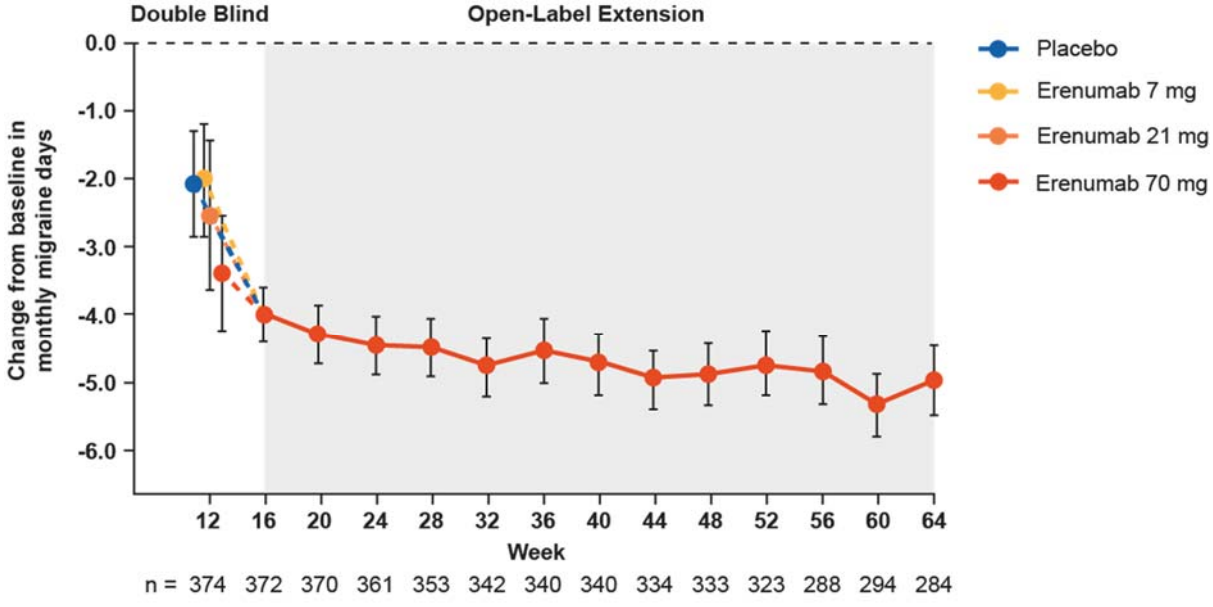
Long-term follow up data from open-label extension (OLE) studies demonstrate sustained efficacy of erenumab up to Week 52 in chronic migraine, and Week 64 in episodic migraine. In an OLE of patients enrolled in Study 295, patients treated with erenumab 70 mg and 140 mg continued to experience a reduction in MMDs (see Figure 7), and at Week 52, 67% of patients in the 140 mg group and 53% of patients in the 70 mg group achieved ≥50% response.[7] In an OLE of the STRIVE study in episodic migraine, patients experienced numerical reductions in MMDs from pre-active treatment phase (ATP) to Week 52; patients who received erenumab 140 mg during the ATP (n=368) experienced mean reductions in MMDs of −1.78 days, and patients who received erenumab 70 mg (n=369) experienced reductions of −1.10 days.[30] Similarly, during an OLE in episodic migraine, patients treated with erenumab 7 mg, 21 mg or 70 mg experienced reductions in MMDs from baseline to Week 64 (see Figure 8) (please note neither 7mg nor 21mg are licensed doses). The proportion of patients who achieved a ≥50% reduction in MMDs was also sustained over the follow-up period, and at Week 64, 65% of patients achieved ≥50% response.[31] Whilst these OLE studies did not contain a control arm as this may have raised ethical challenges, these results support the assumption that the reduction in MMDs in patients treated with erenumab 70 mg and 140 mg is maintained at 64 weeks.

Figure 7: Change from baseline in MMDs in patients with chronic migraine during open-label treatment with erenumab 70 mg and 140 mg



Abbreviations: CI: confidence interval; DBTP: double-blind treatment phase; MMD: monthly migraine day; OLTP: open-label treatment phase; SD: standard deviation.
Source: Tepper et al. (2018)[7]

Figure 8: Change from baseline in MMDs in patients with episodic migraine during open-label treatment with erenumab 7 mg, 21 mg and 140 mg



Data are mean (95% CI)
n = total number of patients with observed monthly migraine days at each visit

Abbreviations: CI: confidence interval; MMD: monthly migraine day.
Source: Ashina *et al.* (2018)[31]

b. Please justify why it is believed that the reduction in MMD frequency while having erenumab at 64 weeks was maintained up to 10 years.

   i. For patients having erenumab at the 70 mg dose

   ii. For patients having erenumab at the 140 mg dose

As discussed in part a), data from OLE studies demonstrate that erenumab provides sustained efficacy up to Week 52 in chronic and episodic migraine, and up to Week 64 in episodic migraine. Whilst no data are available from longer-term follow-up of patients treated with erenumab, the results of these studies provide no indication of a waning in the treatment effect: in both studies, patients experienced numerical reductions in MMDs from the end of the double-blind treatment phase to Week 52 or Week 64.

NICE appraisals of biologics in other chronic diseases have similarly assumed that there is no waning effect following long-term treatment. For example, in the appraisal for omalizumab in chronic urticaria, the Committee concluded that "*the evidence available to date does not support a waning effect on subsequent repeated courses of omalizumab and therefore it is reasonable to assume a constant effect*."[32, 33] In the appraisal of omalizumab in severe persistent allergic asthma, the treatment effect of omalizumab was assumed to continue for 10 years. Additionally, in NICE appraisals of TNF-inhibitor in psoriatic arthritis and ankylosing spondylitis responders to treatment stayed in the treatment health state, thus maintaining benefit no waning of effectiveness.[34, 35]

c. Please justify why the long-term MMD frequency distributions (stratified for responders and non-responders) are assumed to be treatment dependent.

The treatment effect is not fully explained by the probability of response, i.e. it is the reduction in MMDs that ultimately matters and erenumab responders tend to do better than placebo responders.

The data presented in response to part a) above shows that patients treated with erenumab have maintained their response from the end of the double-blind period throughout the OLE studies. In addition, placebo-treated patients have also been observed to maintain their response over a long time period.[36] In a comparison of topiramate versus placebo in patients with migraine, the mean change in migraine frequency in placebo-treated patients continued to reduce over 6 months.[37]

d. Please provide scenarios exploring alternative assumptions about the long-term effectiveness of erenumab/maintenance of MMD frequency. Please also include scenarios where the favourable MMD frequency distribution for responders and erenumab non-responders is linearly altered over time to become identical to the MMD frequency distribution for BSC non-responders.

A scenario analysis has been conducted exploring the long-term effectiveness by reducing linearly over time the health state costs and health state utilities for erenumab and botulinum toxin, which reflect MMD frequency, to reflect the health state costs and health state utilities associated with BSC non-responders. This scenario can be selected by using cell D49 in the 'Summary and settings tab' of the CE model. The results are presented for all populations in Table 28 to Table 35.

Please note that we do think that these analyses are relevant for decision-making because as described above in the response to question 9a and 9b the effect of erenumab treatment has

been shown to be maintained in open-label extension studies. BSC non-responders have the highest MMD frequency of any non-baseline health state and therefore the assumption that all patients revert to this MMD frequency represents an extreme scenario. Additionally, no waning effect has been applied to BSC non-responders and it is highly unlikely that there would be no worsening in this group over time.

Table 28: Summary results for long-term effectiveness scenario in the whole migraine population (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£25,130

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 29: Summary results for long-term effectiveness scenario in the whole migraine population (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£22,109

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 30: Summary results for long-term effectiveness scenario in the chronic migraine population only versus botulinum toxin (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£32,928

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 31: Summary results for long-term effectiveness scenario in the chronic migraine population only versus botulinum toxin (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£31,752

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 32: Summary results for long-term effectiveness scenario in the chronic migraine population only versus BSC (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£30,018

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 33: Summary results for long-term effectiveness scenario in the chronic migraine population only versus BSC (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£21,191

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 34: Summary results for long-term effectiveness scenario in the episodic migraine population only (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£27,237**

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 35: Summary results for long-term effectiveness scenario in the episodic migraine population only (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£31,904**

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

B10. The nature of treatment discontinuation determines whether patients either rebound to the baseline MMD distribution (discontinuation due to adverse events or long-term

discontinuation) or are assumed to maintain the non-responder MMD improvement achieved at week 12 (discontinuation due to non-response at week 12).

a. Please justify why the nature of the discontinuation determines whether patients either rebound to the baseline MMD distribution or maintain the non-responder MMD improvement achieved at week 12.

We assumed that non-responder patients at 12 weeks would behave differently to both those discontinuing in the first cycle due to AEs and to patients discontinuing treatment subsequently due to loss of initial response, and would therefore have different MMD distributions. We assume that response status reveals a heterogeneity within the patient population of interest and thus we assume that a different propensity to respond to treatment also means a different disease status when coming off treatment. In particular, we assumed those who respond to treatment (but have to discontinue due to AEs) would have experienced a 'better' natural improvement in MMDs compared to non-responders. However, we accept that this is assumption-based and an alternative assumption of assuming all discontinuers experience MMDs equivalent to non-responders at 12 weeks is reasonable.

b. Please provide scenario analyses assuming all patients that discontinue have the week 12 non-responder MMD distribution.

The results of scenario analyses which assume that all patients that discontinue maintain the Week 12 non-responder MMD distribution are provided in Table 36 to Table 43 below. The impact on cost-effectiveness in these analyses is limited. These analyses use the updated utility data as requested in Question B14.b.

Table 36: Summary results for discontinuation scenario in the whole migraine population (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,753

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 37: Summary results for discontinuation scenario in the whole migraine population (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,700

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 38: Summary results for discontinuation scenario in the chronic migraine population only versus botulinum toxin (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)

Botulinum toxin	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,060

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 39: Summary results for discontinuation scenario in the chronic migraine population only versus botulinum toxin (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,572

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 40: Summary results for discontinuation scenario in the chronic migraine population only versus BSC (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,199

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 41: Summary results for discontinuation scenario in the chronic migraine population only versus BSC (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£13,120

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 42: Summary results for discontinuation scenario in the episodic migraine population only (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£25,949**

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 43: Summary results for discontinuation scenario in the episodic migraine population only (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£30,212

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

B11. For episodic migraine, data from ARISE, LIBERTY and STRIVE have been pooled to inform clinical effectiveness parameters in the economic model (Sections B.3.3.2 and B.2.7). Please specify how the patient-level data were pooled, and whether the analysis adjusted for differences between studies.

A pooled dataset of STRIVE, ARISE and LIBERTY is used to inform the efficacy calculations for episodic migraine. This analysis assumes that the episodic migraine trial datasets are homogenous. It was assumed that there is no trial-level effect and that the trials sample from the same patient population with the same MMD frequency at baseline. Thus, the patient-level data from the three trials was pooled without adjustment or weighting.

B12. A normal distribution is assumed for the MMD frequency distribution. In Appendix S it is stated "The normal distribution was selected in the base-case for the statistical distribution to fit both the Study 295 data and STRIVE data".

a. Please justify this choice to assume a normal distribution (e.g. by providing data on the statistical goodness of fit for the different distributions).

The normal distribution is used as this distribution provides overall mean MMD values closest to the raw trial data. A table summarising the mean MMDs from the trial data and from the various statistical distributions is presented in Table 44 for the chronic migraine population, as an example.

Table 44: Mean MMDs for responders and non-responders using different statistical distributions for the chronic migraine ≥3 prior prophylactic population

	Non-responders – Mean MMDs at 12 weeks			Responders – Mean MMDs at 12 weeks		
	Placebo	70 mg	140 mg	Placebo	70 mg	140 mg
Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poisson	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best fit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 295	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.

Full tables of statistical parameters that inform the MMD distributions for each distribution type, for each population, for each trial arm can be found in the "Stats_MMD" sheet in the Excel model. The model also allows for the selection of 'best fit' which selects the best fitting statistical model for every distribution required as per the Akaike Information Criterion (AIC).

b. Please justify why only Study 295 data and STRIVE data were used to inform the selection of the normal distribution (i.e. not ARISE and LIBERTY), and include an analysis where ARISE and / or LIBERTY are used, if considered appropriate.

In the final model used in the company submission the selection of the distribution is based on data from all relevant trials based on the population being analysed: the reference to Study 295 and STRIVE only in the text is a typographical error carried forward from an earlier draft of the text. Table 45 shows that inclusion of ARISE and LIBERTY does not alter the decision to select the normal distribution. The selection of the distribution was not only based on Study 295 and STRIVE, as the distribution can be chosen within the model based on any population and any combination of trials. The normal distribution always produces mean values closest to the trial data and is therefore favoured.

Table 45: Mean MMDs for responders and non-responders using different statistical distributions for the episodic migraine ≥3 prior prophylactic population

	Non-responders – Mean MMDs at 12 weeks			Responders – Mean MMDs at 12 weeks		
	Placebo	70 mg	140 mg	Placebo	70 mg	140 mg
Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poisson	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STRIVE, ARISE, LIBERTY combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.

c. Please elaborate on the potential bias and resulting impact on model outcomes when assuming a normal distribution, given the ceiling effect that appears present in Figure 24 of the CS.

Assuming a normal distribution potentially introduces a bias. However, the floor effect at 12 weeks and beyond is more consequential than the ceiling effect. This floor effect introduces a small bias which is conservative with respect to the cost-effectiveness of erenumab. This is because the floor effect biases the estimate of mean MMDs upwards and since the reduction in MMDs is greater with erenumab, the floor effect is more marked with erenumab than placebo.

Adverse events

B13. The impact of adverse events on costs and health-related quality of life is not explicitly considered in the economic model. This is justified by stating that adverse events are usually non-severe. However, adverse events are considered relevant outcomes according to the final scope. Therefore, please provide a scenario analysis explicitly incorporating the impact of adverse

events on costs and health-related quality of life, also considering the adverse event profiles of erenumab 70mg and 140mg separately (in the 70mg, 140mg and blended analyses).

As discussed at the clarification TC and as per our response to Question A9 and Document B, Section B.2.9, the AE profiles for erenumab 70 mg, 140 mg and placebo are similar in the full study population and in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed across all four clinical trials. Overall, erenumab was well-tolerated in clinical trials and demonstrated a safety and tolerability profile comparable to that of placebo. There have been no dose-related adverse events identified, i.e. no difference in safety profile between the doses. Serious adverse events (SAEs) were reported in very few patients across all treatment arms and studies, and AEs leading to discontinuation were again very uncommon across all four studies. Indeed, in some cases the discontinuation rates were higher in the placebo arms of the trials (see Document B, Section B.2.9).

Explicit inclusion of AEs was considered in the model development. However, given the comparable AE profile between erenumab and placebo and the low number of patients reporting SAEs, it was assumed that the costs associated with AEs experienced would not have considerable impact on the analysis. AEs have effectively been captured in the model by applying discontinuation rates.

The omission of costs and utilities due to AEs is likely to represent a conservative approach in the comparison of erenumab to botulinum toxin. It should be noted that this approach was accepted in TA260 where AEs affecting health-related quality of life were captured in the model by applying discontinuation rates and there were assumed to be no additional costs relating to AEs.[13] A scenario analysis explicitly looking at AE-related utility decrement has been included in response to Question B17.

Health related quality of life

B14. **Priority:** Utility values used in the model were mapped from the Migraine-Specific Quality of Life Questionnaire (MSQ) collected in Study 295, STRIVE and ARISE. Utility values were then estimated through multilevel models. However, the description of statistical model selection procedures lacks detail.

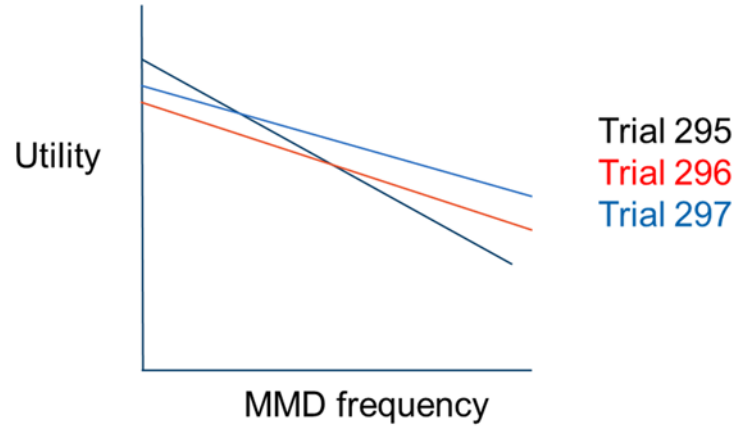
a. Please provide details on:

i. how data from STRIVE and ARISE were pooled (episodic migraine) and how data from all 3 trials were pooled (whole population)

For the multilevel modelling approach, data for the full trial populations from the randomised phase of the three trials (12 weeks for Study 295 and ARISE, 24 weeks for STRIVE) were pooled through the use of a varying intercept and slopes in the utility regression model. Patients from each trial had a different intercept (i.e. B_0 = utility for patients with 0 MMD frequency) and different slope (i.e. B_1). This was added using the following command in the lmer regression equation *(1 + MMD | Trial)* and illustrated in Figure 9 (regression lines and slopes for illustration only).

For the GEE (generalised estimating models) there is no comparable approach to pooling the data and consequently the data was pooled by merging the dataset.

Figure 9: Varying slope, varying intercept model



Abbreviations: MMD: monthly migraine day.

ii. the number of patients and observations included in the analyses (stratified by trial and MMD frequency),

A summary of the number of patients and observations included in these analyses is presented in Table 46 below.

Table 46: Number of observations by MMD frequency

MMD frequency	Study 295	STRIVE	ARISE
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]
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 day; N/A: not applicable.

iii. the number of missing observations and how these were handled,

The number of patients included in the model was 2,171, stratified by treatment arm and trial (see Table 47). The model included 2,520 observations in Study 295, 7,131 observations in STRIVE and 2,221 observations in ARISE.

As four sets of observations were taken for Study 295, nine sets of observations for STRIVE and four sets of observations for ARISE, the hypothetical number of observations in a complete dataset is the number of baseline patients in each trial multiplied by the number of sets of observations.

These figures indicate that 104/2,624 (3.9%), 1,383/8,514 (16.24%) and 59/2,276 (2.5%) of observations were missing for Study 295, STRIVE and ARISE studies, respectively.

In contrast to the efficacy analysis, missing data were not imputed. This approach was considered reasonable because the objective was to model the relationship between MMD frequency and utility, rather than the temporal trend in utilities.

Table 47: Number of observations at baseline

Trial	Arm	Observations at baseline
Study 295	Placebo	[redacted]
	Erenumab 140 mg	[redacted]
	Erenumab 70 mg	[redacted]
STRIVE	Placebo	[redacted]
	Erenumab 140 mg	[redacted]
	Erenumab 70 mg	[redacted]
ARISE	Erenumab 70 mg	[redacted]
	Placebo	[redacted]

iv. the characteristics of patients who were not included in the analysis of health related quality of life data,

Table 48 details the characteristics of patients not included in the analysis. These represent the patients who were included in the baseline dataset but were not included in the efficacy analysis set.

Table 48: Summary characteristics of patients not included in analysis

Trial	Arm	n	Age	% Female	% White	Baseline MMD

Study 295		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STRIVE		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARISE		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.
*Treatment labels were not available in the MSQ dataset for analysis

v. the characteristics of patients included in the analyses (stratified by trial, treatment [erenumab or placebo] and MMD frequency)

Table 49 presents the summary characteristics of patients included in the regression analysis (i.e. the efficacy analysis set) as per the CSRs.

Table 49: Summary characteristic of patients included in the analysis

Trial	Arm	n	Age	% Female	% White	Baseline MMD
Study 295	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STRIVE	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARISE	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.

vi. a description of the covariates included in the statistical models

Table 50 presents the covariates used in the statistical models.

Table 50: Covariates used in the statistical models

Covariate	Description
MMD frequency	MMD frequency
MMD frequency^2	MMD frequency squared – used to incorporate non-linearity
MMD frequency^3	MMD frequency cubed – used to incorporate higher order non-linearity
Erenumab 140 mg	Treatment with erenumab 140 mg (vs placebo)
Erenumab 70 mg	Treatment with erenumab 70 mg (vs placebo)

Abbreviations: MMD: monthly migraine day.

vii. statistical fit statistics of each fitted model (e.g. Akaike information criterion (AIC), R^2)

Please see Table 51 in response B14a.viii.

viii. justification for selecting the models used in the base-case analysis.

Multilevel models

A number of models were fit to the pooled data and are presented in Table 39. In addition to the linear function used in the base case submission, quadratic and cubic terms for MMD frequency were also included to explore non-linearity, and a treatment covariate was added to explore possible improvements in migraine severity associated with being on active treatment.

AIC (resultant χ^2 tests) and BIC values were calculated using "ML" estimations but other parameters (i.e. Beta coefficients and R2 values) and were based on "REML" estimations. The cubic model was found to have the lowest (best) AIC and BIC values. The chi-squared tests are statistically significant when comparing the linear model with the non-linear and treatment effect models (see Table 51).

The R^2 tests indicate that the explained variation is similar across the models and any difference with respect to the ICER is assumed to be quite small. An expert panel suggested the application of a linear model and a comparison between model predictions (see Figure 10), which suggests that the difference between the various models in terms of the predicted utilities is quite small.

Diagnostic plots for the linear multilevel model are shown Figure 12. The residuals show a marked pattern at the lower predicted disutilities. This is due to EQ-5D ceiling effects i.e. the highest mapped EQ-5D utility is approximately 0.85 (and conversely a disutility of 0.15) and the lowest mapped EQ-5D utility is -0.04 (disutility of -1.04). This explains the asymmetry of the residuals shown in Figure 12.

GEE models

In the estimation of GEE models the default correlation structure of "independence" was chosen.

In terms of model fit, AIC values are not available for these models and a modified statistic, QIC was used. Based on the QIC criterion, there was very little difference in between models and therefore the linear model was considered for the base case when considering GEE models (Table 52).

Multilevel was chosen over GEE as this modelling approach accounts for the trial level effects and because we pool data from three trials we consider this a more appropriate approach. Both GEE and Multilevel analysis have been used to account for longitudinal data in economic submissions, so both were provided.

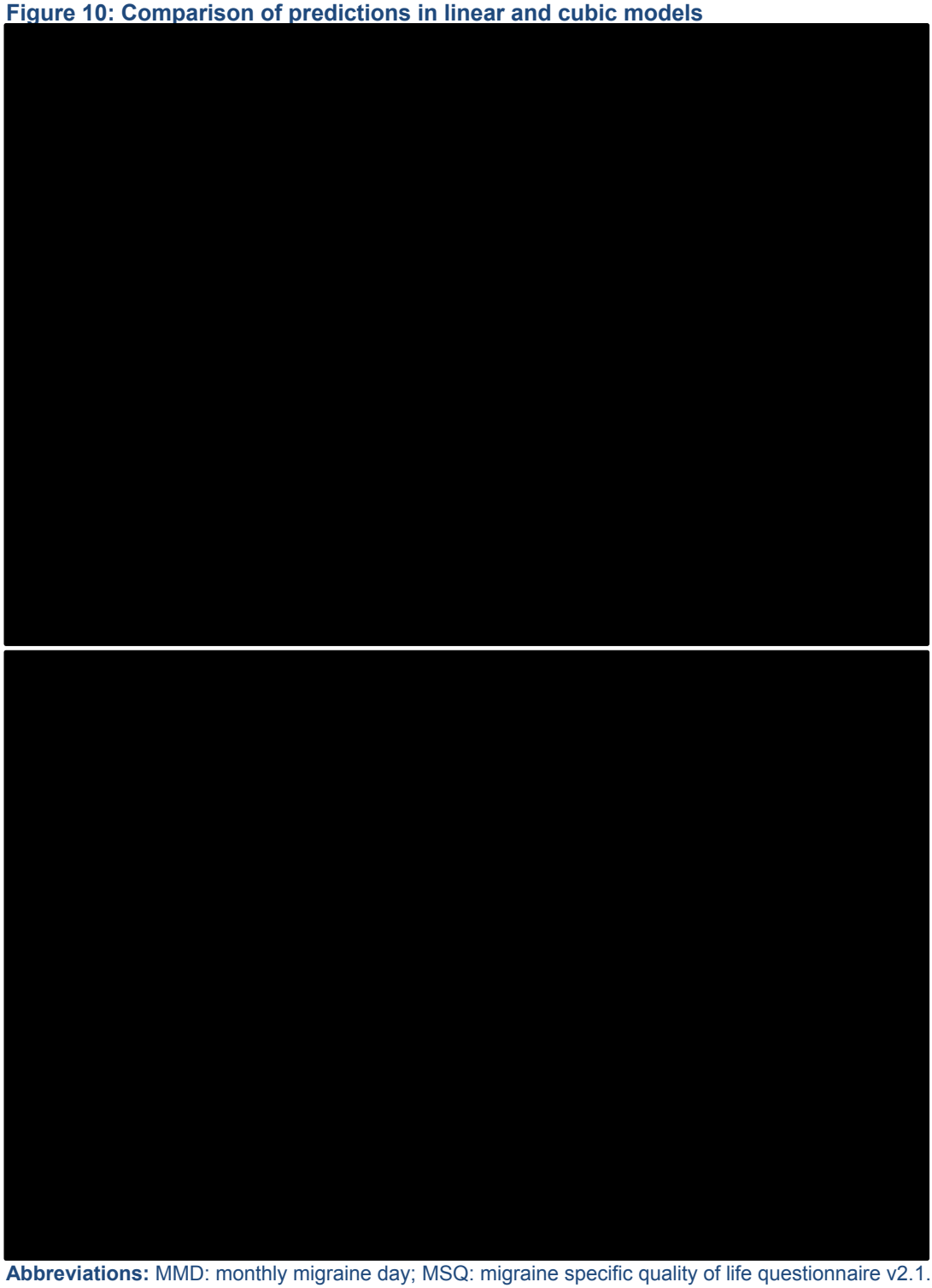
Table 51: Linear Multi-level Models fit to the pooled trial data

	Dependent variable			
	Disutility			
	Linear	Quadratic	Cubic	Linear + Treatment
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency[2]		[redacted]	[redacted]	
		[redacted]	[redacted]	
MMD frequency[3]			[redacted]	
			[redacted]	
Erenumab 140 mg				[redacted]
				[redacted]
Erenumab 70 mg				[redacted]
				[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]	[redacted]	[redacted]	[redacted]
Log Likelihood	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]
χ^2(df)		[redacted]	[redacted]	[redacted]
R^2m	[redacted]	[redacted]	[redacted]	[redacted]
R^2c	[redacted]	[redacted]	[redacted]	[redacted]

Note: *p<0.1; **p<0.05; ***p<0.01.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MMD: monthly migraine day.

Figure 10: Comparison of predictions in linear and cubic models



Abbreviations: MMD: monthly migraine day; MSQ: migraine specific quality of life questionnaire v2.1.

Figure 11: Diagnostic plots for linear model

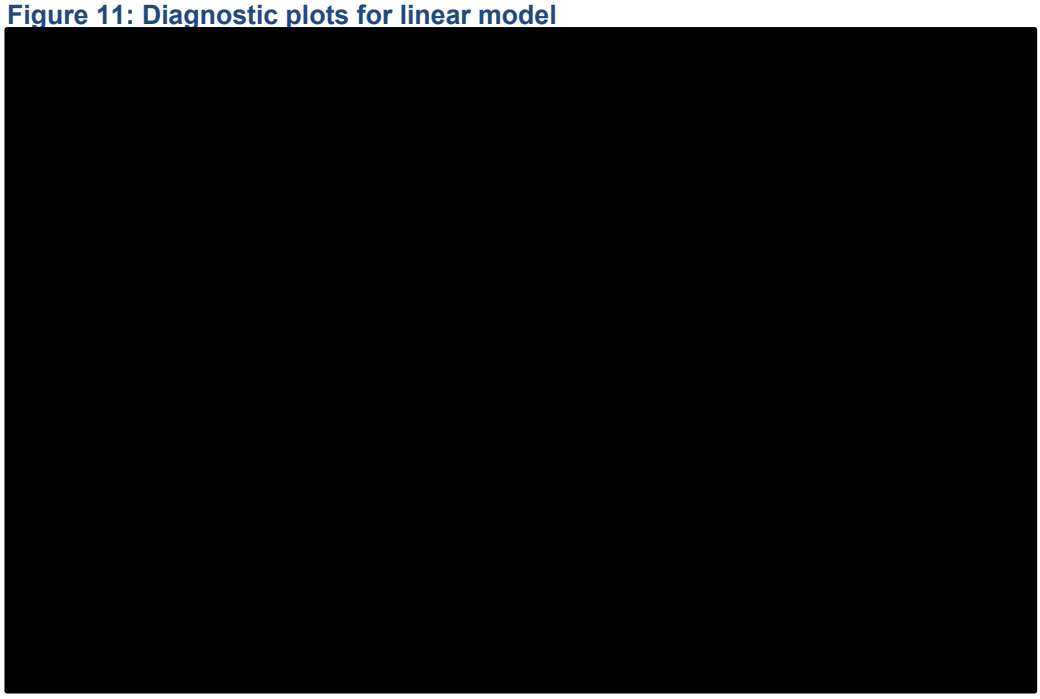


Table 52: Goodness of fit for GEE models (best fitting models displayed first)

	Quadratic	Linear	Cubic	Linear + Treatment
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency^2	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency^3	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 70 mg	[redacted]	[redacted]		[redacted]
Treatment 140 mg				[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
quasi Likehood	[redacted]	[redacted]	[redacted]	[redacted]
QIC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GEE: generalised estimating equations; MMD: monthly migraine day; N/A: not applicable.

b. Are the utility values mapped from the MSQ obtained from the subgroup of patients who received either placebo or erenumab (for both 70mg and 140mg) after ≥3 prior prophylactic treatments? If not, please re-estimate the utility values for this subgroup only (provide the details requested under B14a when performing these analyses). Please use these re-estimated utility values in all requested analyses.

The base case estimates consider the full trial population and are not stratified by treatment failure. Limiting the population to patients for whom ≥3 prior prophylactic treatments have failed considerably reduced the number of patients available in the analysis, particularly for STRIVE and ARISE. Therefore, only pooled not indication specific utility analyses have been conducted for the ≥3 prior prophylactic treatments population. Utility models based on the restricted population typically have a greater increase in disutility associated which each MMD frequency (e.g. 0.019 vs 0.0163), which will improve the cost effectiveness of erenumab, in comparison with using pooled utilities from the full study population.

Table 53 provides the re-estimated utility values for each MMD frequency, mapped from MSQ data obtained from the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in each trial.

Table 53: Summary of derived utility values by MMD frequency (patients for whom ≥3 prior prophylactic treatments have failed)

MMD	Whole migraine (Study 295, STRIVE and ARISE) Multilevel linear
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]
16	[redacted]
17	[redacted]
18	[redacted]
19	[redacted]
20	[redacted]
21	[redacted]

22	[redacted]
23	[redacted]
24	[redacted]
25	[redacted]
26	[redacted]
27	[redacted]
28	[redacted]

Abbreviations: MMD: monthly migraine day.

i. the number of patients and observations included in the analyses (stratified by trial and MMD frequency)

The number of patients and observations included in the analyses (stratified by trial and MMD frequency) is presented in Table 53.

Table 54: Number of observations stratified by MMD frequency and trial (patients for whom ≥3 prior prophylactic treatments have failed)

MMD number	Study 295	STRIVE	ARISE
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]
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 day.

ii. the number of missing observations and how these were handled

The number of patients for whom ≥3 prior prophylactic treatments have failed included in the model was [redacted], stratified by treatment arm and trial, as presented in Table 55. The model included [redacted] observations from Study 295, [redacted] observations from STRIVE and [redacted] observations from ARISE.

Table 55: Number of patients at baseline (patients for whom ≥3 prior prophylactic treatments have failed)

Trial	Treatment	n
Study 295	Erenumab 140 mg	[redacted]
	Erenumab 70 mg	[redacted]
	Placebo	[redacted]
STRIVE	Erenumab 140 mg	[redacted]
	Erenumab 70 mg	[redacted]
	Placebo	[redacted]
ARISE	Erenumab 70 mg	[redacted]
	Placebo	[redacted]

Because four sets of observations were taken in Study 295, nine sets of observations in STRIVE and four sets of observations for ARISE, the hypothetical number of observations should be the number of baseline patients in each trial multiplied by the number of sets of observations.

These figures indicate that [redacted] ([redacted]%), [redacted] ([redacted]%) and [redacted] ([redacted]%) of observations were missing for Study 295, STRIVE and ARISE, respectively.

iii. the characteristics of patients included in the analyses (stratified by trial, treatment [erenumab or placebo] and MMD frequency),

The characteristics of patients included in the analyses (stratified by trial, treatment [erenumab or placebo] and MMD frequency) are provided in Table 56.

Table 56: Characteristics of patients included in the analysis

Trial	Treatment	n	Age	% Female	% White	Baseline MMD
Study 295	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STRIVE	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARISE	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.

iv. the characteristics of patients not included in the analyses (stratified by trial, treatment [erenumab or placebo] and MMD frequency),

The characteristics of patients included in the analyses (stratified by trial, treatment [erenumab or placebo] and MMD frequency) are provided in Table 57.

Table 57: Characteristics of patients not included in the analysis

Trial	Treatment	n	Age	% Female	% White	Baseline MMD
Study 295		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STRIVE		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARISE		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.
*Treatment labels were not available in the MSQ dataset for analysis

v. a description of the covariates included in the statistical models

The covariates included in the statistical model in patients for whom ≥3 prior prophylactic treatments have failed were the same as those used in the full population utility analysis.

vi. statistics of each fitted model (e.g. Akaike information criterion (AIC), R2)

Regression coefficients for the multilevel model and GEE models are presented in Table 58 and Table 59. Based on the AIC and BIC criterion (QIC for GEE models), the best fitting model is the cubic model. Figure 12 presents the linear and cubic models predictions for the multilevel models.

Table 58: Regression outputs for linear mixed effect models (patients for whom ≥3 prior prophylactic treatments have failed)

	Dependent variable			
	Disutility			
	Linear	Quadratic	Cubic	Linear + Treatment

MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency^2		[redacted]	[redacted]	
		[redacted]	[redacted]	
MMD frequency^3			[redacted]	
			[redacted]	
Erenumab 140 mg				[redacted]
				[redacted]
Erenumab 70 mg				[redacted]
				[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]	[redacted]	[redacted]	[redacted]
Log Likelihood	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]

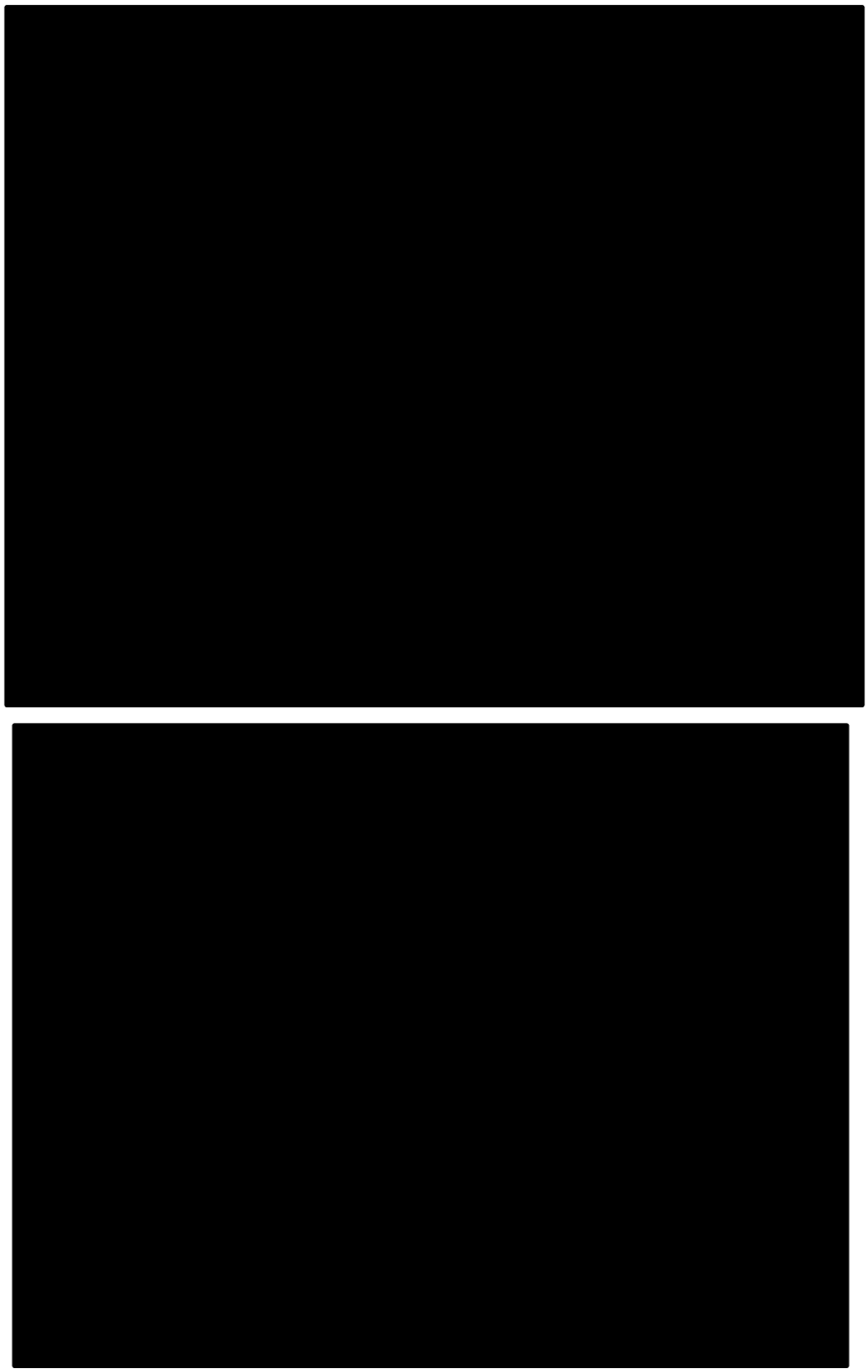
Note: *p<0.1; **p<0.05; ***p<0.01
Abbreviations: Akaike information criterion; BIC: Bayesian information criterion; MMD: monthly migraine day.

Table 59: Regression outputs for GEE models (best fitting models displayed first) (patients for whom ≥3 prior prophylactic treatments have failed)

	Linear	Quadratic	Cubic	Linear + Treatment
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency^2	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency^3	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 70 mg	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 140 mg	[redacted]	[redacted]	[redacted]	[redacted]
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
qLik	[redacted]	[redacted]	[redacted]	[redacted]
QIC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GEE: generalised estimating equation; NA: not applicable.

Figure 12: Predicted Utility for Linear and Cubic (patients for whom ≥3 prior prophylactic treatments have failed)



Abbreviations: MMD: monthly migraine day; MSQ: migraine specific quality of life questionnaire v2.1; TF: treatment failure.

c. Please provide a scenario analysis in which health state utility values are directly estimated for each health state instead of estimating utility values for each MMD frequency (provide the details requested under B14a). Please use the mapped MSQ utility data for this analysis.

As agreed at the technical TC, this scenario has not been conducted. Utility is explained by MMD frequency and a weighted average utility per responder/non-responder health state is currently calculated based on the distribution of MMDs within that health state and the associated utilities. Provided the assumption that a given number of MMDs is associated with a particular utility regardless of health state is accepted, the model is already using average utilities per health state.

B15. **Priority:** Despite having access to EQ-5D data (NICE reference case), mapped utilities were used in the company base-case.

a. Please clarify whether utility data applied in scenario 13 for the episodic migraine population were obtained using the preferred cross-walk algorithm according to the NICE position statement[38]. If not, please re-estimate the utility values based on this algorithm.

The procedure used to derive the utilities follows the NICE position statement and uses the (van Hout et al. 2012) algorithm for mapping EQ-5D-5L to -3L.[39] As agreed at the clarification TC, all responses for this question are applicable to the episodic migraine population only, as only the LIBERTY study included EQ-5D.

b. Please provide details on

i. the number of patients and observations included in the analysis (stratified by MMD frequency),

The number of observations included in the analysis is summarised in Table 60.

Table 60: Observations stratified by MMD frequency (episodic migraine patients)

MMD frequency	n
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]

16	[redacted]
17	[redacted]
18	[redacted]
19	[redacted]
20	[redacted]
21	[redacted]
22	[redacted]
27	[redacted]

Abbreviations: MMD: monthly migraine day.

ii. the number of missing observations and how these were handled

The number of patients at baseline is 242 (Table 61). Because four timepoints were considered, the number of observations with complete data is 968. The number of observations for these timepoints is 962, which means that six observations are missing. The proportion of missing observations is 6/968 (0.62%).

Table 61: Observations at each time-point (episodic migraine population)

Visit	Treatment	n
Baseline	Erenumab 140 mg	[redacted]
	Placebo	[redacted]
Week 4	Erenumab 140 mg	[redacted]
	Placebo	[redacted]
Week 8	Erenumab 140 mg	[redacted]
	Placebo	[redacted]
Week 12	Erenumab 140 mg	[redacted]
	Placebo	[redacted]

iii. the characteristics of patients included in and excluded from the analysis

The characteristics of patients included and excluded in the analysis are presented in Table 62 and Table 63 .

Table 62: Included in episodic migraine analysis (as per efficacy analysis set in CSR)

Treatment	n	Age	Sex (Female) (%)	Race (Caucasian) (%)	Baseline MMD
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR: clinical study report; MMD: monthly migraine day.

Table 63: Excluded from Analysis (as per efficacy analysis set in CSR)

Treatment	n	Age	Sex (Female) (%)	Race (Caucasian) (%)	Baseline MMD

No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR: clinical study report; MMD: monthly migraine day.

iv. the selection procedure of the statistical models used to estimate these utility values (please provide the details requested under B14a).

Goodness of fit statistics (e.g. AIC, BIC) indicate that the cubic model is the best fit (Table 64). The plots of predicted utility vs MMD frequency (Figure 13) indicate that the relationship is approximately linear until 14 MMDs, after which the data becomes very sparse (expected as LIBERTY is an episodic migraine trial) and the general trend is quite uncertain. For simplicity the linear model was chosen.

Table 64: Regression outputs for EQ-5D-3L (full population – episodic migraine)

	Dependent variable		
	Disutility		
	Linear	**Quadratic**	**Cubic**
MMD frequency	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
MMD frequency^2		[redacted]	[redacted]
		[redacted]	[redacted]
MMD frequency^3			[redacted]
			[redacted]
Constant	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Observations	[redacted]	[redacted]	[redacted]
Log Likelihood	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]

Note: *p<0.1; **p<0.05; ***p<0.01
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EQ-5D-3L: EuroQol-5 Dimensions-3 Levels; MMD: monthly migraine day.

Figure 13: Linear mixed effects models

Abbreviations: EQ-5D-3L: EuroQol-5 Dimensions-3 Levels; MMD: monthly migraine day.

c. Please confirm that these utility values were obtained from the subgroup of patients with ≥3 prior prophylactic treatments. If not, please re-estimate these utility values based on this subgroup and provide the details requested in B15b.

The utility values used were obtained from the whole trial population. Please find the re-estimated utility values in patients for whom ≥3 prior prophylactic treatments have failed summarised below in Figure 14.

i. the number of patients and observations included in the analysis (stratified by MMD frequency),

Table 65 summarises the number of patients and observations included in the analysis (stratified by MMD frequency). There were 76 patients in the erenumab 140 mg arm and 72 patients in the placebo arm for whom ≥3 prior prophylactic treatments had failed.

Table 65: Number of observations per MMD frequency

MMD frequency	n
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]

12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]
16	[redacted]
17	[redacted]
18	[redacted]
19	[redacted]
21	[redacted]
22	[redacted]
27	[redacted]

Abbreviations: MMD: monthly migraine day.

ii. the number of missing observations and how these were handled,

148 patients had measurements at baseline and a total of 584 observations were recorded at follow-up. Four measurements were taken during the randomised phase of trial, meaning that 592 observations would be observed if the data were complete. A total of 1.35% (8/592) were considered to be missing. As per the other analyses, missing data was not imputed.

iii. the characteristics of patients included in and excluded from the analysis

The characteristics of patients included/excluded in the analysis are presented in Table 66 and Table 67. Patients excluded from the analysis include those in the baseline dataset who were not included in the efficacy analysis set and patients who did not have three or more previous treatment failures.

Table 66: Characteristics of patients included in the model

Treatment	n	Age	% Female	% White	Baseline MMD
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.

Table 67: Characteristics of patients excluded from the model

Treatment	n	Age	% Female	% White	Baseline MMD
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.

*Two patients who did not have a treatment label in the baseline dataset

iv. the selection procedure of the statistical models used to estimate these utility values (please provide the details requested under B14a).

Regression outputs are presented in Table 68 and the goodness of fit tests indicate that the cubic model provides the best fit relative to the linear and quadratic alternative. Consistent with the EQ-5D analysis in full population, the data is even sparser above 15 MMD frequencies and the regression equations are highly uncertain (see Figure 14).

Table 68: Regression outputs for EQ-5D-3L (patients for whom ≥3 prior prophylactic treatments have failed)

	Dependent variable		
	Disutility		
	Linear	Quadratic	Cubic
MMD frequency	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
MMD frequency^2		[redacted]	[redacted]
		[redacted]	[redacted]
MMD frequency^3			[redacted]
			[redacted]
Constant	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Observations	[redacted]	[redacted]	[redacted]
Log Likelihood	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]

Note: *p<0.1; **p<0.05; ***p<0.01
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MMD: monthly migraine day.

Figure 14: Estimated EQ-5D-3L utilities

Abbreviations: EQ-5D-3L: EuroQol-5 Dimensions-3 Levels; MMD: monthly migraine day.

d. Please provide a scenario analysis using the utility values estimated in B15c in all populations included in the CS.

The scenario analyses using the utility values estimated in Question B15.c are presented in Table 69 and Table 70 for the episodic migraine populations. As discussed in Question B15.a, results are only presented in this population as LIBERTY was the only study that included EQ-5D.

Table 69: Summary results for scenario using EQ-5D-5L data in the episodic migraine population only (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£79,963**

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 70: Summary results for scenario using EQ-5D-5L data in the episodic migraine population only (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£90,854**

Abbreviations: BSC: best supportive care; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

e. Multi-level models were used to estimate base-case utility values conditional on MMD frequency. Please provide a scenario analysis in which health state utility values are directly estimated based on the mapped EQ-5D-5L data, instead of estimating utility values for each MMD frequency (provide the details requested under B15b).

As agreed at the technical TC and discussed in Question B14.c, this scenario has not been conducted. Utility is explained by MMD frequency and a weighted average utility per health state is currently calculated based on the distribution of MMDs within that responder/non-responder health state and the associated utilities. Provided the assumption that a given number of MMDs is associated with a particular utility regardless of health state is accepted, the model is already using average utilities per health state.

B16. Gillard et al. 2012[40] present two algorithms to obtain EQ-5D-3L, one based on the MSQ and one based on the HIT-6.

a. Please provide a scenario analysis using the mapping algorithm based on the HIT-6 instrument (in all populations).

Mixed effect models and GEE models (including MMD frequency as the only predictor) were fit to the HIT-6 derived utility values. The regression coefficients and plots of the predicted utility are presented in Table 71 and Figure 15 respectively.

Table 71: Coefficients for HIT-6 linear mixed effects and GEE model

Term	Mixed Effects models	GEE
(Intercept)	[redacted]	[redacted]
MMD	[redacted]	[redacted]
Observations	[redacted]	[redacted]

Abbreviations: GEE: generalised estimating equation; HIT-6: Headache Impact Test-6; MMD: monthly migraine day.

Figure 15: Predicted HIT-6 scores for Multilevel and GEE models

Abbreviations: GEE: generalised estimating equation; HIT-6: Headache Impact Test-6; MMD: monthly migraine day; MSQ: migraine specific quality of life questionnaire.

Results of the scenario analyses using the mapping algorithm based on the HIT-6 instrument in all populations are presented in Table 72 to Table 79. In these scenarios cost-effectiveness ratios increase, however it should be noted that the HIT-6 is a 6-item questionnaire, and measures the impact of headaches specifically whereas erenumab is licensed for the prophylaxis of migraine. The MSQ contains broader questions about the impact of migraine on daily life and we consider it more appropriate to map from this questionnaire.[41] Additionally, mapping from MSQ was the mapping algorithm used in appraisal TA260.[13]

Table 72: Summary results for scenario analysis using mapped HIT-6 data in the whole migraine population (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£33,740

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; HIT-6: Headache Impact Test-6; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 73: Summary results for scenario analysis using mapped HIT-6 data in the whole migraine population (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£29,804

Abbreviations: BSC: best supportive care; HIT-6: Headache Impact Test-6; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 74: Summary results for scenario analysis using mapped HIT-6 data in the chronic migraine population only versus botulinum toxin (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£35,923

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: HIT-6: Headache Impact Test-6; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 75: Summary results for scenario analysis using mapped HIT-6 data in the chronic migraine population only versus botulinum toxin (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£33,907

Abbreviations: HIT-6: Headache Impact Test-6; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 76: Summary results for scenario analysis using mapped HIT-6 data in the chronic migraine population only versus BSC (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£32,727

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; HIT-6: Headache Impact Test-6; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 77: Summary results for scenario analysis using mapped HIT-6 data in the chronic migraine population only versus BSC (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£25,365

Abbreviations: BSC: best supportive care; HIT-6: Headache Impact Test-6; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 78: Summary results for scenario analysis using mapped HIT-6 data in the episodic migraine population only (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70 mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£46,177**

[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; HIT-6: Headache Impact Test-6; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 79: Summary results for scenario analysis using mapped HIT-6 data in the episodic migraine population only (with PAS), erenumab 140 mg

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	**£52,467**

Abbreviations: BSC: best supportive care; HIT-6: Headache Impact Test-6; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

B17. Disutilities for adverse events and mode of administration (used in scenario analysis 13) have been estimated through a vignette-based study described in Appendix U.

a. Please provide the demographic and clinical characteristics of all respondents, stratified by subgroups (i.e. general public respondents and respondents with migraine).

Demographics and clinical characteristics of all respondents, stratified by subgroup can be found in Appendix C (pages 48–52) and Appendix D (pages 95–99) in the study report.[42]

b. Tables 92 and 93 of Appendix U provide relative utility decrements associated with adverse events and mode of administration for each treatment compared to erenumab. Please provide the absolute utility decrements associated with adverse events and mode of administration for each treatment. Please also provide the estimated utility values for each health state and adverse events described in Appendix U, stratified by subgroups (i.e. general public respondents and respondents with migraine).

Absolute utility decrements associated with AEs and mode of administration for each treatment can be found in Appendix C (pages 62–68) for the general public respondents and in Appendix D (pages 109–117) for the migraine population respondents in the study report.[42] Estimated utility values for each health state and AEs described in Appendix U can be found in Appendix C (pages 65–71) and Appendix D (pages 112–117) in the study report.[42]

c. Please provide the source (both reference and digital copy of the source) from which the adverse event rates have been obtained (i.e. the likelihood of being helped or harmed [LHH] study, as mentioned in Appendix U).

i. Please describe how the study/studies used was/were identified.

Please find enclosed the publication for the likelihood of being helped or harmed (LLH) study mentioned in Appendix U.[43] This was an ongoing Novartis study at the time of the development of the vignette study, and it estimated AE rates from a literature review of safety outcomes.

d. Please provide details on the expert feedback from UK clinicians who supported the inclusion of mode of administration decrements only in a scenario analysis. Please provide

i. The number of experts asked.

ii. The questions asked.

iii. The answer to each question per expert.

The question asked to experts was "*HRQoL measures are unlikely be sensitive to aspects such as mode of administration (even frequency of administration). How might this aspect of benefit be captured in the analysis? Would utility vignette studies be helpful"*. Three UK experts (two Headache Specialists and one Health Economics Professor) were consulted in an advisory capacity during TCs throughout model development. As such verbatim responses are not available. However, all experts agreed that mode of administration disutilities would be best as a scenario analysis, rather than the base case assumption. This was due to the potential biases associated with the vignette study design, wherein utility decrements estimated were entirely dependent on respondent's interpretation of the mode of administration description i.e. they themselves had not actually experienced each alternative mode of administration. Feedback

from other UK clinical experts in an advisory board was that the mode of administration of erenumab is seen as benefit to patients in comparison to botulinum toxin.[44]

e. Please provide a scenario analysis in which both mode of administration and AE-related utility decrements are included (provided in response to question B17b).

Scenario analyses including the mode of administration and AE-related utility decrements are presented in Table 80 and Table 81. These analyses have been conducted using the ≥3 prior prophylactic treatment failure utility data as request in question B14c.These results are similar to those presented in scenario 13 in the main submission.

Table 80: Summary results for scenario analysis including both mode of administration and AE-related utility decrements in the chronic migraine population only population versus botulinum toxin (with PAS), blended dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 70/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£4,390

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 81: Summary results for scenario analysis including both mode of administration and AE-related utility decrements in the chronic migraine only population versus botulinum toxin (with PAS), 140mg dose[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£4,629

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Resource use and costs

B18. Please comment on the medications listed in Appendix V[45]:

a. Are the listed medications in line with NICE guidelines for acute migraine medication?

Yes. NICE Headache in over 12s: diagnosis and management provides the following recommendations regarding acute treatments for the migraine with or without aura:[1]

Migraine with or without aura

Acute treatment

Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of AEs. For young people aged 12–17 years consider a nasal triptan in preference to an oral triptan.

For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:

- offer a non-oral preparation of metoclopramide or prochlorperazine and
- consider adding a non-oral NSAID or triptan if these have not been tried.[8]

The medications listed in Appendix V of the company submission are in line with these recommendations.

b. Are the medications selected comprehensive and representative of resource utilisation for treatment of acute migraine in the UK?

The medications selected are comprehensive, and include analgesics, antiemetics and available $5HT_1$-receptor agonists (triptans) available in the UK.

c. On what grounds were the brands and dosage of medications selected?

A standard dose strength and number of doses consumed per day were informed using posology information in the British National Formulary (BNF). Where a range was provided the lower dose was selected or the dose specifically indicated in the BNF. For many of the triptans, only one dose is licensed (e.g. fovatriptan, eletriptan, naratriptan, almotriptan). A similar process was used for the other headache medications in which the posology from the BNF was used to identify an appropriate strength and a dosing schedule. The specific brands were not chosen using a particular criterion, however where generics were available, the lowest price generic was usually chosen.

d. What weights were applied to calculate the weighted average of triptan medication cost per day and where did these weights come from? Please indicate the source and provide an overview of this data.

The source used was the NHWS data from 2017, which reported prescription medication use for patients with migraine. Migraine medication was assumed to include triptans while headache medication was assumed to be other analgesics. Of the 218 migraine respondents, 49 (22%) had prescriptions for triptan medications while 90 (41%) had prescriptions for analgesic medications. The remainder had prescriptions for preventative medications or combinations of painkillers not licensed in the UK. The weights from the survey for both headache medications and triptans are presented in Table 82 and

Table 83.

Table 82: Proportion of patients receiving each type of other headache medications

	Total (N=218)	
	Column total (%)	**Count**
Ibuprofen	45.56	41
Aspirin	5.56	5
Ketoprofen	2.22	2
Paracetamol	30.00	27
Paracetamol/Metoclopromide	2.22	2
Paracetamol/Codeine	13.33	12
Migraleve (buclizine/paracetamol/codeine)	1.11	1
Total	**100.00**	**90**

Table 83: Proportion of patients on each type of triptan medications

	Total (N=218)	
	Column total (%)	**Count**
Almotriptan	6.12	3
Naratriptan	4.08	2
Frovatriptan	8.16	4
Sumatriptan Injection	18.37	9
Rizatriptan	18.37	9
Eletriptan	6.12	3
Sumatriptan	20.41	10
Zolmitriptan	18.37	9
Total	**100.00**	**49**

e. If sumatriptan injections are used for acute migraine treatment in line with guidelines, why were sumatriptan injections excluded from the triptan medication cost?

It was noted that the cost of triptans was quite sensitive to the inclusion of sumatriptan injection. In relation to the botulinum toxin submission, the ERG implied that the cost of triptan medications should be quite low as "*non-propriety sumatriptan is by far the cheapest of the triptan medications, being an order of magnitude (less than other triptans) at £0.27 per 50mg tablet*".[13] Therefore, the cost of triptan medication was assumed to be £2.55, in which the cost of sumatriptan injections are not considered.

B19. Please comment on the sources used for resource use and costs (including the National Health and Wellness survey (NHWS) of 2017 and 2018, Study 295, ARISE, LIBERTY and STRIVE):

a. Are all estimates obtained from a UK population with ≥3 prior failed prophylactic treatments?

No, all estimates are obtained from the UK population in the NHWS study and were not restricted to the ≥3 prior prophylactic treatment population. Estimates defined resource utilisation by frequency of migraine, from not experiencing migraine (0 MMD) to chronic migraine (≥15 MMDs).

b. If not, please re-estimate and present adjusted estimates for the population with ≥3 prior failed treatments and provide a scenario analysis using these estimates (in all populations included in the company submission).

It is not possible to provide these analyses as do not have access to the individual level data from the NHWS survey in order to identify the ≥3 prior prophylactic treatment population as this was a third party study. However, we do not believe that any differences in the subgroup data resource use will impact significantly on the cost-effectiveness results.

B20. For the regression models of migraine drug days and other medication days (Table 97, Appendix V[45]):

a. Please detail the method used, i.e. describe how the data from Study 295, STRIVE and ARISE have been pooled.

Data from Study 295, STRIVE and ARISE were pooled by merging the datasets, therefore no adjustments or weighting was taken into account. We assume the populations are homogenous.

b. Describe the methods used to fit the models as well as other relevant information (e.g. proportion missing data, number of patients included in the analyses, number of observations) and provide statistical fit statistics (such as the Akaike Information Criterion, R^2) of each model fitted to the data.

The numbers of patients with migraine medication information at baseline is presented in Table 84. Patients in Study 295 and ARISE had four timepoints at which medication information was collected, while there were nine timepoints at which medication information was collected in STRIVE. Therefore, the complete dataset contains 13,418 observations, while the actual dataset contains 12,364 observations meaning that 1,054 (7.8%) observations were missing. The regression coefficients are presented Table 85 for both linear and quadratic models.

Table 84: Numbers of patients with medication information at baseline

Trial	Treatment	n
Study 295	Erenumab 140 mg	[redacted]
	Erenumab 70 mg	[redacted]
	Placebo	[redacted]
STRIVE	Erenumab 140 mg	[redacted]
	Erenumab 70 mg	[redacted]
	Placebo	[redacted]
ARISE	Erenumab 70 mg	[redacted]
	Placebo	[redacted]

Table 85: Regression outputs for medication day models

	Dependent variable			
	Acute Medication Days	**Other Headache Medication Days**	**Acute Medication Days (Quadratic)**	**Other Headache Medication Days (Quadratic)**
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency^2			[redacted]	[redacted]
			[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]	[redacted]	[redacted]	[redacted]

R^2	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted R^2	[redacted]	[redacted]	[redacted]	[redacted]

Note: *p<0.1; **p<0.05; ***p<0.01
Abbreviations: MMD: monthly migraine day.

c. Please describe the model selection procedure.

A scatterplot of MMD frequency versus migraine and headache medication showed a reasonably linear relationship and therefore a simple linear relationship was considered appropriate (Figure 16 and Abbreviations: MMD: monthly migraine day.

Figure 17). The R^2 presented in Table 85 show no difference (to the 3rd decimal place) between the linear and quadratic models and therefore the linear model was chosen as the base case.

Figure 16: Scatterplot of average acute medication days and MMD frequency

[redacted]

Abbreviations: MMD: monthly migraine day.

Figure 17: Scatterplot of average other medication days and MMD frequency

Abbreviations: MMD: monthly migraine day.

B21. The CS states that in the NHWS study, patients were grouped into categories based on MHDs or number of migraines, the latter grouping being used in the model, assuming number of migraines better approximates MMD.[46] However, Table 58 of the CS[46] presents NHWS by MMD and Table 96 of Appendix V[45] presents NHWS data by MHD.

a. Please clarify which grouping method was used.

The grouping was based on MHDs and not MMDs; this was a typographical error in Document B, Table 58 of the company submission.

b. Please provide a scenario analysis using the alternative assumption of MHD approximating MMD.

This question is not applicable, as the analyses are based on the assumption of MHDs approximating MMDs. There was a typographical error in the submission; in the NHWS survey respondents were separately grouped into categories based on number of headache days per month not the number of migraine days per month. Although headache days and migraine days are separate outcomes, it was assumed that resource utilisation per headache day frequency would provide a good approximation for resource utilisation per migraine day frequency.

Cost effectiveness results

B22. **Priority:** The NICE reference case requires that uncertainty be explored through appropriate sensitivity analyses. However, not all the parameters are examined for their impact on model outcomes.

a. All relevant parameters should be included in the probabilistic sensitivity analysis (PSA). However, influential parameters associated with treatment and relative effectiveness, such as response rates for erenumab, treatment effect compared with BSC, treatment discontinuation and frequency of MMDs for responders and non-responders, are currently excluded from the PSA. It is important to note that the distributions of frequency of MMDs only reflects first order uncertainty (heterogeneity) and not second order uncertainty, which needs to be incorporated in the PSA. Please provide a model enabling a PSA that incorporates all relevant parameters, including response rates, relative effectiveness compared with BSC, treatment discontinuation and MMD frequency.

The PSA has been updated in the model and a summary of the updates are provided below:

- Treatment discontinuation has been included in the PSA [Parameters Cell 32]
- The percentage of patients that do not return to treatment is already included in the PSA [Parameters Cell E31]
- Not all parameters feeding through the model can go through the parameters worksheet. Efficacy parameters are varied probabilistically through the ‘Stats Analysis’ Worksheets at the back end of the model. The variation can be seen when the model is made probabilistic [switch Cell E9 in Parameters worksheet to 1] and using the F9 key, note the response rates and MMD distributions changing on the ‘Settings and Summary Results’ worksheet. These feed directly from the Stats Summary worksheet at the rear of the model.

- The frequency of MMDs for responders and non-responders are also probabilistic: See Efficacy worksheets [Efficacy Cells H53:J81, Efficacy Cells P53:R81 and Efficacy Cells X53:Z81].

The incremental results from the probabilistic sensitivity analyses are presented below for the whole migraine base case population and are very similar to the results provided in the original submission. These analyses have been conducted using the ≥3 prior prophylactic treatment failure utility data as request in question B14c.

The incremental results from the probabilistic analysis for the whole migraine base case population are presented in Table 86 and Table 87 for the blended and 140 mg dose, respectively. Scatter plots of incremental costs and QALYs for erenumab (with PAS) versus BSC are presented in Figure 18 and Figure 20, and the cost-effectiveness acceptability curve for these analyses is shown in

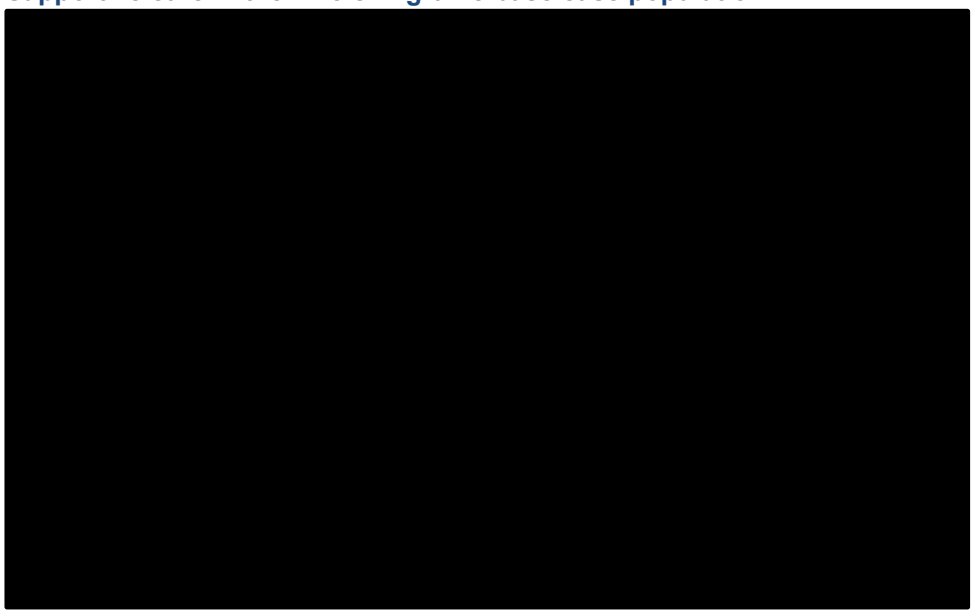
Figure 19 and Figure 21, respectively. When considering a cost-effectiveness threshold of £20,000 per QALY and the PAS price, erenumab has a probability of cost-effectiveness of 55% and 52% against BSC in the whole population base case, for the blended dose and 140 mg dose, respectively. When considering a cost-effectiveness threshold of £30,000 per QALY and the PAS price, erenumab has a probability of cost-effectiveness of 75% and 73% against BSC in the whole population base case, for the blended dose and 140 mg dose, respectively.

Table 86: Probabilistic results for the whole migraine base case population: blended dose of erenumab versus best supportive care[a]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,865

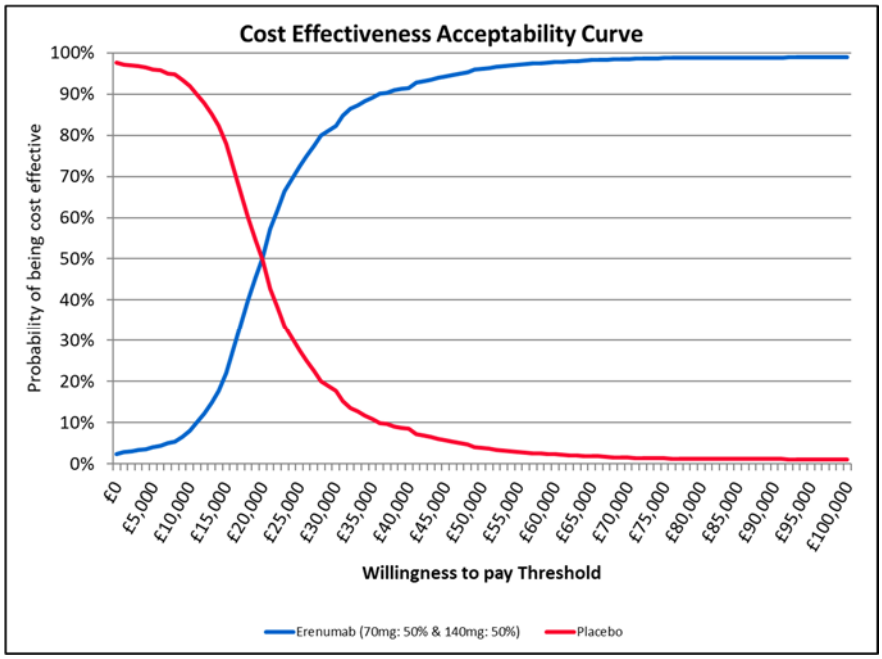
[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 18: Cost-effectiveness plane for blended dose[a] of erenumab (with PAS) versus best supportive care in the whole migraine base case population



[a]The "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 19: Cost-effectiveness acceptability curve for blended dosea of erenumab (with PAS) versus best supportive care in the whole migraine base case population



aThe "blended dose" refers to the assumption that 50% of patients initiate treatment on erenumab 70 mg and 50% of patients initiate on erenumab 140 mg

Abbreviations: BSC: best supportive care.

Table 87: Probabilistic results for the whole migraine base case population: erenumab 140 mg versus best supportive care

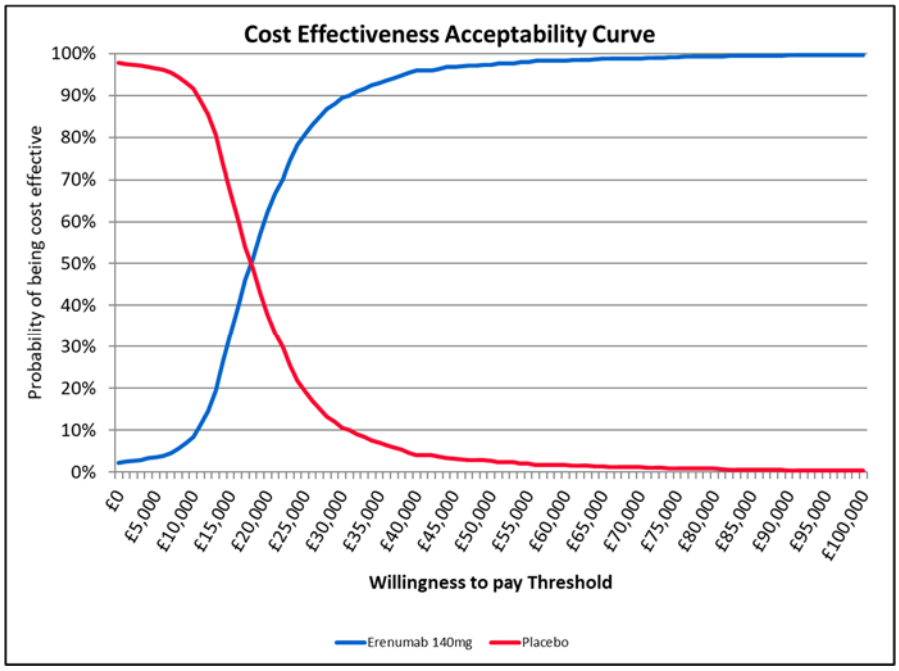
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 70mg/140 mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,038

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

Figure 20: Cost-effectiveness plane for erenumab 140 mg (with PAS) versus best supportive care in the whole migraine base case population

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 21: Cost-effectiveness acceptability curve for erenumab 140 mg (with PAS) versus best supportive care in the whole migraine base case population



Abbreviations: BSC: best supportive care.

b. Please also submit a model file providing fully incremental probabilistic analyses for all interventions (including erenumab 70mg and 140mg as separate interventions instead of using the blended dose) and comparators, such that the CEAC represents all treatments simultaneously. Please enable this for comparisons in all populations considered in the base-case (whole migraine population, chronic migraine population and episodic migraine population).

Please find enclosed an adapted model which enables fully incremental probabilistic analyses for all interventions in all populations. It should be noted that both doses remain cost-effective compared to BSC in the base case whole population.

Validation and transparency

B23. **Priority:** Please provide a cross-validation of the submitted cost effectiveness analysis compared with NICE TA260,[47] including a table overview that considers:

a. Model structure and major assumptions

b. Intervention and comparators

c. Response rates and other influential transition probabilities

d. HRQoL data used

e. Results

f. If applicable, possible explanations for different results compared with NICE TA260.

A cross-validation of the submitted cost-effectiveness analysis compared to NICE TA260 is provided in Table 88 below.

Table 88: Cross-validation of current appraisal and TA260

Factor	Previous appraisals	Current appraisal
	Botulinum toxin (TA260)[13]	**Chosen values**
Model structure	Markov model	Decision tree plus Markov model
Intervention	Botulinum toxin type A, used in combination with standard management	Erenumab 70 mg or 140 mg, used in combination with BSC
Comparators	Standard management without botulinum toxin type A excluding invasive procedures	BSC Botulinum toxin (in a small proportion of patients for whom ≥3 prior prophylactic treatments have failed and who are classified as having chronic migraine)
Definition of response	Response defined by a ≥30% reduction from baseline in MMDs. Response assessed at 24 weeks	Response defined by a ≥50% reduction from baseline in MMDs. Response assessed at 12 weeks
Response rates and other influential transition probabilities	≥30% responder rates were derived from the pooled PREEMPT trials. Responder rate data are redacted in the NICE documentation for this appraisal. Two separate transition probabilities were applied for Weeks 0–12 and Weeks 12–24. Clinical data from Weeks 12–24 were used to inform transition probabilities for the rest of the time horizon	Probability of response to erenumab and BSC derived from Study 295 in chronic migraine and the pooled STRIVE, ARISE and LIBERTY trials in episodic migraine. Probability of response for the comparison between erenumab and botulinum toxin derived from an ITC (see Document B, Section B.2.8). Chronic migraine • Erenumab 70 mg: [redacted]% • Erenumab 140 mg: [redacted]% • BSC: [redacted]% • Botulinum toxin: [redacted]% (when compared to erenumab 70 mg), [redacted]%

		(when compared to erenumab 140 mg) Episodic migraine • Erenumab 70 mg: [redacted]% • Erenumab 140 mg: [redacted]% • BSC: [redacted]%
HRQoL data used	Patient-level MSQ data from clinical trials (values ranged from 0.479 to 0.746)	Patient-level MSQ v.2.1 data from Study 295, STRIVE and ARISE mapped onto EQ-5D utility scores (values ranged from [redacted] to [redacted] in the full population)
Results	The ICER for botulinum toxin versus placebo was estimated to be £24,500 per QALY, after amending a mistake in the model originally submitted as part of the appraisal for botulinum toxin in chronic migraine. This revised model also assumed that both treatments had identical utility values for each health state.	These analyses have been conducted using the updated utility data requested in question Q14b. Erenumab is a cost-effective treatment in the whole migraine population base case versus BSC at a cost-effectiveness threshold of £30,000, with an ICER of £19,286 per QALY gained for the blended dose (i.e. 50% 70 mg and 50% 140 mg), and £17,037 per QALY gained for the 140 mg dose. The blended dose of erenumab is also a cost-effective treatment in the chronic migraine population versus botulinum toxin, with an ICER of £19,381 per QALY gained, and versus BSC, with an ICER of £18,707 per QALY gained. In the chronic migraine population erenumab 140 mg is cost-effective versus both botulinum toxin, with an ICER of £20,534, and versus BSC, with an ICER of £14,499 per QALY gained. Erenumab is a cost-effective treatment in the episodic migraine population versus BSC at a cost-effectiveness threshold of £30,000, with an ICER of £26,395 per QALY gained for the blended dose (i.e. 50% 70 mg and 50% 140 mg), and £29,991 per QALY gained for the 140 mg dose.

Abbreviations: BSC: best supportive care; EQ-5D: EuroQol-5 Dimensions; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; MHD: monthly headache day; MMD: monthly migraine day; MSQ: migraine specific quality of life questionnaire; QALY: quality-adjusted life year.

Source: Manufacturer submission of evidence: Botulinum toxin type A for the prophylaxis of headaches in adults with chronic migraine, 2011[48]

Appendix A – Updated economic SLR

Objective

An SLR was conducted in July 2017 to identify economic evidence to support the development of a cost-effectiveness model for erenumab for the prophylaxis of chronic or episodic migraine. A single SLR was conducted, and subsequently updated in January 2018 and September 2018, to identify all literature published since database inception on any of the following topics:

- Economic evaluations of pharmacological interventions for the treatment of chronic or episodic migraine
- Health state utility values for chronic or episodic migraine patients
- Cost and resource use data for chronic or episodic migraine patients

The SLR and updates were performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and Dissemination's "Guidance for Undertaking Reviews in Health Care".[49]

Search strategy

Electronic databases

The following electronic databases were searched:

- MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print; 1946 to present (original and both updates)
- Embase; 1974 to 2017 June 30 (original); 1974 to 2018 January 03 (first update); 1974 to 2018 September 04 (second update)
- The Cochrane Library, specifically the following:
  - Health Technology Assessment (HTA) Database; Issue 4 of 4, October 2016
  - NHS Economic Evaluation Database (NHS-EED); Issue 2 of 4, April 2015
- EconLit; 1886 to June 2017 (original); 1886 to January 2018 (first update); 1886 to September 2018 (second update)

MEDLINE and Embase were searched separately via the Ovid SP platform on 3rd July 2017 for the original SLR, 5th January 2018 for the first update and 5th September 2018 for the second update. The Cochrane Library databases were searched simultaneously via the Wiley Online platform on 3rd July 2017 for the original review and EconLit was searched via the EBSCO platform on 6th July 2017 for the original review, and 4th January 2018 for the first update and 5th September 2018 for the second update. The Cochrane Library databases were not searched again for the updates as these databases are no longer updated so no new results would have been found.

Manual congress searches

In addition to the electronic database searches, the conference proceedings of the following major migraine and neurological congresses were manually searched as part of the original review and the updates to identify any recent economic evidence which may not have been published as full-text journal articles at the time of the database search. Searches were

performed on congresses held over the prior three years (2015–2018) as any high-quality studies reported in abstract form before that time would have since been published as full-text articles.

- American Academy of Neurology (AAN) 2016, 2017 and 2018
- American Headache Society (AHS) 2016, 2017 and 2018
- Association of British Neurologists (ABN) 2016, 2017 and 2018
- European Academy of Neurology (EAN) 2016, 2017 and 2018
- European Association of Neurosurgical Societies (EANS) 2015, 2016 and 2017
- European Headache and Migraine Trust International Congress (EHMTIC) 2016 (not held in 2015 or 2017)
- European Headache Federation (EHF) 2015 (not held in 2016) and 2017
- International Headache Society (IHS) 2015 (not held in 2016 or 2018) and 2017
- World Congress of Neurology (WCN) 2015 (not held in 2016 or 2018) and 2017
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European and Annual International meetings (2015, 2016 and 2017 [European]; 2016 and 2017 [International]).

The search terms used in the congress searches and website searches are provided in Table 1.

Grey literature searching

The NICE, SMC, All Wales Medicines Strategy Group (AWMSG) and National Centre for Pharmacoeconomics (NCPE) websites were manually searched for previous, relevant HTA submissions and the following websites were also manually searched to ensure that no relevant publications were missed:

- The Cost-effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center (available at healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx)
- The University of Sheffield Health Utilities Database (ScHARRHUD; available at www.scharrhud.org/)
- The EuroQol-Five Dimensions (EQ-5D) Publications Database (available at www.euroqol.org/eq-5d-publications/search.html)
- EconPapers at Research Papers in Economics (RePEc) (www.econpapers.repec.org/)

The search terms used in the congress searches and website searches are provided in Table 1.

Reference list searching

Finally, the bibliographies of all relevant SLRs, meta-analyses, HTA submissions and economic evaluations identified through the electronic database, conference and HTA agency website searches were also manually searched to identify any additional studies of relevance.

The search terms used in the congress searches and website searches are provided in Table 1.

Database search terms

A list of search terms used in the MEDLINE, MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print electronic databases for both the original review and the updates is provided in Table 89. Search terms used in the Embase database for both the original review and the updates are presented in Table 90 while search terms used in the Cochrane Library databases for the original review are presented in Table 91. Search terms used in the EconLit search for both the original review and the updates are provided in Abbreviations: SLR: systematic literature review.

Table 92.

Table 89: Search terms for use in MEDLINE databases (searched via the Ovid SP platform)

Term group	#	Terms	# Hits (3rd July 2017)	# Hits (5th January 2018)	# Hits (5th September 2018)
Disease area: chronic or episodic migraine	1	exp migraine disorders/	25891	28087	25158
	2	migraine$.tw.	31090	34198	31187
	3	1 or 2	35723	39050	35661
Study design: economic evaluations and cost & resource use studies	4	Economics/	27123	27561	26950
	5	"costs and cost analysis"/	46187	48758	46370
	6	Cost allocation/	2023	2087	1987
	7	Cost-benefit analysis/	71995	79587	74004
	8	Cost control/	21381	21986	21238
	9	Cost savings/	10497	11169	10890
	10	Cost of illness/	22862	25375	23914
	11	Cost sharing/	2288	2406	2363
	12	"deductibles and coinsurance"/	1621	1661	1671
	13	Medical savings accounts/	522	525	524
	14	Health care costs/	34148	37741	35527
	15	Direct service costs/	1144	1226	1150
	16	Drug costs/	14417	15733	14806
	17	Employer health costs/	1093	1119	1088
	18	Hospital costs/	9661	10509	9970
	19	Health expenditures/	16800	18194	17813
	20	Capital expenditures/	2001	2009	1981
	21	Value of life/	5698	5879	5609
	22	exp economics, hospital/	22649	23876	23069
	23	exp economics, medical/	14201	14456	14043
	24	Economics, nursing/	3986	4020	3981
	25	Economics, pharmaceutical/	2777	3412	2798
	26	exp "fees and charges"/	29229	30249	29391
	27	exp budgets/	13282	13721	13358
	28	(low adj cost).mp.	40027	44731	45370
	29	(high adj cost).mp.	11296	12382	12236
	30	((healthcare or health care) adj cost$).mp.	49490	54668	52418

Term group	#	Terms	# Hits (3rd July 2017)	# Hits (5th January 2018)	# Hits (5th September 2018)
	31	(fiscal or funding or financial or finance).tw.	121759	132870	125277
	32	(cost adj estimate$).mp.	1908	2153	2005
	33	(cost adj variable).mp.	39	45	39
	34	(unit adj cost$).mp.	2103	2374	2228
	35	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	240381	265775	257193
	36	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or consequence$)).tw.	130220	144891	138549
	37	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	80439	89625	86654
	38	or/4-37	744205	810390	782161
Study design: utility studies	39	(health utilit$ or health state$ utilit$ or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based or utilities or disutilities).tw.	8017	9150	8485
	40	(preference$ adj2 elicit$).tw.	889	1018	962
	41	utility.ab. /freq=2	13712	15524	14699
	42	Quality adjusted life year/ or (QALY$ or quality adjusted life$ or quality adjusted survival$ or qald$ or qale$ or qtime$).tw.	15329	17761	16384
	43	(health$ year$ equivalent$ or hye$).tw.	878	946	901
	44	(eq-5d$ or eq5d$ or euroqol$ or euro qol$).tw.	7577	9165	8603
	45	(sf 6$ or sf6$ or short form 6$ or shortform 6$ or shortform6$ or sf six$ or sfsix$ or short form six$ or shortform six$ or shortformsix$).tw.	2723	3031	2864
	46	("HUI" or "HUI2" or "HUI3" or "15D").tw.	2713	3045	2870
	47	("standard gamble" or "SG" or "time trade off" or "time tradeoff" or "TTO").tw.	9730	11057	10355
	48	Visual analog$ scale$.tw.	42788	48079	46310
	49	HALex.tw.	30	34	29
	50	(quality of well being or quality of wellbeing or qwb).tw.	437	480	431
	51	Discrete choice experiment$.tw.	1001	1223	1190
	52	or/39-51	93143	105560	100647
Exclusion terms	53	Animals/ not humans/	4391739	4777642	4461110
	54	(comment or letter or editorial or "case reports" or "clinical trial, phase I").pt.	3302630	3563136	3369178
	55	(case stud$ or case report$).ti.	248724	269298	261371
	56	Letter/ or historical article/	1317859	1409022	1338722
	57	or/53-56	7994448	8653322	8137794

Term group	#	Terms	# Hits (3rd July 2017)	# Hits (5th January 2018)	# Hits (5th September 2018)
Total	58	38 or 52	818507	893995	862454
	59	3 and 58	1412	1590	1462
	60	59 not 57	1339	1510	1390

Table 90: Search terms for use in the Embase database (searched via the Ovid SP platform)

Term group	#	Terms	# Hits (3rd July 2017)	# Hits (5th January 2018)	# Hits (5th September 2018)
Disease area: chronic or episodic migraine	1	exp migraine/	53205	55221	55791
	2	Migraine$.tw.	43150	44930	45957
	3	1 or 2	58569	60814	61430
Study design: economic evaluations and cost & resource use studies	4	Socioeconomics/	127756	131566	127619
	5	Cost benefit analysis/	75006	77170	78384
	6	Cost effectiveness analysis/	125943	132019	134308
	7	Cost of illness/	16891	17393	17685
	8	Cost control/	59622	61522	62638
	9	Economic aspect/	109956	111305	107938
	10	Financial management/	109124	110658	108045
	11	Health care cost/	161898	168183	171104
	12	Health care financing/	12457	12698	12783
	13	Health economics/	35168	35714	31196
	14	Hospital cost/	17683	18503	18969
	15	(fiscal or funding or financial or finance).tw.	145107	153929	159763
	16	Cost minimization analysis/	3003	3136	3167
	17	(cost adj estimate$).mp.	2697	2861	2927
	18	(cost adj variable).mp.	53	54	55
	19	(unit adj cost$).mp.	3478	3736	3836
	20	Economics/	225733	228242	229461
	21	"costs and cost analysis"/	52190	53371	50158
	22	Cost allocation/	57249	58430	55416
	23	Cost savings/	52906	54806	55643
	24	Cost sharing/	57249	58430	55416
	25	"deductibles and coinsurance"/	57249	58430	55416
	26	Medical savings accounts/	57249	58430	55416
	27	Direct service costs/	161898	168183	171104
	28	Drug costs/	65789	67944	68633
	29	Employer health costs/	161898	168183	171104
	30	Health expenditures/	135840	142125	142326
	31	Capital expenditures/	161898	168183	171104
	32	Value of life/	123120	126930	121245
	33	exp economics, hospital/	737551	763201	762172

Term group	#	Terms	# Hits (3rd July 2017)	# Hits (5th January 2018)	# Hits (5th September 2018)
	34	exp economics, medical/	737551	763201	762172
	35	Economics, nursing/	33428	33974	29324
	36	Economics, pharmaceutical/	6512	6710	6788
	37	exp "fees and charges"/	38277	39102	37760
	38	exp budgets/	24167	25203	25699
	39	(low adj cost).mp.	43807	47028	48947
	40	(high adj cost).mp.	13609	14583	15306
	41	((healthcare or health care) adj cost$).mp.	171962	179409	183328
	42	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	303796	320521	326742
	43	*Health economics/ or exp *Economic evaluation/	64448	67664	67043
	44	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or consequence$)).tw.	169899	180010	185553
	45	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	105093	112278	117150
	46	or/4-45	1514630	1575594	1581787
Study design: utility studies	47	(health utilit$ or health state$ utilit$ or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based or utilities or disutilities).tw.	11893	12873	13260
	48	(preference$ adj2 elicit$).tw.	1115	1206	1254
	49	utility.ab. /freq=2	19832	21420	22347
	50	Quality adjusted life year/ or (QALY$ or quality adjusted life year$ or quality adjusted life expectanc$ or quality adjusted survival$ or qald$ or qale$ or qtime$).tw.	24725	26695	27548
	51	(health$ year$ equivalent$ or hye$).tw.	1324	1384	1347
	52	(eq-5d$ or eq5d$ or euroqol$ or euro qol$).tw.	13110	14689	15798
	53	(sf 6$ or sf6$ or short form 6$ or shortform 6$ or shortform6$ or sf six$ or sfsix$ or short form six$ or shortform six$ or shortformsix$).tw.	3376	3516	3623
	54	("HUI" or "HUI2" or "HUI3" or "15D").tw.	3833	4038	4152
	55	("standard gamble" or "SG" or "time trade off" or "time tradeoff" or "TTO").tw.	13382	14257	14976
	56	Visual analog$ scale$.tw.	58095	61934	65076
	57	HALex.tw.	45	45	46
	58	(quality of well being or quality of wellbeing or qwb).tw.	494	511	520
	59	Discrete choice experiment$.tw.	1407	1613	1732

Term group	#	Terms	# Hits (3rd July 2017)	# Hits (5th January 2018)	# Hits (5th September 2018)
	60	or/47-59	133186	142990	149455
Exclusion terms	61	Animals/ not humans/	1294861	1319875	907064
	62	(letter or editorial).pt.	1520787	1564936	1600935
	63	(case stud$ or case report$).ti.	305240	317514	314378
	64	Case study/ or letter/	983276	1009935	1032166
	65	("conference abstract" or "conference paper").pt.	3352706	3590384	3883168
	66	limit 65 to yr="1974-2014"	2622400	2626496	3336187
	67	or/61-64,66	5717462	5805932	6124355
Total	68	46 or 60	1615611	1683670	1695114
	69	3 and 68	4110	4305	4483
	70	69 not 67	3240	3428	3385

Table 91: Search terms used in The Cochrane Library databases for the original SLR (searched via the Wiley Online platform on 3rd July 2017)

Term group	#	Terms	# Hits
Disease area: chronic or episodic migraine	#1	[mh "migraine disorders"]	1918
	#2	Migraine*:ti,ab,kw	4100
Total	#3	#1 or #2 in Technology Assessments and Economic Evaluations	93

Abbreviations: SLR: systematic literature review.

Table 92: Search strategy used for EconLit (via EBSCO)

Term group	#	Search strings	# Hits (6th July 2017)	# Hits (4th January 2018)	# Hits (5th September 2018)
Disease area: chronic or episodic migraine	#1	migraine or migraines	35	35	34

Results from the database searches were downloaded into an Endnote® database and de-duplicated before being transferred into a bespoke Microsoft Excel®-based platform designed to enable record screening.

Study selection

To be included in the review, articles had to meet pre-defined eligibility criteria which are detailed in

Table 93 for the economic evaluations, Table 94 for the utilities studies and Table 95 for the cost/resource use studies, respectively. The same eligibility criteria were used for both the original review and the updates.

The citations found through the searches were first assessed against the eligibility criteria by two independent reviewers based on abstract and title. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Full-text copies of publications potentially meeting the eligibility criteria were then obtained and reviewed against the same eligibility criteria by two independent reviewers. In cases where the article did not give enough information to be sure it met the inclusion criteria at the full text screening stage, the article was excluded to ensure that only relevant articles were ultimately included in the review.

At both the title/abstract and full-text review stages, any disagreements between the reviewers were resolved by discussion until a consensus was met, with a third independent reviewer making the final decision if necessary. For studies meeting the eligibility criteria after the second (full-text) screening stage, data were extracted by a single reviewer into a pre-specified data extraction grid and verified by a second individual.

Table 93. Eligibility criteria for the SLR and updates (economic evaluations)

Domain	Inclusion criteria		Exclusion criteria
Population	Adult patients with chronic or episodic migraine		• Articles that do not include patients with chronic or episodic migraine • Articles reporting populations with ≥50% children *Studies with mixed populations (e.g. where some patients had migraine and some had non-migraine headaches, or where both adults and children were included) were initially considered for inclusion if all or most (≥50%) patients were relevant (i.e. had migraine and were adults), or if separate relevant results were reported for relevant patients.*
Interventions	Prophylactic pharmacological interventions listed below:		• Non-pharmacological interventions • Acute treatments (i.e. treatments providing symptomatic relief) • Herbal remedies, such as butterbur or feverfew • Specific prophylactic treatments listed below
	Class	**Include**	**Exclude**
	Alpha-blockers	-	• Clonidine
	Angiotensin-converting-enzyme inhibitors	• Lisinopril	• Captopril • Enalapril
	Angiotensin receptor blockers	• Candesartan	• Telmisartan
	Anticonvulsants	• Gabapentin • Topiramate • Valproate (also known as sodium valproate or	• Acetazolamide • Carbamazepine • Carisbamate

Domain	Inclusion criteria		Exclusion criteria
		divalproex)	• Clonazepam • Lamotrigine • Levetiracetam • Oxcarbazepine • Pregabalin • Vigabatrin
	Beta-blockers	• Atenolol • Bisoprolol • Metoprolol • Propranolol (LA or standard formulation) • Nadolol • Timolol • Any of these beta-blockers used in combination with amitriptyline	• Acebutolol • Alprenolol • Cyclandelate • Nebivolol • Oxprenolol • Pindolol
	Botox	• OnabotulinumtoxinA (also known as botulinum toxin [type] A or Botox)	-
	Calcium channel blockers	• Flunarizine • Verapamil	• Nicardipine • Nifedipine • Nimodipine
	CGRP inhibitors[a]	• Eptinezumab (ALD-403) • Fremanezumab (TEV-48125) • Galcanezumab (LY2951742)	-
	CGRP receptor inhibitors	• Erenumab (AMG 334)	• Telcagepant
	Leukotriene receptor antagonists	• Montelukast	-

Domain	Inclusion criteria		Exclusion criteria
	Selective serotonin reuptake inhibitors (SSRIs)	• Citalopram • Dapoxetine • Femoxetine • Escitalopram • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline • Trazodone • Zimelidine	-
	Serotonin norepinephrine reuptake inhibitors (SNRIs)	• Venlafaxine	• Desvenlafaxine • Duloxetine • Levomilnacipran • Milnacipran
	Serotonin agonists	• Methysergide • Pizotifen	-
	Tricyclic antidepressants	• Amitriptyline • Desipramine • Nortriptyline • Protriptyline	• Opipramol • Clomipramine
	Vitamins, minerals and co-enzymes	• Riboflavin • Co-enzyme Q10	• Magnesium
Comparators	Any comparator		N/A

Domain	Inclusion criteria	Exclusion criteria
Outcomes	Outcomes of relevant study designs, including: • Costs • Life years gained (LYG) • Quality-adjusted life years (QALYs) • Incremental costs and QALYs • Incremental cost-effectiveness ratios (ICERs)	Studies not reporting relevant outcomes
Study design	Original economic evaluations considering both the costs and benefits of alternative interventions. Specifically, the following types of analysis: • Cost-effectiveness • Cost-utility • Cost-benefit • Cost-minimisation • Cost-consequence In addition, SLRs of economic evaluations were included at the abstract review stage, then excluded following hand-searching of their reference lists at the full-text review stage.	• Publications without original data • Comments • Letters • Editorials • Non-systematic/narrative reviews
Other	• Economic evaluations from a UK or Irish perspective • English language only • Human subjects only	• Studies not conducted from a UK or Irish perspective • Articles not in the English language • Studies not in human subjects

Abbreviations: ICER: incremental cost-effectiveness ratio; LA: long-acting; LYG: life years gained; N/A: not applicable; QALY: quality-adjusted life year; SLR: systematic literature review; UK: United Kingdom.

Table 94. Eligibility criteria for the SLR and updates (utilities studies)

	Inclusion criteria	Exclusion criteria
Population	• Adult patients with chronic or episodic migraine	• Articles that did not include patients with chronic or episodic migraine

	Inclusion criteria	Exclusion criteria
		• Articles reporting populations with ≥50% children *Studies with mixed populations (e.g. where some patients had migraine and some had non-migraine headaches, or where both adults and children were included) were initially considered for inclusion if all or most (≥50%) patients were relevant (i.e. had migraine and were adults), or if separate relevant results were reported for relevant patients.*
Interventions	Any or no intervention	N/A
Comparators	Any or no comparator	N/A
Outcomes	Original health state utility data, for example those measured using: • EQ-5D • SF-6D • HUI3 • Time trade-off • Standard gamble	Studies not reporting relevant outcomes
Study design	• Primary research publications on any study design • HTAs, or SLRs of relevant primary publications were included at the abstract review stage, then excluded following hand-searching of their reference lists at the full-text review stage	• Publications without original data • Comments • Letters • Editorials • Non-systematic/narrative reviews
Other	• English language only • Human subjects only	• Articles not in the English language • Studies not in human subjects

Abbreviations: EQ-5D: EuroQol-5 Dimensions; HTA: Health Technology Assessment; HUI3: Health Utilities Index; N/A: not applicable; SF-6D: Short-Form Six-Dimension; SLR: systematic literature review.

Table 95. Eligibility criteria for the SLR and updates (cost/resource use studies)

Domain	Inclusion Criteria	Exclusion Criteria
Population	Adult patients with chronic or episodic migraine	• Articles that did not include patients with chronic or episodic migraine • Articles reporting populations with ≥50% children *Studies with mixed populations (e.g. where some patients had migraine and some had non-migraine headaches, or where both adults and children were included) were initially considered for inclusion if all or most (≥50%) patients were relevant (i.e. have migraine and are adults), or if separate relevant results were reported for relevant patients.*
Interventions	Any or no intervention	N/A
Comparators	Any or no comparator	N/A
Outcomes	Original costs or resource use data relevant to a cost-utility analysis from the perspective of the UK NHS and personal and social services (PSS) (or social work in Scotland) or the Health Service Executive in Ireland	Studies not reporting relevant outcomes
Study design	• Primary research publications on any study design • HTAs, or SLRs of relevant primary publications were included at the abstract review stage, then excluded following hand-searching of their reference lists at the full-text review stage	• Publications without original data • Comments • Letters • Editorials • Non-systematic/narrative reviews
Other	• Studies conducted in the UK or Ireland • English language only • Human subjects only	• Articles not in the English language • Studies not conducted in the UK or Ireland • Studies not in human subjects

Abbreviations: HTA: Health Technology Assessment; NHS: National Health Service; PSS: Personal and Social Services; SLR: systematic literature review; UK: United Kingdom.

Grey literature searches

The search terms used in the grey literature and HTA website searches are provided in

Table 96. The conference searches were conducted on 29th September 2017 for the original review, 11th January 2018 for the first update and 21st September 2018 for the second update. The searches of the CEA Registry, ScHARRHUD, EQ-5D Publications Database and RePEc websites were conducted on 29th September 2017, and the NICE, SMC, AWMSG and NCPE websites were searched on 10th October 2017 for the original review. All website searches were conducted on the 11th January 2018 for the first update and the 20th September for the second update.

Table 96: Search strategies used in congress searching

Conference	Link	Search strategy	Total unique hits (original review: 29th September 2017)	Relevant results	January 2018 update: Total unique hits (11th January 2018)	January 2018 update: Relevant results	September 2018 update: Total unique hits (21st September 2018)	September 2018 update: Relevant results
American Academy of Neurology (AAN) • 2016 • 2017 • 2018	2016: http://www.abstractsonline.com/pp8/#!/4046/sessions/@sessionCategory=Headache/1 2017: http://submissions.mirasmart.com/AAN2017/itinerary/login.asp 2018: https://submissions.mirasmart.com/AAN2018/itinerary/SearchHome.asp	2016: The 'Headache' session category was selected, then each session was expanded, the 'Full Session Details' was clicked before the following search term was searched for using the 'ctrl-f' function: - Migraine 2017: The 'browse' button was clicked, then the topic was set to 'Headache' and the 'search' button was clicked. The search term	2016: 72 2017: 9	2016: 0 2017: 0	N/A	N/A	2018: 88	2018: 0

		'migraine' was searched for using the 'ctrl-f' function for each session. 2018: The 'Headache' session category was selected, then each session was expanded, the 'Full Session Details' was clicked before the following search term was searched for using the 'ctrl-f' function: - Migraine						
American Headache Society (AHS) • 2016 • 2017 • 2018	Abstract books were in PDF form	2016, 2017 and 2018: The PDF was searched using the 'ctrl-f' function for the following terms: - cost - resource - utility - EQ-5D - EuroQol - quality of life - QoL	2016: 33 2017: 38	2016: 0 2017: 0	N/A	N/A	2018: 54	2018: 1
Association of British Neurologists (ABN) • 2016 • 2017	2016: http://jnnp.bmj.com/content/87/12#ABNAbstracts2016	2016: Using the 'ctrl-f' function, the abstract titles were screened for 'migraine' 2017: N/A	2016: 3 2017: N/A	2016: 0 2017: N/A	N/A	N/A	2018: 15	2018: 0

• 2018	2017: Abstract book not available 2018: Abstract book was in PDF form	2018: Using the ctrl-f function, the abstract titles were screened for 'migraine'						
European Academy of Neurology (EAN) • 2016 • 2017 • 2018	2016: Abstract book was in PDF form, posters were online, http://eanposters2016.conference2web.com/resourcegroups#~searches/migraine/filters/tag=* 2017: Abstract book was in PDF form 2018: Abstract book was in PDF form	2016: The PDF was searched using the 'ctrl-f' ' function for the following terms: - cost - resource - utility - EQ-5D - EuroQol - quality of life - QoL On the website, the term 'migraine' was entered into the search box 2017: The PDF was searched using the 'ctrl-f' function for the following terms: - cost - resource - utility - EQ-5D - EuroQol	2016: 200 (abstracts), 81 (posters) 2017: 108	2016: 2 2017: 1	N/A	N/A	2018: 172	2018: 0

		- quality of life - QoL 2018: The PDF was searched using the 'ctrl'f' function for the following terms: - cost - resource - utility - EQ-5D - EuroQol - quality of life - QoL						
European Association of Neurosurgical Societies (EANS) • 2015 • 2016 • 2017	Abstract books not available online	N/A	N/A	N/A	N/A	N/A	N/A	N/A
European Headache and Migraine Trust International Congress (EHMTIC) 2016 Migraine Trust International	Abstract books were in PDF form	2016: The PDF was searched using the 'ctrl-f' function for the following terms: - cost - resource - utility - EQ-5D - EuroQol	2016: 40	2016: 0	N/A	N/A	2018: 43	2018: 2

Symposium (MTIS) 2018		- quality of life - QoL 2018: The PDF was searched using the 'ctrl'f' function for the following terms: - cost - resource - utility - EQ-5D - EuroQol - quality of life - QoL						
European Headache Federation (EHF) • 2015 • 2017	Abstracts book not available online	N/A	N/A	N/A	N/A	N/A	N/A	N/A
International Headache Society (IHS) • 2015 • 2017	Abstract books were in PDF form	2015: The PDF was searched using the 'ctrl-f' function for the following terms: - cost - resource - utility - EQ-5D - EuroQol - quality of life - QoL	2015: 78	2015: 0	2017: 89	2017: 2	N/A	N/A

		2017: The PDF was searched using the 'ctrl'f' function for the following terms: - cost - resource - utility - EQ-5D - EuroQol - quality of life - QoL						
World Congress of Neurology (WCN) • 2015 • 2017	http://www.jns-journal.com/issue/S0022-510X(15)X0014-1	'Search within this issue' was selected and 'migraine' was entered into the search box. 'All content' was selected from the drop-down.	2015: 56	2015: 0	2017: 63	2017: 0	N/A	N/A
ISPOR Annual European meeting • 2015 • 2016 • 2017 • 2018	https://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	'Migraine' was selected from the disease/disorder drop-down and the relevant meeting was selected before clicking the 'Search' button	2015: 0 2016: 0	2015: 0 2016: 0	2017: 0	2017: 0	2018: 22	2018: 1
ISPOR Annual International meeting • 2016 • 2017	https://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	'Migraine' was selected from the disease/disorder drop-down and the relevant meeting was selected before clicking the 'Search' button	2016: 0 2017: 0	2016: 0 2017: 0	N/A	N/A	N/A	N/A

The University of Sheffield Health Utilities Database (ScHARRHUD)	www.scharrhud.org/	The 'search' tab was selected, 'migraine' was entered into the search box and 'Search' was clicked	2	0	2	0	0	0
The Cost-effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center	healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx	Using the 'basic search' function, 'Articles' was selected before 'migraine' was entered into the search box	12	0	12	0	12	0
The EQ-5D Publications Database	https://euroqol.org/search-for-eq-5d-publications/	'Migraine' was entered into the search box and 'search' was clicked	18	0	8	0	18	0
EconPapers at Research Papers in Economics (RePEc)	www.econpapers.repec.org/	Using the 'advanced search' function, 'migraine' was added to the search box and only 'journal articles' was selected before clicking the 'search!' button	20	0	40	0	2	0
NICE website	www.nice.org.uk	'Migraine' was entered into the search box and 'search' was clicked	48	2	24	0	0	0
SMC website	https://www.scottishmedicines.org.uk/	'Migraine' was entered into the search box and 'search' was clicked. Search results were confined to publications listed under ‘SMC Advice’	9	4	9	0	0	0

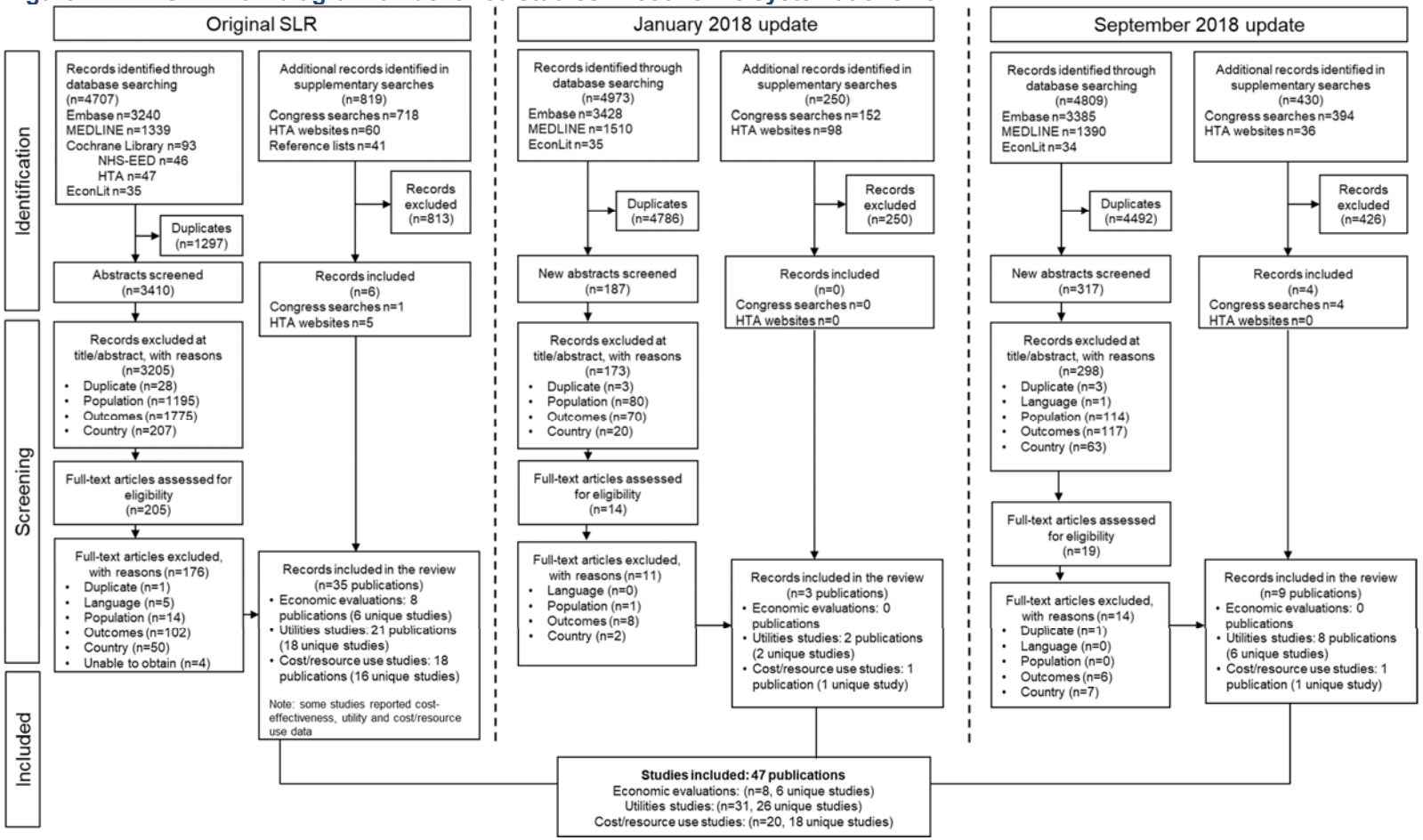
AWMSG website	http://www.awmsg.org/	'Migraine' was entered into the search box and 'search' was clicked. Search results were confined to publications listed under ‘Appraisals’ or ‘Appraisal documents’	3	0	3	0	3	0
NCPE website	http://www.ncpe.ie/	'Migraine' was entered into the search box and 'search' was clicked	0	0	0	0	1	0

Abbreviations: AWMSG: All Wales Medicines Strategy Group; EQ-5D, EuroQol 5-dimensions; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; N/A, not applicable; NCPE, National Centre for Pharmacoeconomics; NICE, National Institute for Health and Care Excellence; QoL, quality of life; SMC: Scottish Medicines Consortium.

Results

A total of 3,410 unique articles were identified in the original SLR from the electronic database searches and reviewed at the title/abstract review stage. In the January 2018 update, a further 187 unique articles were identified from the electronic database searches. In the September 2018 update, an additional 317 unique articles were identified from the electronic database searches. After title/abstract review in the original SLR, 205 articles were reviewed at the full-text stage with 29 articles ultimately meeting the inclusion criteria. In the first update, 14 articles were reviewed at the full-text stage with three articles meeting the inclusion criteria. In the second update, 19 articles were reviewed at the full-text stage with five articles meeting the inclusion criteria. An additional six articles to those captured through the database searches were identified through congress searching, website searching and through hand searching of bibliographies in the original review. No extra articles were identified through hand searches in the first update but four were identified in the second update. The flow of studies through the systematic review process is presented in Figure 22.

Figure 22: PRISMA flow diagram of identified studies in economic systematic review



Abbreviations: HTA: health technology assessment; NHS-EED: National Health Service Economic Evaluation Database; SLR: systematic literature review. A complete list of studies excluded after the full-text review stage for both the original review and the update is presented below in Table 97.

Table 97: List of excluded studies after the full-text review stage

Author	Year	Title	Journal	Volume	Issue	Pages	Reason for exclusion
-	1996	Meta-analysis and economic evaluation of sumatriptan for migraine (Structured abstract)	Health Technology Assessment Database	-	4	-	Study design
-	2006	Evaluation of new drugs for treatment of migraine (Project record)	Health Technology Assessment Database	-	4	-	Language
-	2006	Triptan overuse in migraine in primary care, a proactive approach (Project record)	Health Technology Assessment Database	-	4	-	Language
-	2008	Triptans as treatment for moderate to severe migraine attacks (Structured abstract)	Health Technology Assessment Database	-	4	-	Language
-	2012	Injection of botulinum toxin (Botox) for prophylaxis of headaches in adults with chronic migraine (Structured abstract)	Health Technology Assessment Database	-	4	-	Study design
Adams, A. M.;Serrano, D.;Buse, D. C.;Reed, M. L.;Marske, V.;Fanning, K. M. ;Lipton, R. B.	2015	The impact of chronic migraine: The Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results	Cephalalgia	35	7	563-78	Study design
Adelman, J. U.;Adelman, L. C. ;Von Seggern, R.	2002	Cost-effectiveness of antiepileptic drugs in migraine prophylaxis	Headache	42	10	978-983	Study design/non-UK perspective

Adelman, J. U. ;Adelman, R. D.	2001	Current options for the prevention and treatment of migraine	Clinical Therapeutics	23	6	772-788	Study design
Adelman, J. U.;Brod, A.;Von Seggern, R. L.;Mannix, L. K. ;Rapoport, A. M.	1998	Migraine preventive medications: a reappraisal	Cephalalgia	18	9	605-11	Study design/non-UK perspective
Adelman, L. C.;Adelman, J. U.;Freeman, M. C. ;Von Seggern, R. L.	2004	Pharmacoeconomics: the cost of prophylactic migraine treatments	Headache	44	10	1050-5	Study design/non-UK perspective
Ambrosio, E. M. M.;Bloor, K. ;MacPherson, H.	2012	Costs and consequences of acupuncture as a treatment for chronic pain: A systematic review of economic evaluations conducted alongside randomised controlled trials	Complementary Therapies in Medicine	20	5	364-374	Study design
Anand, K. S.;Sharma, S.	2007	Quality of life in migraine	Drug Development Research	68	7	403-411	Study design
Andlin-Sobocki, P.;Jonsson, B.;Wittchen, H. U. ;Olesen, J.	2005	Cost of disorders of the brain in Europe	European Journal of Neurology, Supplement	12	Suppl. 1	i-27	Study design
Andres, J. M. L.	1998	Migraine and quality of life. [Spanish]	Neurologia	13	Suppl. 2	01-Aug	Study design
Anonymous	1992	Special report. Controlling headache costs	Business & Health		-	Jun-30	Study design
Anonymous	1995	Potential for cost savings with prophylactic migraine therapy	Drugs and Therapy Perspectives	6	6	14-16	Study design
Anonymous	1996	Migraine indication for divalproex	P and T	21	6	30-Oct	Study design
Anonymous	1999	Investment in effective migraine therapy could reduce the overall costs of the disorder	Drugs and Therapy Perspectives	14	1	14-16	Study design

Anonymous	1999	Erratum: Changes in resource use and outcomes for patients with migraine treated with sumatriptan	Archives of Internal Medicine	159	-	2228	Study design
Anonymous	1999	The economics of migraine. Based on a presentation by Stuart O. Schweitzer, PhD	American Journal of Managed Care	5	Suppl 2	S91-8	Study design
Anonymous	2001	The real world cost of treating migraine	Economics of Neuroscience	3	3	23	Unable to acquire full text
Anonymous	2002	Acute migraine therapy: Triptan quantity limit maintains total health care savings 1 year out	Formulary	37	1	49+51	Study design/non-UK perspective
Anonymous	2003	Antiepileptics for migraine prophylaxis only cost-effective with frequent episodes	Expert Review of Pharmacoeconomics and Outcomes Research	3	1	05-Dec	Study design
Anonymous	2006	Topiramate: new indication. Migraine prevention: best avoided	Prescrire International	15	24-Mar	132-3	Study design
Anonymous	2010	Pharmacological prophylaxis of migraine reduces migraine frequency and may be cost effective	Drugs and Therapy Perspectives	26	3	24-26	Study design
Anonymous	2012	Modest benefit of botulinum toxin A for prophylaxis of migraines and headaches	Drug and Therapeutics Bulletin	50	7	75	Study design
Archibald, N;Lipscomb, J ;McCrory, Dc	1999	Resource utilization and costs of care for treatment of chronic headache (Structured abstract)	Health Technology Assessment Database	-	4	-	Study design

Asensio, M.;Sanchez, R. ;Montiel, I.	1996	[Quality of life and migraine]	Revista de Neurologia	24	132	926-9	Study design
Asseburg, C.;Peura, P.;Oksanen, T.;Turunen, J.;Purmonen, T. ;Martikainen, J.	2012	Cost-effectiveness of oral triptans for acute migraine: Mixed treatment comparison	International Journal of Technology Assessment in Health Care	28	4	382-389	Study design/non-UK perspective
Baker, A.;Sawyer, J.	1999	Impact of zolmitriptan on migraineur lifestyle - An observational study	Journal of Outcomes Research	3	01-Oct	01-Sep	Study design
Balbisi, E. A.	2002	Efficacy and safety of almotriptan malate for migraine	American Journal of Health-System Pharmacy	59	22	2184-2193	Study design/non-UK perspective
Becker, W. J.	2000	Are the triptans for migraine therapy worth the cost?	Canadian Journal of Neurological Sciences	27	2	111-115	Study design
Belsey, J.	2000	The clinical and financial impact of oral triptans in the management of migraine in the UK: A systematic review	Journal of Medical Economics	3	35-47	35-47	Study design
Belsey, J. D.	2002	The clinical and financial impact of oral triptans - An updated meta-analysis	Journal of Medical Economics	5	79-89	79-89	Study design
Belsey, J. D.	2004	Cost effectiveness of oral triptan therapy: A trans-national comparison based on a meta-analysis of randomised controlled trials	Current Medical Research and Opinion	20	5	659-669	Study design
Berg, J.	2004	Economic evidence in migraine and other headaches: A review	European Journal of Health Economics	5	SUPPL. 1	S43-S54	Study design
Berg, J.;Stovner, L. J.	2005	Cost of migraine and other headaches in Europe	European Journal of Neurology, Supplement	12	SUPPL. 1	59-62	Study design

Bhambri, R.;Mardekian, J.;Liu, L. Z.;Schweizer, E. ;Ramos, E.	2015	A review of the pharmacoeconomics of eletriptan for the acute treatment of migraine	International journal of general medicine	8	-	27-36	Study design
Biddle, A. K.;Shih, Y. C. T. ;Kwong, W. J.	2000	Cost-benefit analysis of sumatriptan tablets versus usual therapy for treatment of migraine	Pharmacotherapy	20	11 I	1356-1364	Study design/non-UK perspective
Blumenfeld, A.	2004	Botulinum toxin type A for the treatment of headache: Pro	Headache	44	8	825-830	Study design
Blumenfeld, A. M.;Varon, S. F.;Wilcox, T. K.;Buse, D. C.;Kawata, A. K.;Manack, A.;Goadsby, P. J. ;Lipton, R. B.	2011	Disability, HRQoL and resource use among chronic and episodic migraineurs: Results from the International Burden of Migraine Study (IBMS)	Cephalalgia	31	3	301-315	Study design/non-UK perspective
Brito, V;Pichon-Riviere, A;Augustovski, F;GarcÝa, MartÝ S;Alcaraz, A;Bardach, A;Ciapponi, A;Glujovsky, D;L¾pez, A ;Rey-Ares, L	2015	Subcutaneous histamine in migraine prevention (Structured abstract)	Health Technology Assessment Database	-	4	-	Language
Brixner, D. I.	2007	Prevalence and burden of migraine and the impact on managed care	Managed Care	16	7 Suppl 7	2-3; discussion 15-7	Study design
Brown, J. S.;Rupnow, M. F. T.;Neumann, P.;Friedman, M. ;Menzin, J.	2006	Cost effectiveness of topiramate in the prevention of migraines in the United States: An update	Managed Care Interface	19	12	31-38	Study design/non-UK perspective
Cadth	2014	OnabotulinumtoxinA (Botox - Allergan Inc.) indication: chronic migraine (Structured abstract)	Health Technology Assessment Database	-	4	-	Study design/non-UK perspective

Campinha-Bacote, D. L.;Kendle, J. B.;Jones, C.;Callicoat, D.;Webert, A.;Stoukides, C. A. ;Kaul, A. F.	2005	Impact of a migraine management program on improving health outcomes	Disease Management	8	6	382-91	Study design
Carmona, S.;Bruera, O.	2009	Prophylatic treatment of migraine and migraine clinical variants with topiramate: an update	Therapeutics & Clinical Risk Management	5	3	661-9	Study design/non-UK perspective
Caro, J. J.;Caro, G.;Getsios, D.;Raggio, G.;Burrows, M. ;Black, L.	2000	The migraine ACE model: evaluating the impact on time lost and medical resource use	Headache	40	4	282-91	Study design/non-UK perspective
Caro, J. J.;Getsios, D.	2002	Pharmacoeconomic evidence and considerations for triptan treatment of migraine	Expert Opinion on Pharmacotherapy	3	3	237-48	Study design
Caro, J. J.;Getsios, D.;Raggio, G.;Caro, G. ;Black, L.	2001	Treatment of migraine in Canada with naratriptan: a cost-effectiveness analysis	Headache	41	5	456-64	Study design/non-UK perspective
Cerbo, R.;Pesare, M.;Aurilia, C.;Rondelli, V. ;Barbanti, P.	2001	Socio-economic costs of migraine	Journal of Headache and Pain	2	Suppl. 1	S15-S19	Study design
Clarke, C. E.;MacMillan, L.;Sondhi, S. ;Wells, N. E. J.	1996	Economic and social impact of migraine	QJM - Monthly Journal of the Association of Physicians	89	1	77-84	Study design
Coeytaux, R. R. ;Befus, D.	2016	Role of acupuncture in the treatment or prevention of migraine, tension-type headache, or chronic headache disorders	Headache	56	7	1238-40	Study design
Cohen, J. A.;Beall, D.;Beck, A.;Rawlings, J.;Miller, D. W.;Clements,	1999	Sumatriptan treatment for migraine in a health maintenance organization:	Clinical Therapeutics	21	1	190-204	Study design/non-UK perspective

B.;Pait, D. G. ;Batenhorst, A.		economic, humanistic, and clinical outcomes					
Cohen, J. A.;Beall, D. G.;Miller, D. W.;Beck, A.;Pait, G. ;Clements, B. D.	1996	Subcutaneous sumatriptan for the treatment of migraine: humanistic, economic, and clinical consequences	Family Medicine	28	3	171-7	Study design/non-UK perspective
Coloprisco, G.;De Filippis, S.;Santi, P. G.;Fiore, G.;Rodio, A. ;Martelletti, P.	2003	Reduction in expenditures on analgesics during one year of treatment of chronic tension headache with BoNT-A	Journal of Headache and Pain	4	2	88-91	Population
Coukell, A. J. ;Lamb, H. M.	1997	Sumatriptan. A pharmacoeconomic review of its use in migraine	Pharmacoeconomics	11	5	473-90	Study design
Cowan, S.	1994	Sumatriptan in acute migraine therapy	Axone (Dartmouth, N.S.)	15	4	95-96	Study design/non-UK perspective
Cull, R.	2001	Almotriptan: a balanced approach to migraine	Hospital medicine (London, England: 1998)	62	2	96-100	Study design
Curtiss, F. R.	2005	Best value for money in triptans	Journal of managed care pharmacy: JMCP	11	5	419-421	Study design/non-UK perspective
Dahlof, C. G. H.	1995	Health-related quality of life under six months' treatment of migraine - An open clinic-based longitudinal study	Cephalalgia	15	5	414-422	Study design
Davey, Peter J.;Leeder, Stephen R.	1992	The Cost of Migraine: More Than Just a Headache?	PharmacoEconomics	2	1	5	Study design
Davis, J. A.;Robinson, R. L.;Le, T. K. ;Xie, J.	2011	Incidence and impact of pain conditions and comorbid illnesses	Journal of pain research	4	-	331-45	Study design/non-UK perspective

de Lissovoy, G. ;Lazarus, S. S.	1994	The economic cost of migraine. Present state of knowledge	Neurology	44	6 Suppl 4	S56-62	Study design
Deleu, D. ;Hanssens, Y.	1999	Guidelines for the prevention of migraine	Saudi Medical Journal	20	7	495-500	Study design
Desai, P.;Ahuja, A.;Pietri, G. ;Sapra, S.	2016	Systematic literature review of health state utility values in patients with migraine	European Journal of Neurology	23	-	180	Study design
Desai, P. R.;Ahuja, A.;Pietri, G. ;Sapra, S.	2015	Systematic Literature Review of Health State Utility Values In Patients With Migraine	Value in Health	18	7	A760	Study design
Dowson, A. J.;Fuat, A. ;Gruffydd-Jones, K.	2005	Clinical and economic issues associated with switching between triptans in clinical practice	Current Medical Research and Opinion	21	3	375-379	Study design
Ergun, H.;Gulmez, S. E. ;Tulunay, F. C.	2007	Cost-minimization analysis comparing topiramate with standard treatments in migraine prophylaxis	European Neurology	58	4	215-217	Study design/non-UK perspective
Essink-Bot, M. L.;Krabbe, P. F.;Bonsel, G. J. ;Aaronson, N. K.	1997	An empirical comparison of four generic health status measures. The Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts, and the EuroQol instrument	Medical care	35	5	522-537	Study design
Essink-Bot, M. L.;van Royen, L.;Krabbe, P.;Bonsel, G. J. ;Rutten, F. F.	1995	The impact of migraine on health status	Headache	35	4	200-6	Study design

Evans, K. W.	1997	Economic evaluation of oral sumatriptan compared with oral caffeine/ergotamine for migraine	PharmacoEconomics	12	5	565-577	Study design/non-UK perspective
Fabbrini, G.;Barbanti, P.;Pascali, M. P.;Lenzi, G. L. ;Cerbo, R.	1999	Impact of the International Headache Society criteria on the use of neuroimaging for headache diagnosis in a headache clinic	Headache	39	10	747-751	Study design/non-UK perspective
Ferrari, Michel D.	1998	The Economic Burden of Migraine to Society	PharmacoEconomics	13	6	667-676	Study design
Folino-Gallo, P.;Palazzo, F.;Stirparo, G.;De Filippis, S. ;Martelletti, P.	2003	Price differentials of oral triptans in eight European Union countries	Journal of Headache and Pain	4	SUPPL. 1	S67-S69	Study design
Fontebasso, M.	2007	Topiramate for migraine prophylaxis	Expert Opinion on Pharmacotherapy	8	16	2811-23	Study design
Ford, J. H.;Jackson, J.;Nyhuis, A.;Cotton, S. ;Ahl, J.	2016	Migraine patients with cluster headache: Exploratory study of the burden of illness	Headache	56	-	83	Population
Freitag, F. G.	2007	The cycle of migraine: Patients' quality of life during and between migraine attacks	Clinical Therapeutics	29	5	939-949	Study design
Friedman, D.;Feldon, S.;Holloway, R. ;Fisher, S.	2009	Utilization, diagnosis, treatment and cost of migraine treatment in the emergency department	Headache	49	8	1163-73	Study design/non-UK perspective
Goldberg, L. D.	2005	The cost of migraine and its treatment	American Journal of Managed Care	11	SUPPL. 2	S62-S67	Study design/non-UK perspective
Goldfarb, N.;Weston, C.;Hartmann, C.	2004	Impact of appropriate pharmaceutical therapy	Disease Management	7	1	61-75	Study design

W.;Sikirica, M.;Crawford, A.;He, H.;Howell, J.;Maio, V.;Clarke, J.;Nuthulaganti, B. ;Cobb, N.		for chronic conditions on direct medical costs and workplace productivity: a review of the literature					
Gross, M. L. P.;Dowson, A. J.;Deavy, L. ;Duthie, T.	1996	Impact of oral sumatriptan 50 mg on work productivity and quality of life in migraineurs	British Journal of Medical Economics	10	3	231-246	Study design
Guidotti, M. ;Ravasio, R.	2009	Clinical and economic comparison of frovatriptan versus other oral triptans in the treatment of acute migraine in the real-world setting	Clinical Drug Investigation	29	11	693-702	Study design
Gustavsson, A.;Svensson, M.;Jacobi, F.;Allgulander, C.;Alonso, J.;Beghi, E.;Dodel, R.;Ekman, M.;Faravelli, C.;Fratiglioni, L.;Gannon, B.;Jones, D. H.;Jennum, P.;Jordanova, A.;Jonsson, L.;Karampampa, K.;Knapp, M.;Kobelt, G.;Kurth, T.;Lieb, R.;Linde, M.;Ljungcrantz, C.;Maercker, A.;Melin, B.;Moscarelli, M.;Musayev, A.;Norwood, F.;Preisig, M.;Pugliatti, M.;Rehm, J.;Salvador-Carulla, L.;Schlehofer, B.;Simon, R.;Steinhausen, H. C.;Stovner, L. J.;Vallat, J. M.;den Bergh, P. V.;van Os, J.;Vos, P.;Xu,	2011	Cost of disorders of the brain in Europe 2010	European Neuropsychopharmacology	21	10	718-779	Study design

W.;Wittchen, H. U.;Jonsson, B. ;Olesen, J.							
Halpern, M. T.;Lipton, R. B.;Cady, R. K.;Kwong, W. J.;Marlo, K. O. ;Batenhorst, A. S.	2002	Costs and outcomes of early versus delayed migraine treatment with sumatriptan	Headache	42	10	984-999	Study design/non-UK perspective
Harrison, D. L.;Coons, S. J.;Jones, W. N. ;Labadie, E. L.	1996	The economic impact of a protocol for the management of migraine headaches	Journal of Research in Pharmaceutical Economics	7	3	35-48	Study design/non-UK perspective
Hayes, Inc	2010	Botulinum toxin for primary headache (Structured abstract)	Health Technology Assessment	-	4	-	Unable to acquire full text
Hayes, Inc	2011	Botulinum toxin for migraine headache (Structured abstract)	Health Technology Assessment	-	4	-	Unable to acquire full text
Hens, M.;Villaverde-Hueso, A.;Alonso, V.;Abaitua, I. ;De La Paz, M. P.	2014	Comparative cost-effectiveness analysis of oral triptan therapy for migraine in four European countries	European Journal of Health Economics	15	4	433-437	Study design
Herman, P. M.;Craig, B. M. ;Caspi, O.	2005	Is complementary and alternative medicine (CAM) cost-effective? A systematic review	BMC Complementary & Alternative Medicine	5	-	11	Study design
Ilerisch, L	1997	An economic analysis of sumatriptan for acute migraine (Structured abstract)	Health Technology Assessment Database	-	4	13	Study design/non-UK perspective
Joish, V. N.;Armstrong, E. P.	2000	Use of decision analysis in modeling the cost-effectiveness of oral vs SC sumatriptan	Formulary	35	6	532-539	Study design/non-UK perspective

Joish, V. N. ;Cady, P. S.	2001	Effect of sumatriptan on health care resource use among patients with migraine	Managed care interface	14	1	68-72	Study design/non-UK perspective
Kelley, K.;Schoenbrunner, A. ;Murphy, J.	2016	Cost-effectiveness of initial prophylactic treatment of chronic migraine: Oral medications versus onabotulinumtoxina	Neurology. Conference: 68th American Academy of Neurology Annual Meeting, AAN	86	16, Suppl. 1		Study design/non-UK perspective
Kim, M;Danielsson, A;Ekelund, A-C;Kemppainen, E;Sj÷gren, P;Svanberg, T;Szalo, G ;Samuelsson, O	2014	Botulinum toxin type A for prophylactic treatment of chronic migraine (Structured abstract)	Health Technology Assessment Database	-	4	-	Study design
Kollewe, K.;Oberling, M.;Kiszka, M.;Gunther, O.;Antonakakis, A. ;Brown, S.	2016	Healthcare resource utilisation with onabotulinumtoxina for the symptomatic treatment of chronic migraine: Repose study 12-month interim analysis	Cephalalgia	36	-	26	Study design/non-UK perspective
Lainez, M. J. A.	2009	The effect of migraine prophylaxis on migraine-related resource use and productivity	CNS Drugs	23	9	727-738	Study design
Laloux, P;Vakaet, A;Monseu, G;Jacquy, J;Bourgeois, P ;Linden, C	1998	Subcutaneous sumatriptan compared with usual acute treatments for migraine: clinical and pharmacoeconomic evaluation (Structured abstract)	Acta Neurologica Belgica	98	4	332-341	Study design/non-UK perspective

Lanteri-Minet, M.	2014	Economic burden and costs of chronic migraine	Current Pain and Headache Reports	18 (1) (no pagination)	385	-	Study design
Lanteri-Minet, M.;Duru, G.;Mudge, M. ;Cottrell, S.	2011	Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review	Cephalalgia	31	7	837-50	Study design
Legg, R. F.;Sclar, D. A.;Nemec, N. L.;Tarnai, J. ;Mackowiak, J. I.	1997	Cost-effectiveness of sumatriptan in a managed care population	The American journal of managed care	3	1	117-122	Study design/non-UK perspective
Linde, M.;Gustavsson, A.;Stovner, L. J.;Steiner, T. J.;Barre, J.;Katsarava, Z.;Lainez, J. M.;Lampl, C.;Lanteri-Minet, M.;Rastenyte, D.;Ruiz de la Torre, E.;Tassorelli, C. ;Andree, C.	2012	The cost of headache disorders in Europe: the Eurolight project	European Journal of Neurology	19	5	703-11	Study design/non-UK perspective
Linde, M.;Steiner, T. J. ;Chisholm, D.	2015	Cost-effectiveness analysis of interventions for migraine in four low- and middle-income countries	Journal of Headache and Pain	16	1		Study design/non-UK perspective
Linde, M.;Steiner, T. J. ;Chisholm, D.	2015	Cost-effectiveness analysis of interventions for migraine in four low- and middle-income countries	Cephalalgia	1)		145	Study design/non-UK perspective
Litaker, D G;Solomon, G D ;Genzen, J R	1996	Impact of sumatriptan on clinic utilization and costs of care in migraineurs (Structured abstract)	Headache	36	9	538-541	Study design/non-UK perspective

Maasumi, K.;Thompson, N. R.;Kriegler, J. S. ;Tepper, S. J.	2015	Effect of onabotulinumtoxinA injection on depression in chronic migraine	Headache	55	9	1218-1224	Study design
MacPherson, H.;Vickers, A.;Bland, M.;Torgerson, D.;Corbett, M.;Spackman, E.;Saramago, P.;Woods, B.;Weatherly, H.;Sculpher, M.;Manca, A.;Richmond, S.;Hopton, A.;Eldred, J. ;Watt, I.	2017	Acupuncture for chronic pain and depression in primary care	NIHR Journals Library	-	-	-	Study design
Maertens de Noordhout, C.;Devleesschauwer, B.;Gielens, L.;Plasmans, M. H. D.;Haagsma, J. A. ;Speybroeck, N.	2017	Mapping EQ-5D utilities to GBD 2010 and GBD 2013 disability weights: results of two pilot studies in Belgium	Archives of Public Health	75	-	6	Population
Maliwa, M. A.;van der Heijden, G. J.;Bots, M. L.;van Hout, B. A.;Casselman, F. P.;van Swieten, H. ;Vermeulen, F. E.	2003	Quality of life and NYHA class 30 years after mechanical aortic valve replacement	Cardiovascular Surgery	11	5	381-7	Population
Mannix, L. K.	2002	Effect of triptans on the quality of life of patients with migraine	Headache Quarterly	13	3	Nov-21	Study design
Martelletti, P.	2002	Pharmacoeconomics of migraine	Journal of Headache and Pain	3	1	54	Study design
Mayo, K. W.;Osterhaus, J. T.	2002	Health outcomes evaluations: estimating the impact of almotriptan in managed care settings	American Journal of Managed Care	8	3 Suppl	S85-93	Study design/non-UK perspective
McCormack, P. L.;Foster, R. H.	2005	Rizatriptan: a pharmacoeconomic review of its use in the	Pharmacoeconomics	23	12	1283-98	Study design

		acute treatment of migraine					
McHugh, J. C.;Sobocki, P. ;Murphy, R. P.	2007	Cost of disorders of the Brain in Ireland	Irish Medical Journal	100	7	-	Study design
Membe, S;McGahan, L;Cimon, K;Gawel, M;Giammarco, R ;Mierzwinski-Urban, M	2007	Triptans for acute migraine: comparative clinical effectiveness and cost-effectiveness (Structured abstract)	Health Technology Assessment Database	-	4	47	Study design
Mennini, F. S.;Gitto, L. ;Martelletti, P.	2008	Improving care through health economics analyses: Cost of illness and headache	Journal of Headache and Pain	9	4	199-206	Study design
Millier, A.;Cohen, J. ;Toumi, M.	2013	Economic impact of a triptan Rx-to-OTC switch in six EU countries	PLoS ONE	8 (12) (no pagination)	e84088	-	Study design
Moja, L.;Cusi, C.;Sterzi, R. ;Canepari, C.	2009	Selective Serotonin Re-uptake Inhibitors (SSRIs) for preventing migraine and tension-type headaches	Cochrane Database of Systematic Reviews	(4) (no pagination)	CD002919	-	Study design
Moja, P. L.;Cusi, C.;Sterzi, R. R. ;Canepari, C.	2005	Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches	Cochrane Database of Systematic Reviews	-	3	CD002919	Study design
Mutebi, A.;Pike, J.;Shah, N.;Jackson, J.;Cotton, S.;Desai, P. ;Sapra, S.	2016	Unmet need in migraine prophylaxis treatment in the United States of America: Data from clinical practice	Headache	56	-	70	Study design
Mutebi, A.;Pike, J.;Shah, N.;Jackson, J.;Cotton, S.;Desai, P. R. ;Sapra, S.	2016	The use of migraine prophylaxis treatment: Analysis of clinical practice data from The	Value in Health	19 (3)	-	A68	Study design

		United States, Germany, France, and Japan					
Olesen, J.;Lekander, I.;Andlin-Sobocki, P. ;Jonsson, B.	2007	Funding of headache research in Europe	Cephalalgia	27	9	995-999	Study design
Oliver, A.;Wolff, J.	2014	Are people consistent when trading time for health?	Economics and Human Biology	15	-	41-46	Population
Payne, K. A.;Varon, S. F.;Kawata, A. K.;Yeomans, K.;Wilcox, T. K.;Manack, A.;Buse, D. C.;Lipton, R. B.;Goadsby, P. J. ;Blumenfeld, A. M.	2011	The International Burden of Migraine Study (IBMS): Study design, methodology, and baseline cohort characteristics	Cephalalgia	31	10	1116-1130	Study design
Peng, K. P. ;Wang, S. J.	2012	Migraine diagnosis: screening items, instruments, and scales	Acta Anaesthesiologica Taiwanica: Official Journal of the Taiwan Society of Anesthesiologists	50	2	69-73	Study design
Phillips, C. J.	2003	Health economic and quality of life considerations in the management of pain. [French]	Drugs	63	SPEC. ISS. 2	47-50	Study design
Phillips, C. J.	2006	Economic burden of chronic pain	Expert Review of Pharmacoeconomics and Outcomes Research	6	5	591-601	Study design
Pike, J.;Mutebi, A.;Shah, N.;Jackson, J.;Cotton, S.;Desai, P. R. ;Sapra, S.	2016	Factors associated with a history of failure and switching migraine prophylaxis treatment: An analysis of clinical practice data from the United States, Germany, France, and Japan	Value in Health	19 (3)	-	A68	Study design

Ramsberg, J. ;Henriksson, M.	2007	The cost-effectiveness of oral triptan therapy in Sweden	Cephalalgia	27	1	54-62	Study design/non-UK perspective
Rapoport, A. M. ;Adelman, J. U.	1998	Cost of migraine management: A pharmacoeconomic overview	American Journal of Managed Care	4	4	531-545	Study design
Reason, T.;Dias, S. ;Welton, N.	2014	Dose-Response Network Meta-Analysis To Address Dose Heterogeneity In A Cost-Effectiveness Analysis In Acute Migraine	Value in Health	17	7	A563	Study design
Reeder, C. E.;Steadman, S. ;Goldfarb, S. D.	2002	Economic comparison of oral triptans for management of acute migraine: implications for managed care	American Journal of Managed Care	8	3 Suppl	S80-4	Study design
Remenschneider, A. K.;Scangas, G.;Meier, J. C.;Gray, S. T.;Holbrook, E. H.;Gliklich, R. E. ;Metson, R.	2015	EQ-5D-derived health utility values in patients undergoing surgery for chronic rhinosinusitis	Laryngoscope	125	5	1056-1061	Population
Rencz, F.;Brodszky, V.;Pentek, M.;Bereczki, D. ;Gulacsi, L.	2014	Health-Related Quality of Life in Migraine Without Aura Based on Attack Frequency: A time Trade-Off Study	Value in Health	17	7	A401	Population
Rencz, F.;Brodszky, V.;Pentek, M.;Bereczki, D. ;Gulacsi, L.	2015	Health state utilities for migraine based on attack frequency: a time trade-off study	Neurological Sciences	36	2	197-202	Population
Ridsdale, L.;Osumili, B. ;McCrone, P.	2015	Cost-effectiveness of self-management education versus usual care for patients with migraine	Cephalalgia	1)	-	273	Study design

		headache: A pilot randomized controlled trial					
Ridsdale, L.;Osumili, B. ;McCrone, P.	2015	Cost-effectiveness of self-management education versus usual care for patients with migraine headache: A pilot randomized controlled trial	European Journal of Neurology	22	-	285	Study design
Rodriguez-Leyva, I.;Sanchez Aguilar, M. C. J. M.;Hernandez-Sierra, J. F.;Mandeville, P. B.;Rodriguez Leyva, M. D. R.;Shiguetomi-Medina, J. M. ;Tapia-Perez, J. H.	2010	Topiramate vs. Amitriptyline in prophylactic treatment of migraine: A controlled clinical trial	Revista Mexicana de Neurociencia	11	5	338-342	Study design
Rossi, P.;Faroni, J.;Tassorelli, C. ;Nappi, G.	2009	Diagnostic delay and suboptimal management in a referral population with hemicrania continua	Headache	49	2	227-234	Population
Ruggeri, M.	2014	The cost effectiveness of Botox in Italian patients with chronic migraine	Neurological Sciences	35	1	45-47	Study design/non-UK perspective
Ruggeri, M.;Carletto, A. ;Marchetti, M.	2013	Cost-effectiveness of onabotulinumtoxinA for the prophylaxis of chronic migraine. [Italian, English]	PharmacoEconomics - Italian Research Articles	15	1	19-33	Language
Sachin, S.;Padma, M. V.;Bhatia, R.;Prasad, K.;Gureshkumar, C. ;Tripathi, M.	2008	Psychosocial impact of epilepsy in women of childbearing age in India	Epileptic Disorders	10	4	282-9	Study design
Savani, N.;Martin, A. ;Browning, D.	2004	Switching patients with migraine from sumatriptan to other triptans increases primary care costs	International Journal of Clinical Practice	58	8	758-63	Study design
Scharff, L. ;Etherage, J.	2000	The role of minimal- and no-contact behavioural	Disease Management and Health Outcomes	8	6	313-325	Study design

		treatments in migraine: A review of efficacy and cost effectiveness					
Sculpher, M.;Millson, D.;Meddis, D. ;Poole, L.	2002	Cost-effectiveness analysis of stratified versus stepped care strategies for acute treatment of migraine: The Disability in Strategies for Care (DISC) study	PharmacoEconomics	20	2	91-100	Study design
Shah, N.;Pike, J.;Mutebi, A.;Jackson, J.;Cotton, S.;Desai, P. ;Sapra, S.	2016	The use of migraine prophylaxis treatments in the United States of America: Analysis of data from clinical practice	Headache	56	-	69-70	Study design
Shamliyan, Ta;Kane, Rl ;Taylor, Fr	2013	Migraine in adults: preventive pharmacologic treatments (Structured abstract)	Health Technology Assessment Database	-	4	-	Study design
Silberstein, S. D	2000	Epidemiology and the economic impact of migraine	Drug Benefit Trends	12	Suppl. D	4-6	Unable to acquire full text
Silva Junior, A. A.;Bigal, M.;Vasconcelos, L. P.;Rodrigues, J.;Gomez, R. S.;Krymchantowski, A. V.;Moreira Filho, P. ;Teixeira, A. L.	2012	Prevalence and burden of headaches as assessed by the health family program.[Erratum appears in Headache. 2012 May;52(5):861]	Headache	52	3	483-90	Study design
Slof, J.	2012	Cost-effectiveness analysis of early versus non-early intervention in acute migraine based on evidence from the 'Act when mild' study	Applied Health Economics and Health Policy	10	3	201-215	Population

Slof, J;Badia, X;Magaz, S;Lainez, M J;Galvan, J ;Heras, J	2005	Cost-efficacy of oral triptans in the treatment of acute migraine (Structured abstract)	Journal of Medical Economics	8	2	27-43	Study design/non-UK perspective
Slof, J.;Lainez, J. M.;Comas, A. ;Heras, J.	2009	Almotriptan vs. ergotamine plus caffeine for acute migraine treatment. A cost-efficacy analysis. [Spanish]	Neurologia	24	3	147-153	Study design/non-UK perspective
Smith, D. G.	2003	Cost-effectiveness of migraine treatment: A commentary	Value in Health	6	4	436-437	Study design
Smolen, L. J.;Klein, T. M. ;Kelton, K.	2015	Replication of a published markov chronic migraine cost-effectiveness analysis model for purposes of early phase adaptation and expansion	Value in Health	18 (3)	-	A19	Study design
Solomon, G. D.	2009	Reducing the cost of headache medication	Current Pain & Headache Reports	13	3	227-30	Study design
Stalmeier, P. F.;Verheijen, A. L.	2013	Maximal endurable time states and the standard gamble: more preference reversals	European Journal of Health Economics	14	6	971-7	Population
Stalmeier, P. F. M.;Chapman, G. B.;De Boer, A. G. E. M. ;Van Lanschot, J. J. B.	2001	A fallacy of the multiplicative QALY model for low-quality weights in students and patients judging hypothetical health states	International Journal of Technology Assessment in Health Care	17	4	488-496	Population
Steiner, T. J.	2000	Headache burdens and bearers	Functional Neurology	15 Suppl 3	-	219-23	Study design
Tai, M. L.;Norhatta, N.;Goh, K. J.;Moy, F. M.;Sujarita, R.;Asraff, A. A.;Lee, Q. Z.;Ng, J.	2015	The impact of dyspepsia on symptom severity and quality of life in adults with headache	PLoS ONE [Electronic Resource]	10	1	e0115838	Population

H.;Tan, E. C. ;Mahadeva, S.							
Takiya, L.;Piccininni, L. C. ;Kamath, V.	2006	Safety and efficacy of eletriptan in the treatment of acute migraine	Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy	26	1	115-28	Population
Tepper, S. J.	2006	Goldberg LD. The cost of migraine and its treatment: Commentary	Headache	46	3	535-536	Study design
Tfelt-Hansen, P.;Steiner, T. J.	2007	Over-the-counter triptans for migraine: What are the implications?	CNS Drugs	21	11	877-883	Population
Thompson, M.;Gawel, M.;Desjardins, B.;Ferko, N. ;Grima, D.	2005	An economic evaluation of rizatriptan in the treatment of migraine	PharmacoEconomics	23	8	837-850	Study design/non-UK perspective
Toth, C.;Lander, J. ;Wiebe, S.	2009	The prevalence and impact of chronic pain with neuropathic pain symptoms in the general population	Pain Medicine	10	5	918-929	Study design
Trakas, K.;Oh, P. I.;Singh, S.;Risebrough, N. ;Shear, N. H.	2001	The health status of obese individuals in Canada	International Journal of Obesity	25	5	662-668	Population
Turner, I. M.;Newman, S. M.;Entin, E. J. ;Agrillo, T.	2007	Prophylactic treatment of migraine with botulinum toxin type A: A pharmacoeconomic analysis in a community setting	Journal of Medical Economics	10	4	355-366	Study design
Upreti, A. R.	2015	Cost effectiveness analysis of most commonly prescribed drugs in migraine	Value in Health	18 (3)	-	A283	Study design/non-UK perspective
Walbert, T.;Reese, J. P. ;Dodel, R.	2007	Cost-of-illness in neurological diseases in Germany. [German]	Nervenheilkunde	26	4	260-268	Study design

Weber, W.	2000	Neurologists determine the effect of migraine on quality of life	Lancet	356	9234	1007	Study design
Weitzel, K. W.;Levin, G. M.	2005	The economic and psychosocial impact of migraine before and after diagnosis and treatment	Journal of Pharmacy Technology	21	3	129-136	Study design/non-UK perspective
Wells, N.;Hettiarachchi, J.;Drummond, M.;Carter, D.;Parpia, T. ;Pang, F.	2003	A cost-effectiveness analysis of eletriptan 40 and 80 mg versus sumatriptan 50 and 100 mg in the acute treatment of migraine	Value in Health	6	4	438-447	Study design
Williams, P.;Dowson, A. J.;Rapoport, A. M. ;Sawyer, J.	2001	The cost effectiveness of stratified care in the management of migraine	PharmacoEconomics	19	8	819-829	Study design
Witt, C. M.;Reinhold, T.;Jena, S.;Brinkhaus, B. ;Willich, S. N.	2008	Cost-effectiveness of acupuncture treatment in patients with headache	Cephalalgia	28	4	334-45	Study design/non-UK perspective
Yu, J.;Smith, K. J. ;Brixner, D. I.	2010	Cost effectiveness of pharmacotherapy for the prevention of migraine: A markov model application	CNS Drugs	24	8	695-712	Study design/non-UK perspective
Zhang, L.;Hay, J. W.	2005	Cost-effectiveness analysis of rizatriptan and sumatriptan versus Cafergot in the acute treatment of migraine	CNS Drugs	19	7	635-642	Study design/non-UK perspective
Full Texts Excluded After Full-Text Review in January 2018 Update							
Davies, B.;Gaul, C.;Martelletti, P.;Garcia-Monco, J. C. ;Brown, S.	2017	Real-life use of onabotulinumtoxinA for symptom relief in patients with chronic migraine: REPOSE study	Journal of Headache & Pain	18	1	93	Study design/non-UK perspective

		methodology and baseline data					
Guerzoni, S.;Pellesi, L.;Baraldi, C.;Cainazzo, M. M.;Negro, A.;Martelletti, P. ;Pini, L. A.	2017	Long-term treatment benefits and prolonged efficacy of OnabotulinumtoxinA in patients affected by chronic migraine and medication overuse headache over 3 years of therapy	Frontiers in Neurology	8 (NOV)	586	No pagination	Study design
Lampl, C.	2017	The Eurolight Project 2017	Journal of Headache and Pain. Conference: 11th European Headache Federation Congress Jointly with 31st Congress of the Italian Society for the Study of Headaches. Italy.	18	1 Supplement 1	-	Study design/non-UK perspective
Lipton, R. B.;Brennan, A.;Palmer, S.;Jansen, J. P.;Hatswell, A. J.;Porter, J. K.;Di Tanna, G. L.;Villa, G.;Shah, N. ;Sapra, S.	2017	Novel biologics versus conventional preventive therapies in migraine: A framework for economic evaluation	Value in Health	20	9	A732	Study design
Lipton, R. B.;Gandhi, S. K.;Fitzgerald, T.;Yeung, P. P.;Cohen, J. M.;Ma, Y. ;Aycardi, E.	2017	The impact of fremanezumab on migraine-specific health-related quality of life and overall health status in chronic migraine	Journal of Headache and Pain. Conference: 11th European Headache Federation Congress Jointly with 31st Congress of the Italian Society for the Study of Headaches. Italy.	18	1 Supplement 1	-	Study design
Mahmoudzadeh Zarandi, F.;Raiesifar, A. ;Ebadi, A.	2016	The Effect of Orem's Self-Care Model on Quality of Life in Patients with Migraine: a Randomized Clinical Trial	Acta Medica Iranica	54	3	159–164	Study design
Minen, M. T.;Anglin, L.;Boubour, A.;Squires, A. ;Herrmann, L.	2017	Migraine patients' perspectives on migraine management: A meta-synthesis	Headache	57	-	160	Study design

Ramos, C. J.;Fernandez, M. D. A.;Martinez, S. S.;Izquierdo, M. M. ;Aznar, M. D. G.	2017	Botulinum toxin type a for the treatment of neurological diseases: Drug utilisation review	European Journal of Hospital Pharmacy	24	-	A155	Population
Sinclair, A.;Herd, C. P.;Tomlinson, C. L.;Rick, C.;Scotton, W. J.;Edwards, J.;Ives, N. ;Clarke, C. E.	2017	Systematic cochrane review of botulinum toxins for the prevention of migraine in adults	Journal of Headache and Pain. Conference: 11th European Headache Federation Congress Jointly with 31st Congress of the Italian Society for the Study of Headaches. Italy.	18	1 Supplement 1	-	Study design
Stillman, M. J.	2008	Dowson AJ, Bundy M, Kilminster S. Assessing patients with episodic tension-type headache, migraine or chronic daily headache using the short pain inventory: A within-group, comparative study to assess ability to cope with headache, emotional function and healthcare utilization: Comment	Headache	48	9	1390	Study design
Vo P, Bilitou A, Fang J, Laflamme A, Gupta S.	2017	Healthcare resource utilisation amoung migraine sufferers in the EU5 from the patient perspective	Journal of Headache and Pain. Conference: 11th European Headache Federation Congress Jointly with 31st Congress of the Italian Society for the Study of Headaches. Italy.	18	1 Supplement 1	-	Study design/non-UK perspective
Full Texts Excluded After Full-Text Review in September 2018 Update							
Aggarwal, A.;Barad, M.;Sturgeon, D. ;Mackey, S.	2018	Characterizing patients with migraines compared to patients with co-morbid non-cephalic pain	Headache	58	(Supplement 2)	94-95	Outcomes not presented
Boudreau, G.;Becker, W. J.;Graboski, C.;Ong-Lam, M.;Finkelstein, I.;Christie,	2018	Impact of onabotulinumtoxina on quality of life, health resource utilization, and	Headache	58	(Supplement 2)	94	Outcomes not presented

S.;Bhogal, M. ;Davi-Dovic, G.		work productivity in people with chronic migraine: Interim results from a prospective, observational study (PREDICT)					
Boudreau, G.;Becker, W. J.;Graboski, C.;Ong-Lam, M.;Stewart, B. ;Davidovic, G.	2017	Impact of chronic migraine on health resource utilization, quality of life, and work productivity: Baseline results from a prospective, observational study (PREDICT)	Cephalalgia	37	(1 Supplement 1)	105	Outcomes not presented
Chu, M. K.;Kim, J.;Kim, W. J.;Cho, S. J.;Yang, K. I. ;Yun, C. H.	2017	Sex differences in prevalence, symptoms, impact and comorbidities in migraine and probable migraine: Results from Korean Headache-Sleep Study	Cephalalgia	37	(1 Supplement 1)	243-244	Outcomes not presented
Fernandez, C. G.;Rustarazo, S. B.;Corpas, M. V.;Gomez, P. N.;Hidalgo, I. C. ;Raya, P. M.	2018	Economic study of the diagnosed population of chronic migraine treated with botulinum toxin	International Journal of Clinical Pharmacy	40	(1)	297	Outcomes not presented
Ford, J. H.;Foster, S. A.;Detke, H. C.;Stauffer, V. L.;Ruff, D. D. ;Aurora, S. K.	2018	Effects of galcanezumab on healthcare resource utilization and acute medication use in patients with migraine: Results from two global phase 3 clinical trials	Value in Health	21	(Supplement 1)	S208-S209	Outcomes not presented
Guerzoni, S.;Pellesi, L.;Baraldi, C.;Cainazzo, M. M.;Negro, A.;Martelletti, P. ;Pini, L. A.	2018	Addendum: Long-term treatment benefits and prolonged efficacy of onabotulinumtoxina in patients affected by chronic migraine and	Frontiers in Neurology	9 (AUG)	641	(no pagination)	Outcomes not presented

		medication overuse headache over 3 years of therapy [Front. Neurol, 8, (2017) (586)] DOI: 10.3389/fneur.2017.00586					
Jones, S.;Zermansky, A.;Szpakowski, J.;Button, P. ;Button, J.	2017	Improved efficiency of a nurse-led Migraine Botox service by implementation of a 'lean' management approach	Cephalalgia	37	(1 Supplement 1)	92-93	Outcomes not presented
Kawata, A. K.;Shah, N.;Poon, J. L.;Shaffer, S.;Sapra, S.;Mutebi, A.;Wilcox, T. K.;Tepper, S. J.;Dodick, D. W. ;Lipton, R. B.	2017	Characteristics of patients newly initiating a preventive treatment for migraine: Baseline data from the Assessment of Tolerability and Effectiveness in MigrAINeurs using preventive treatment (ATTAIN) study	Cephalalgia	37	(1 Supplement 1)	273-274	Outcomes not presented
Lipton, R. B.;Fanning, K. M.;Reed, M. L.;Murray, S.;Dumas, P. K.;Manack Adams, A. ;Buse, D. C.	2018	Self perceptions of what life would be like without migraine in major life domains: Results of the chronic migraine epidemiology and outcomes (cameo) study	Headache	58	(Supplement 2)	85-86	Outcomes not presented
Lipton, R. B.;Hutchinson, S.;Ailani, J.;Reed, M. L.;Fanning, K. M.;Manack Adams, A. ;Buse, D. C.	2018	Patterns and characterization of acute prescription headache medication use: Results from the cameo study	Headache	58	(Supplement 2)	121-122	Outcomes not presented
Lombard, L.;Schroeder, K.;Nichols, R.;Kar-Chan Choong, C. ;Ye, W.	2018	Characteristics, treatment patterns, and healthcare resource utilization in patients with migraine who initiated a triptan	Headache	58	(Supplement 2)	182-183	Outcomes not presented

Manack Adams, A.;Buse, D. C.;Fanning, K. M.;Murray, S.;Dumas, P. K.;Reed, M. L. ;Lipton, R. B.	2018	Perceived effect of migraine on career and finances: Results of the chronic migraine epidemiology and outcomes (cameo) study	Headache	58	(Supplement 2)	79	Outcomes not presented
Osumili, B.;McCrone, P.;Cousins, S. ;Ridsdale, L.	2018	The Economic Cost of Patients With Migraine Headache Referred to Specialist Clinics	Headache	58	2	287-294	Duplicate

Abbreviations: ACE: adaptive cost-effectiveness; EQ-5D: EuroQol-5 Dimensions; EU: European Union; GBD: Global Burden of Disease; HRQoL: health-related quality-of-life; NYHA: New York Heart Association; OTC: over-the-counter; SC: subcutaneous; UK: United Kingdom.

Description of identified studies: economic evaluations

In total, eight records reporting on six published economic evaluations were identified in the original SLR (see Table 98). No further economic evaluations were identified during the updates. Critical appraisals of each published economic evaluation included in the SLR were conducted using the checklist adapted from Drummond *et al.* (1996).[50] The results of these critical appraisals are presented in Table 99 below.

Table 98. Details of the relevant economic evaluations identified in the systematic review

Author, Year	Country and perspective	Summary of model	Patient population	QALYs (interventions and comparators)	Costs and outcomes	ICER (cost per QALY gained)
NICE, 2012[13, 51]	England and Wales; NHS perspective	• Cost-utility analysis using a state-transition (Markov) model to estimate the cost-effectiveness of onabotulinumtoxin A versus placebo (triptans plus pain relief only) in patients with chronic migraine • Six health states according to number of headache days/month: 0–3; 4–9; 10–14; 15–19; 20–23; ≥24. Patients could enter the model in any of the three chronic migraine states • Clinical data were incorporated from the pooled phase III PREEMPT clinical trials programme • Health state utility values were collected in PREEMPT using the MSQ and mapped to the EQ-5D • Costs included medicine acquisition and administration costs, cost of care consisting of GP visits, ED visits, hospitalisation costs and triptan costs • The model used 12-week cycles with a time horizon of 2 years	Patients with chronic migraine, defined as ≥15 headache days/month, for ≥ 3 months, of which at least 8 days are with migraine	**Discounted Totals** **≥1 prior oral prophylactic population:** • Onabotulinumtoxin A: 1.31 • Placebo: 1.22 • Incremental QALYs: 0.09 **≥3 prior oral prophylactic population:** • Onabotulinumtoxin A: 1.29 • Placebo: 1.20 • Incremental QALYs: 0.09 **Totals** **≥1 prior oral prophylactic population:** • Onabotulinumto	**Discounted Totals** **≥1 prior oral prophylactic population:** • Onabotulinumtoxin A total costs: £2,388 • Placebo total costs: £1,839 • Incremental total costs: £549 **≥3 prior oral prophylactic population:** • Onabotulinumtoxin A total costs: £2,438 • Placebo total costs: £1,895 • Incremental total costs: £543	**≥1 prior oral prophylactic population:** • £5,828/QALY gained **≥3 prior oral prophylactic population:** • £6,083/QALY gained

Author, Year	Country and perspective	Summary of model	Patient population	QALYs (interventions and comparators)	Costs and outcomes	ICER (cost per QALY gained)
		• Deterministic and probabilistic sensitivity analyses were conducted • The cost year was 2009/2010 • Costs and QALYs were discounted at 3.5% per annum		xin A: 1.34 • Placebo: 1.24 **≥3 prior oral prophylactic population:** • Onabotulinumtoxin A: 1.32 • Placebo: 1.23	**Totals** **≥1 prior oral prophylactic population:** • Onabotulinumtoxin A total costs: £2,419 • Placebo total costs: £1,879 **≥3 prior oral prophylactic population:** • Onabotulinumtoxin A total costs: £2,471 • Placebo total costs: £1,936	
Batty, 2013[41]	England and Wales; NHS perspective	• Cost-utility analysis using a state-transition (Markov) model to estimate the cost-effectiveness of onabotulinumtoxin A versus placebo in patients with chronic migraine • 13 health states: 6 on treatment, 6 off treatment and death. The on- and off-treatment states were divided by the number of headache days per 28 days • Clinical data were incorporated from the pooled phase III PREEMPT	Patients with chronic migraine, defined as ≥15 headache days/month	**Discounted Totals** • Onabotulinumtoxin A: 1.30 • Placebo: 1.20 • Incremental QALYs: 0.09 **Totals** • Onabotulinumtoxin A: 1.34 • Placebo: 1.24	**Discounted Totals** **Costs:** • Onabotulinumtoxin A total costs: £2,997 • Placebo total costs: £1,630 • Incremental total costs: £1,367	£15,028/QALY gained (discounted)

Author, Year	Country and perspective	Summary of model	Patient population	QALYs (interventions and comparators)	Costs and outcomes	ICER (cost per QALY gained)
		clinical trials programme • Health state utility values were collected in PREEMPT using the MSQ (Migraine Specific Quality of Life Questionnaire) and mapped to the EQ-5D • Costs included cost of care, consisting of GP visits, ED visits, hospitalisation costs and triptan costs • The model used 12-week cycles with a time horizon of 2 years • Scenario and probabilistic sensitivity analyses were conducted (5000 simulations were performed) • The cost year was 2010 • Costs and QALYs were discounted at 3.5% per annum			**Totals** **Costs:** • Onabotulinumtoxin A total costs: £3,077 • Placebo total costs: £1,680 • Incremental total costs: £1,367 **Life years (undiscounted):** • Onabotulinumtoxin A: 2.06 • Placebo: 2.06 • Incremental LYs: 0.00	
SMC, 2011[52]	Scotland; NHS perspective	• Cost-utility analysis using a state-transition model to estimate the cost-effectiveness of onabotulinumtoxin A injections given every 12 weeks, versus best supportive care (BSC) in patients with chronic migraine who had previously failed on oral prophylactic therapy due to side effects or lack of efficacy and were in the care of a headache specialist in a secondary care centre	Patients with chronic migraine, defined as headaches on at least 15 days per month of which at least 8 days are with migraine, who have	QALY gain: 0.08 (onabotulinumtoxin A versus BSC)	Incremental total costs: £1,394	£17,436/QALY gained

Author, Year	Country and perspective	Summary of model	Patient population	QALYs (interventions and comparators)	Costs and outcomes	ICER (cost per QALY gained)
		• Best supportive care was assumed to encompass use of off-label treatments such as gabapentin, venlafaxine and GON blocks or alternatively patients may not have been given prophylaxis but managed by acute treatments only • Clinical trial data were used to categorise patients into various health states in the model using mean headache days over a 28-day period. There were seven health states in total • Clinical data were incorporated from patient-level data from the post-hoc pooled analysis of key clinical trials • Health state utility values were derived using EQ-5D data from the IBMS • Costs included medicine acquisition and administration costs. Other resource use was estimated from the IBMS • The model used a time horizon of 2 years • Sensitivity analyses were conducted • The model cycle length was not reported • No discounting was reported	failed oral prophylactic therapy due to side effects or lack of efficacy and were in the care of a headache specialist at a secondary care centre			

Author, Year	Country and perspective	Summary of model	Patient population	QALYs (interventions and comparators)	Costs and outcomes	ICER (cost per QALY gained)
SMC, 2013[19]	Scotland; NHS perspective	• Cost-utility analysis using a state-transition model to estimate the cost-effectiveness of onabotulinumtoxin A injections given every 12 weeks versus best supportive care (BSC) in patients with chronic migraine who had failed ≥3 oral prophylactic therapies, where medication overuse has been appropriately managed and who are in the care of a headache specialist in a secondary care centre • Clinical trial data were used to categorise patients into on-treatment and off-treatment health states within the model using mean headache days over a 28-day period • Clinical data were incorporated from the post-hoc pooled analysis of the phase III PREEMPT clinical trials programme • Health state utility values were derived from estimating EQ-5D values by transforming MSQ scores collected from the clinical studies • Costs included medicine acquisition and administration costs, cost of care, consisting of GP visits, ED visits and hospitalisation costs • The model used a time horizon of 2 years	Patients with chronic migraine, defined as headaches on at least 15 days per month of which at least 8 days are with migraine, who have failed ≥3 oral prophylactic therapies, where medication overuse has been appropriately managed and who are in the care of a headache specialist in a secondary care centre	QALY gain (onabotulinumtoxin A versus BSC): 0.08	Incremental total costs (onabotulinumtoxin A versus BSC): £1,012	£12,176/QALY gained

Author, Year	Country and perspective	Summary of model	Patient population	QALYs (interventions and comparators)	Costs and outcomes	ICER (cost per QALY gained)
		• Scenario analyses were conducted • The model cycle length was not reported • No discounting was reported				
SMC, 2017[53]	Scotland; NHS perspective	• Cost-utility analysis using a state-transition Markov model to estimate the cost-effectiveness of onabotulinumtoxin A versus best supportive care (BSC) in patients with chronic migraine who had failed ≥3 oral prophylactic therapies and for whom medication overuse is appropriately managed • Clinical trial data were used to categorise patients into on-treatment and off-treatment health states in the model using mean headache days over a 28-day period • Clinical data were incorporated from the post-hoc pooled analysis of the phase III PREEMPT clinical trials programme • Health state utility values were based on EQ-5D values from a European observational study of onabotulinumtoxin A in patients with chronic migraine • Costs included medicine acquisition and administration costs, cost of care, consisting of GP visits, ED visits,	Patients with chronic migraine, defined as headaches on at least 15 days per month of which at least 8 days are with migraine, who have failed ≥3 oral prophylactic therapies and for whom medication overuse is appropriately managed	QALY gain (onabotulinumtoxin A versus BSC): 0.12	Incremental total costs (onabotulinumtoxin A versus BSC): £1,301	£10,816/QALY gained

Author, Year	Country and perspective	Summary of model	Patient population	QALYs (interventions and comparators)	Costs and outcomes	ICER (cost per QALY gained)
		hospitalisation costs and triptan costs • The model used 12-week cycles with a time horizon of 3 years • Scenario analyses were conducted • No discounting was reported				
SMC, 2006[54]; Brown, 2006[55]	UK; UK NHS and societal perspectives	• Cost-utility analysis using a decision-tree model to estimate the cost-effectiveness of topiramate versus no preventative treatment ('acute treatment only') in patients with migraine • Clinical data were incorporated from topiramate clinical trials • On entering the model patients could either receive topiramate or no treatment. Those receiving topiramate treatment could have one of the following clinical responses: ≥75%, 75-50%, <50% for mean reduction in monthly migraine frequency • The model assumed 40% of topiramate patients drop out in the first month of treatment and receive no clinical benefit for the 1-year period. • Health state utility values were derived from transformations of SF-36 data collected as part of topiramate clinical trials • Costs included cost of care,	Patients with migraine (base-case frequency is 6/month)	• QALY gain (topiramate vs. no preventative treatment): 0.0384 • No treatment: NR • Incremental QALYs: NR	• Costs/month: • Topiramate total costs: £37.13 • No treatment total costs: £18.80 • Incremental total costs per migraine averted: £10.13	£5,728/QALY gained

Author, Year	Country and perspective	Summary of model	Patient population	QALYs (interventions and comparators)	Costs and outcomes	ICER (cost per QALY gained)
		consisting of GP visits, ED visits, hospitalisation costs and triptan costs • The time horizon was 1 year • Sensitivity analyses were conducted • The cost year was 2005 • No discounting was reported				

Abbreviations: AE: adverse event; CEA: cost-effectiveness analysis; ED: emergency department; GP: general practitioner; IBMS: International Burden of Migraine Study; ICER: incremental cost-effectiveness ratio; IPD: individual patient data; LY: life year; MAIC: matched adjusted indirect comparison; MSQ: migraine specific quality of life questionnaire v2.1; OSA: one-way sensitivity analysis; PREEMPT: Phase III REsearch Evaluating Migraine Prophylaxis Therapy: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; RCT: randomised controlled trial; SF-36: Short-Form 36 Health Survey; UK: United Kingdom

Quality assessment of the identified studies

The studies identified as relevant for inclusion were assessed using the Drummond (1996) checklist.[50] The results of the quality assessment for these studies is presented in Table 99.

Table 99. Quality appraisal of included studies

	NICE, 2012[13]	SMC, 2011[52]	SMC, 2013[19]	SMC, 2017[53]	Batty, 2013[41]	SMC, 2006[54]; Brown, 2006[55]
Study design						
Was the research question stated?	Y	Y	Y	Y	Y	Y
Was the economic importance of the research question stated?	Y	Y	Y	Y	Y	Y
Was/were the viewpoint(s) of the analysis clearly stated and justified?	Y	Y	Y	Y	Y	Y
Was a rationale reported for the choice of the alternative programs or interventions compared?	Y	Y	Y	Y	Y	Y
Were the alternatives being compared clearly described?	Y	Y	Y	Y	Y	Y
Was the form of economic evaluation stated?	Y	Y	Y	Y	Y	Y
Was the choice of form of economic evaluation justified in relation to the questions addressed?	Y	Y	Y	Y	Y	Y
Data collection						
Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y	Y	Y	Y
Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	N/A	N/A	N/A	N/A	N/A
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Y	N	N	N	Y	N
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y	Y	N	N	Y	Y
Were the methods used to value health states and other benefits stated?	Y	Y	Y	Y	Y	Y
Were the details of the subjects from whom valuations were obtained given?	N	N	N	N	N	N
Were productivity changes (if included) reported separately?	N	N/A	N/A	N/A	Y	N

	NICE, 2012[13]	SMC, 2011[52]	SMC, 2013[19]	SMC, 2017[53]	Batty, 2013[41]	SMC, 2006[54]; Brown, 2006[55]
Was the relevance of productivity changes to the study question discussed?	Y	N	N	N	Y	Y
Were quantities of resources reported separately from their unit cost?	N	N/A	N	N	Y	Y
Were the methods for the estimation of quantities and unit costs described?	Y	N/A	Y	Y	Y	Y
Were currency and price data recorded?	Y	Y	Y	Y	Y	Y
Were details of price adjustments for inflation or currency conversion given?	N/A	N/A	N/A	N/A	N/A	Y
Were details of any model used given?	Y	Y	Y	Y	Y	Y
Was there a justification for the choice of model used and the key parameters on which it was based?	Y	Y	Y	Y	Y	Y
Analysis and interpretation of results						
Was the time horizon of cost and benefits stated?	Y	Y	Y	Y	Y	Y
Was the discount rate stated?	Y	N	N	N	Y	N
Was the choice of rate justified?	N	N/A	N/A	N/A	Y	N/A
Was an explanation given if cost or benefits were not discounted?	N/A	N	N	N	N/A	N
Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	N/A	N/A	N/A	N/A	N/A
Was the approach to sensitivity analysis described?	Y	Y	Y	Y	Y	Y
Was the choice of variables for sensitivity analysis justified?	Y	Y	Y	Y	Y	Y
Were the ranges over which the parameters were varied stated?	Y	N	Y	N	Y	Y
Were relevant alternatives compared in the incremental analysis?	Y	Y	Y	Y	Y	Y
Was an incremental analysis reported?	Y	Y	Y	Y	Y	Y
Were major outcomes presented in a disaggregated as well as aggregated form?	Y	Y	Y	Y	Y	Y
Was the answer to the study question given?	Y	Y	Y	Y	Y	Y

	NICE, 2012[13]	SMC, 2011[52]	SMC, 2013[19]	SMC, 2017[53]	Batty, 2013[41]	SMC, 2006[54]; Brown, 2006[55]
Did conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y
Were conclusions accompanied by the appropriate caveats?	Y	Y	Y	Y	Y	Y

Abbreviations: N: no; N/A: not applicable; SMC: Scottish Medicines Consortium; Y: yes.

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Single technology appraisal

Erenumab for preventing migraine [ID1188]

Dear Anna,

Thank you for the opportunity to respond to the additional clarification questions from the Evidence Review Group, Kleijnen Systematic Reviews, following the pre-meeting briefing. We hope that our responses to the individual questions below provide clarity on our approach in the submission and the necessary additional information where this has been possible.

As requested, we have uploaded to NICE Docs two versions of this response letter: one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please do not hesitate to get in touch should you have any questions regarding our response.

Kind regards,

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- **What is the definition of treatment failure, as applied to the subgroup of interest (people who have failed ≥3 previous prophylactic treatments)?**

The definition of treatment failure, as applied to the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in the erenumab studies and in the optimised NICE positioning for erenumab, is a broad definition encompassing insufficient efficacy and/or unacceptable toxicity.[1] Insufficient efficacy here indicates that there may have been some response to the initial treatment, however this was not considered adequate to continue on the same treatment.

- **Does failure of ≥3 previous prophylactic treatments mean failure of ≥3 individual treatments (possibly including multiple treatments within the same class), failure of ≥3 treatment classes, or failure of the three treatments specified in the proposed care pathway (propranolol, amitriptyline and topiramate)?**

Failure of ≥3 previous prophylactic treatments as per the optimised positioning of erenumab in the NICE submission means failure of ≥3 individual treatments, regardless of whether or not the treatments were in the same class. However in clinical practice, it is expected that most patients will have tried treatments from different classes rather than several treatments from the same class. Further discussion on this is provided below.

As described in our submission, the clinical evidence for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed is for patients who have failed ≥3 treatment classes/categories (topiramate; beta blockers [e.g. propranolol or metoprolol]; tricyclic antidepressants [e.g. amitriptyline or nortriptyline]; divalproex sodium or sodium valproate; calcium channel blockers [e.g. flunarizine or verapamil]; serotonin-norepinephrine reuptake inhibitors; botulinum toxin; antihypertensives [lisinopril or candesartan]; or other medications).[1-4] However, the trial data used within the economic model is for the subgroup of patients for whom ≥3 prior individual treatments have failed, in line with the optimised treatment position sought. This difference in subgroup definition used for presentation of clinical data and data included in the health economic model is because at the time of submission efficacy data were not available for all scope outcomes in the subgroup of patients for whom ≥3 prior individual treatments have failed. Therefore, in order to comprehensively address the final scope outcomes, clinical data for treatment category failures was presented in the clinical sections. In contrast, the outcomes required for the cost-effectiveness models were available for the subgroup defined as patients for whom ≥3 prior individual treatments have failed and these data were therefore used in the economic model as these data reflect the optimised positioning for erenumab in clinical practice.

In clinical practice it is thought that patients who do not respond to one treatment category are likely to move to another treatment category, rather than trying a subsequent treatment within the same category. Indeed, in England and Wales, the first three treatments recommended for the prophylaxis of migraine are propranolol, amitriptyline and topiramate; this reflects the notion that patients would move to a different treatment category with each line of treatment. Guidelines recommend that patients switch to an alternative treatment category if treatment at the maximum tolerated dose in the first-line is ineffective or poorly tolerated.[5] As such, whilst there is a difference between definitions of ≥3 prior prophylactic treatment categories and ≥3 prior individual treatments, in practice these two definitions would be expected to converge to the same patient population. In the erenumab studies, the difference in the number of patients between the subgroup of patients for whom ≥3 prior prophylactic individual treatments had failed and the subgroup of patients for whom ≥3 prior prophylactic treatment categories had failed was minimal (see Table 1), further supporting the notion that patients are likely to switch to a different treatment category after lack of efficacy/tolerability to a prior treatment. For avoidance of doubt, “failure of ≥3 previous prophylactic treatments” does not refer specifically to the failure of the three treatments specified in the proposed care pathway (propranolol, amitriptyline and

topiramate). However, these are considered to represent the three therapies that patients would receive in clinical practice and hence it is expected that in the majority of cases in UK clinical practice these would represent the three prior prophylactic treatments (and indeed treatment categories) that patients would have failed previously in meeting the proposed positioning of erenumab. As noted in the response to the ERG clarification questions (Question A10), the treatment categories with the highest proportion of patients who had failed across all four trials were topiramate, amitriptyline and beta-blockers, which supports the notion that these treatments are the ones most commonly failed in clinical practice.

Table 1: Number of patients in each trial arm for the subgroups of patients for whom ≥3 treatment categories and ≥3 individual treatments have failed

		Number of patients in each trial arm	
		≥3 treatment category failures (data presented in submission)	≥3 individual treatment failures (from economic model)
Chronic migraine	Placebo	XX	XX
	Erenumab 70 mg	XX	XX
	Erenumab 140 mg	XX	XX
Episodic migraine*	Placebo	XX	XX
	Erenumab 70 mg	XX	XX
	Erenumab 140 mg	XX	XX

*note that the episodic migraine numbers include the STRIVE, ARISE and LIBERTY trials.

- **Based on the study exclusion criteria (described in appendix M of the CS and reproduced in Tables 1 to 4 below) how many people, who would have been in the subgroup of interest, were excluded from each study?**

Treatment failure is a broad definition encompassing both efficacy and tolerability failures whereas the exclusion criteria 'no therapeutic response' to ≥2/3 preventative therapies is very specific, defined as no reduction in headache frequency, duration and severity after at least 6 weeks' administration of the medication at the accepted therapeutic dose. In practice, it is likely that only small number of patients are truly refractory to multiple previous treatments.

Study 295, STRIVE and ARISE had trial exclusion criteria that excluded any patients with 'no therapeutic response' to a number (>3 in Study 295, >2 in STRIVE and ARISE) of specified medicine categories. No therapeutic response is described as no reduction in headache frequency, duration or severity after administration of the medicine for at least six weeks, based on the investigator's assessment.[6-8]. In the text accompanying the ERG's letter, it is stated that these exclusion criteria appear to indicate that "patients who had failed at least two of propranolol, amitriptyline and topiramate**…**would have been excluded from these studies, unless the definition of failure did not include lack of response (e.g. definition of failure based on tolerability rather than efficacy)". To clarify, this exclusion criterion only excluded patients from the Study 295, STRIVE and ARISE studies if they had no therapeutic response to the specified number of prior therapies, defined as no reduction in headache frequency, duration or severity after administration of the medication for at least six weeks at the generally accepted therapeutic dose(s), based on the investigator's assessment. History of partial response (i.e. lack of efficacy) or tolerability issues did not constitute no therapeutic response.[1] Therefore, as an example, a patient could have failed 4 previous treatments but only had 'no therapeutic response' to 2

previous treatments and still be included in the study This exclusion criterion served to exclude patients from the pivotal clinical trials who were highly refractory and had cycled through multiple therapies without showing any therapeutic response. In clinical practice many patients would be expected to exhibit some level of response but ultimately be deemed a failure on a given therapy due to loss of response or intolerance, and hence progress to the next line of therapy.

Similarly, the ERG's statement "Patients who had failed **≥3 prior prophylactic treatments** could have been included in these studies provided that they had failed multiple treatments in the same category (e.g. 2 beta-blockers and1 tricyclic antidepressant)" is not entirely accurate. It is not a requirement that patients must have failed multiple treatments in the same category in order to be eligible for inclusion in this subgroup; if a patient had previously received 3 different prophylactic treatments from different treatment categories (e.g. propranolol, topiramate and amitriptyline) and ultimately been deemed to have "failed" on these therapies due to loss of response or withdrawal prior to achieving a therapeutic response as a result of tolerability then these patients would be considered to have failed ≥3 prior prophylactic treatments, but would not be excluded on the basis of having had "no therapeutic response" to >2 (STRIVE, ARISE) or >3 (Study 295) prior therapies. It is correct that the subgroup of patients "for whom ≥3 prior treatments have failed" in Study 295, STRIVE and ARISE would exclude any patients who might have previously tried 2 or 3 prior therapy categories and had no therapeutic response to any of these. However, in practice this is expected to constitute a very small number of patients.

In the LIBERTY study, the definitions were slightly different from the regulatory studies. Patients were excluded from the study if they had failed >4 prior prophylactic treatments, with failure defined in terms of efficacy, tolerability or were non-suitability for treatment. 'Efficacy failure' was defined as no meaningful reduction in headache frequency after administration of the respective medication for an adequate period of time at generally accepted therapeutic doses based on the investigator's assessment within the five years prior to screening. 'Tolerability failure' was defined as documented discontinuation due to adverse events of the respective medication at any previous time. Finally, 'not suitable for the purpose of this study' was defined as patient is not considered to be suitable for the treatment for medical reasons such as contraindications or precautions included in local labels, national guidelines or other locally binding documents, or other medically relevant reasons as confirmed by the treating physician.[9] The LIBERTY study therefore does not provide evidence for patients who have failed >4 prior treatments by these definitions, though in practice it is thought that few patients would get to this stage.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Erenumab for preventing migraine [ID1188]

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.

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 a patient focussed research driven charity. We provide evidence based information, campaign for and support those affected by migraine in the UK. We are committed to reducing the burden of migraine – on individuals, their families, schools and employers, the health system, the economy and society as a whole. Research is at the heart of our work. We fund and encourage the highest quality of medical research into the causes and treatments for migraine. We believe in advancing knowledge through the dissemination of scientific learning and the sharing of best practice. We provide evidence-based information to empower and educate. We campaign to position migraine as a serious public health issue and promote improved understanding and awareness. Our funding is from legacies, individual donations, events fundraising, corporate partners, trusts and foundations. More information on how we are funded can be found in our annual report and accounts.
4b. 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	The Trust has taken information gathered from our surveys which seek the views of people living with migraine. We have also spoken to healthcare professionals who support people with migraine. **The chronic migraine survey (n=221)** The survey gathered views from people living with chronic migraine about the impact of migraine on their lives, current medications and new treatments for the prevention of migraine. **Work, health and migraine survey (n=9**61)

carers to include in your submission?	The number of people who responded to the survey who lived with either episodic or chronic was 514 (53%) and 399 (42%) respectively. **What Matters Most to Patients with Headaches and Migraines? (n=116)** A collaborative study between The Migraine Trust and the Headache Service at St George' University NHS Hospital Trust in order to understand the views of patients with migraine and headaches. Nineteen "I statements" produced as a result of a focus group carried out by the Migraine Trust were used as the basis of a semi structured interview during hospital outpatient attendances. Carers or friend's responses were included with the patient's response in order to gain the widest experience. 118 patients agreed to participate with 116 interviews carried out. Thematic analysis of the responses was carried out with codes and themes identified. **Neurological Alliance: Patient Experience survey 2016 (n=1838 people with migraine)** Out of the 7048 responses to the survey, 1,838 answered that they have a migraine condition. Of these 1,359 stated that migraine was their main neurological condition. The Neurological Alliance agreed to share data for the migraine respondents with the Migraine Trust, which was analysed. It is the analysis of just people with migraine responses that will be used in this submission. We have also taken quotes from these surveys from people with migraine who have taken the time to write up their experience of living with migraine. **Erenumab survey** - To directly support this submission the Migraine Trust sought the views of people with episodic and chronic migraine who have used erenumab. A short six question survey asked people about the impact of migraine on their lives and their experience of using erenumab.
Living with the condition	
6. What is it like to live with the condition? What do carers	<u>What is migraine?</u> Migraine is a moderate to severe pulsating or throbbing primary headache disorder that can present with or without aura, (visual, sensory, motor, speech, brainstem or retinal symptoms) accompanied with other symptoms such as

experience when caring for someone with the condition?	increased sensitivity to light and/or sound, nausea and/or vomiting and aggravation by physical activity which can last four to 72 hours in adults. Chronic migraine is highly debilitating, it present as migraine for 15 days per month and for more than three consecutive months. Episodic migraine is another migraine sub-type, which is defined as less than 15 headache days per month. For some people there is a steady progression in headache frequency, especially in long term sufferers. This can lead to the migraines becoming so frequent that they cross the threshold of more than 15 days per month and become defined as chronic migraine. Every year between 2.5 and 4.6% of people with episodic migraine experience progression to chronic migraine <u>What is it like to live with the condition?</u> In all of the surveys the areas of a person's day-to-day life most affected were social life, family life, work life/ability to work, and ability to take part in hobbies/leisure activities. Due to the nature and length of time that they are affected, people with chronic migraine spend significantly more time absent from work, school, leisure, home and social activities than episodic migraine patients. Respondents told us that the unpredictable nature of the migraine, both episodic and chronic, prevents people from being able to make plans or commit to family, work or leisure activities. Respondents described the social isolation, depression, loneliness and poor quality of life as a result of missing out on the aforementioned areas of their lives. On rare migraine/headache free days the anxiety of a migraine attack occurring continues to restrict an individual's life and their activities. Inability to attend work, maintain a job, impaired productivity, losing or fear of losing a job due to chronic migraine are commonly occurring themes for the people we spoke to. The high frequency and severity of migraine attacks experienced by chronic migraine sufferers, means that they are regularly unable to spend time with family and fulfilling normal family activities/duties. 65% of respondents to our survey said that chronic migraine has a negative impact on their family and loved ones. Partners and family members become carers to chronic migraine sufferers. Sufferers often cannot be left alone or travel, particularly to new places, unaccompanied in case an attack occurs and they cannot get back. *'A migraine attack takes time away from me and my family.'*

	'Not knowing when you are going to have a migraine and if the medication is going to work has an effect on planning any activity and it annoys people if you call off due to migraine. Family suffer as you may have to go to bed and can not be a fully functioning member of the family. The pain at time can be unbearable and this then effects relationships. Side effects of medication make you tired.' *'Difficult to make plans, as may not be able to fulfil. Time off work sick. Can't travel on my own in case unable to get back if I get migraine.'* Employment The work, health and migraine survey found that the fluctuating and unpredictable nature of a headache/migraine disorder was one of the biggest barriers to managing the impact of headache/migraine condition at work for all organization sizes. Additional pressure comes when the chronic migraine sufferer is forced to give up work due to the illness. 50% of the chronic migraine survey respondents said that their condition negatively impacts on their financial circumstances. This is supported by the Work, Heath and Migraine Survey which found that in the United Kingdom, 19% of survey participants have previously lost a job as result of their migraine or headache disorder (*n = 961*). This rate doubles to 38% when we look solely at the survey participants that recognise as having a disability (*n = 320*). With a prevalence of 10 million people living with migraine in the UK, (adults aged 15-69), this would put the number of people considered disabled due to migraine at 3.8 million. 81% of people with either chronic or episodic migraine who answered the work health and migraine survey either agreed or strongly agreed that when their migraine disorder worsened that it would have a negative effect on their employment. The nature of the condition and how sickness policies are currently written, often unfairly penalises people with migraine. The number of short term sickness absence taken to manage the condition means that people with migraine are more likely to trigger disciplinary action.

	'I have taken a lot of sick days due to migraine but only recently I've been allowed occasionally to work from home instead to alter my hours around when I can work which is an improvement but I still don't feel my employer understands migraine enough or has enough access to research or resources to put proper support in place.' *'My employer's sickness procedure is very aggressive. They have allowed me two additional days sickness before I hit the next sickness trigger, which means I move onto the next level in the sickness procedure, which ultimately could lead to me lose my job.'* *'I have face HR based attendance review meetings due to medical absences, some of which were due to both long & short term absences related to migraine.*' '*Trigger sickness policy - formal warning due to taking 8 days off due to migraine in a year'* *'I find it a real struggle coping with chronic migraine and full time but have been refused part time and can't afford to pack up working. Because I am older less chance of getting another job'* *'It's not just work it affects my whole life - time with my children and family life. It's grim but survivable. No other long term health impacts (unless I damage my kidneys through medication over use) just an enormous amount of lost days which puts pressure on everything. There doesn't seem to be a lot of help or answers for that.'* *'I had to give up work because of chronic migraine four years ago. There are days when I feel useless, hopeless and a failure. I feel selfish when I complain about my pain and I miss my life so much.'*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In the chronic migraine survey, 67% of people living with migraine had tried five or more NHS treatments to manage their migraine. There are numerous acute and preventative treatments available for migraine. However many of the current treatments for migraine are drugs that have been developed for other medical conditions that have been repurposed for migraine. They often have unwanted side effects for people with migraine who use

	them. Erenumab is the first specific preventative treatment designed for migraine. It is a targeted treatment that is highly specific and as such it has been proven to have a side effect profile comparable to placebo. This is very important as most current proven preventative therapies have severe side effects that are commonplace – topiramate for example is very poorly tolerated in > 50% of patients with severe mood distrurbance, cognitive dysfunction, renal calculi etc. Proranalol causes weight gain, fatigue, nightmares, poor circulation etc. The anticnovulsants are teratogenic and sodium valproate causes learning disability in approximately 40% of babies born to mothers taking this medication. Botox is very effective but is hugely demanding of limited healthcare professional resources where there are very few decidated headache nurses or doctors who can administer. There is no standard treatment for migraine, so the choice of medication should always be made on an individual basis. Existing preventative medicine for episodic migraine may not benefit everyone with chronic migraine and side effects or co-existing medical conditions also limit their use. 75% of respondents to the chronic migraine survey had tried over five different medications or treatments for their condition. Only 19% of respondents to our survey were happy with their current treatment for chronic migraine and 58% were not satisfied. People who use acute pain-relief medicine, including codeine, triptans and paracetamol more than two or three times a week or more than 10 days out of the month can set off medication-overuse headaches. This is common amongst people with chronic migraine and can lead to daily headaches. Migraine sufferers can experience intolerable side effects from their medication which impact on their every day life. Respondents to the chronic migraine survey gave details of fatigue, incoherence and weight gain as the most unbearable side effects. For many this limits the number of treatment options available to them. Where patients suffer from multi morbidities the treatment options are limited further due to contraindications and the implications of managing side effects. 54.5% of respondents to the survey

	suffered from 1 or more other long-term health condition that they are required to take regular medication and/or treatment for. Being pregnant or breastfeeding can limit the treatment options available to female chronic migraine sufferers. Since migraine affects three times as many women as men this is a prominent concern amongst sufferers and their clinicians. Injectable treatments, such as the triptans are also generally well tolerated by people with the condition and increase the number of administration options of treatments for people with migraine. The What Matter Most project findings showed that people with migraine, (many of whom were very disabled due to the pain caused by migraine) prioritised the need for better access to migraine specific treatments. 'Effective in lifting the migraine episode. Although as topical no effect on the frequency' 'The preventative medicines have side effects which actually outweigh any positive impact they have on reducing the pain. I fell asleep at my desk at work once because of the side effects. Luckily I was on my own so nobody noticed. I went for years trying one drug and then another but I stopped because of the side effects and the minimal reduction in pain.'
8. Is there an unmet need for patients with this condition?	There is need for more treatments for people living with migraine because: • There are limited migraine specific treatments to prevent migraine. Many of the current treatments are not effective in many people living with the condition. This includes poor tolerance of first line preventative treatments such as topiramiate. • Many of the current preventive treatments are not well tolerated by people with migraine. This is in part because many of the current treatments are repurposed drugs used to treat other conditions and people experience unwanted side effects.

	• Many current preventative treatments often require a person with migraine to use the treatment for a few months before they it is effective, however the side effects of the treatments mean than many people with migraine are unable to tolerate the treatments to the point of it being effective. • The lack of targeted and effective treatments for migraine can lead to increased use of medication as people try to need to reduce the pain and severity of migraine. This can lead to the development of medication overuse headache in addition to their migraine. Effective treatments would reduce the frequency and severity of migraine attacks, the use of medications and the development of medication overuse headache. • A need for treatment designed specifically to treat migraine without side effects. • This supports the need for an increase the number of viable and effective alternative treatments for people designed specifically for migraine. • Therefore is a need for an increase in preventative treatments options for people with migraine. '*As I have not responded to taking preventatives, I want to try the Botox injections in the hope it will lead to a reduction in my headache days. Sumatriptan helps to treat the attack but a new drug is required to successfully reduce the number of headache free days'* *'My current treatment has reduced the severity of my attacks, however the frequency of attacks has increased over the past while and side effects have worsened meaning another change is on e horizon.'*
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	• It's a preventative treatment that can significantly reduce the frequency and severity of migraine attacks for people with either episodic or chronic migraine. • There is a faster rapidity of onset compared with current preventative treatments. People with migraine will know within the first month whether or not erenumab is effective. This is advantageous for both the person with migraine and healthcare professionals. People with migraine will have an improved quality of life faster as they will be able to know quicker whether or not the treatment is effective and partake in their daily lives without the having to overcome side effects of the treatment before it is effective (this is the case of some of the current preventative treatments). Additionally healthcare professionals will have more time to treat

	patients and write prescriptions for a shorter period of time - this has a potential time and cost saving for the NHS • In comparison with the preventative Botox, which requires multiple injections by a trained healthcare professional, erenumab is a single self-injectable treatment. • The treatment administered once a month and no further prophylactics are needed for the following thirty days. There is less need to train healthcare professionals to administer the treatment and set up specific specialist clinics to administer the treatment, unlike Botox. • As a fast, effective and well tolerated preventive treatment erenumab is able to reduce the number of headache days and the use of acute treatments for migraine attacks. This has a huge positive impact on people with migraine's general well being and quality of life. • Erenumab is well tolerated and given most likely by a healthcare professional; where we know compliance with oral preventative therapies is reported to be less than 20% at 1 year into therapy, this ensures far higher rates of compliance. Erenumab has been shown to have definite and good efficacy in a significant proportion of patients, it will be likely complied with and it will be highly likely to be safe. • The reduction in acute treatments and painkillers will also help alleviate the development of headache induced by medication overuse. • Erenumab is the first preventative treatment to be developed using the scientific understanding of the pathophysiology of migraine (bench to bedside treatment for migraine). '*The impact for me was life changing. I was able to plan ahead with confidence rather than always being a maybe for events and outings. It gave me confidence and energy. This is the only thing that has helped me in 35 years to the extent it has*.' *'The drug changed my life. I hardly had a migraine'*

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	It is felt that there are few disadvantages to the use of erenumab as a preventative treatment for migraine. • Some people with migraine may from have trypanophobia (needle phobia) which could be a problem as erenumab is administered via an injection • Some may experience mild pain at the injection site and/or an allergic reaction • Although generally well tolerated there is a need for long term studies to understand if there are any long term side effects of erenumab. However research has already begun in this area.
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.	There are less treatment options available for people with chronic migraine. Therefore this group of people with migraine are in need of alternative treatment options. People who have tried three or four preventative medicines have found that erenumab is effective in treating their migraine. Chronic migraine – fewer treatment options for this group of people with migraine and these people are often the most disabled by the condition.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• Migraine can be classed as a disability under the Equality Act 2010 • Women are three times more likely to be affected by migraine and most common in people of working age. Therefore women who already face inequality in the work place are further disadvantaged by migraine. • The 2014 Headache Services report by the APPG on Primary Headache Disorders found that patients in England have non-equivocal access to specialist headache clinics and face barriers accessing appropriate and recommended treatments.
Other issues	
13. Are there any other issues that you would like the committee to consider?	• There is concern about the availability of erenumab on the NHS for two reasons. One is the uncertainly around the cost of the drug and whether it will made available on the NHS – we await with much anticipation the outcome of this technology appraisal • The second, if a positive recommendation for this technology appraisal is the outcome, how uniformly will erenumab be listed in local CCG formularies to ensure people who would benefit from the treatment have equal opportunity to access the treatment • Given the high prevalence of migraine, the lack of effective preventative treatments without side effects the cost of the new treatments – there is concern whether the NHS will be able to afford the erenumab given the huge unmet need The National Neurology Advisor Group (NNAG) in England chaired by Professor [redacted], has prioritised headache and migraine as one of the condition areas thy are focusing on, due to the large number of people living with migraine in England and the lack of infrastructure within the NHS to support these people. This is in part being addressed through the Migraine Trust and NHS Right Care working together to develop a framework/pathway for optimised care for clinical commissioner groups (CCG) to use when assessing how to manage and care for people with migraine in their local area. This will help address variation in care and services at CCG level. If appropriately used and learning implemented by CCGs then people will migraine will have access to treatments and services that best support their needs, improve

	management of their migraine and so reduce the number of headrace days. This will lead to improvement in their quality of life living with a currently incurable condition. Public Health England's Neurology Intelligence Network (NIN) is in the process of finalising a piece of work into the prevalence of migraine in the UK. The NIN are working with the NNAG and NHS England to better understand the prevalence and data associated with neurology of which headache is currently a priority area. The Specialised commissioning specification for neurology is currently undergoing a review. There will need to be consideration of how treatments and devices of headache such as erenumb will be considered as part of specialised commissioning by NHS England or routine commissioning by CCGs. The Migraine Trust is also in the process for formalising a UK Headache Network. The UK Headache Network will bring the headache community together to reduce unwarranted variation in care and outcomes for people living with migraine and other headache disorders. The above initiatives are to help improve the NHS infrastructure so that people with migraine have timely access to effective treatments for migraine. *'Chronic migraine infiltrates all parts of my life. On the odd day when I'm not in pain, I worry about being in pain. Will it be worse the next time? Will I have to stay home from work (again)? Who am I going to let down next? What special occasion am I going to miss out on? How long will my partner put up with taking care of the house? Does he think I'm pretending? The pain varies in intensity each day and I can't predict how I will feel from one day to the next but most often it's a safe bet to assume that I'll be suffering. People don't understand this invisible condition and just because you get up for work each day it doesn't mean you're ok. I rarely feel that I am operating to full capacity. Sometimes I can't think straight or it takes me a little longer than others to process something. I do think it has held me back in my career.'*

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Erenumab is the first treatment for migraine that has be developed rationally to treat migraine. • It has fewer side effects that many of the other current preventative treatments. • It's rapidity of onset is faster than many other current preventative treatments. This is beneficial to the person with migraine in term of improved quality of life. It is also beneficial to the reducing the cost of NHS prescribing and time with clinicians. • It required one self-administered injection a month and reduces the frequency and severity of migraine attacks. This also reduces the need for painkillers and risk of developing medication overuse headache. • There is a motivation in NHS England to ensure that the care pathways, services and treatments for people with migraine are considered at national level and local levels. The headache community of healthcare professionals and national charities are supporting initiatives and working with the NHS to ensure that people have access to effective treatments for migraine.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Erenumab for preventing migraine [ID1188]

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.

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	OUCH (UK)
3. Job title or position	Administration officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Support organisation for sufferers of cluster headache and other severe headache conditions. Funded by member subscriptions, donations and fund raising events. Approx 3,000 members
4b. 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 do not have any documented patient response as the technology in this appraisal has only just started trials for treatment of cluster headache. We wish to be part of the appraisal as some of members suffer migraine as well as cluster headache or another TAC. However, great interest has been shown in the outcome of the trials in migraine, this response via e-mail, our forum and our Facebook page.**
Living with the condition	
6. What is it like to live with the condition? What do carers	Extremely difficult, as it is a hidden disability. Attacks of pain severe pain can strike at any time in a 24 hour period. GP s frequently misdiagnose it, or fail to diagnose it at all; misprescribe medications or fail to

experience when caring for someone with the condition?	prescribe those licensed and approved by the BNF, NICE and the NHS/DOH. It is difficult to maintain regular employment and carers/supporters do not always understand what the patient is coping with. Byt the same token, carers/supporters feel deep frustration and sadness that there is so little they can do to help a sufferer particularly if it is a close family member or a child.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The two approved abortives for the pain work well, but the sufferer is dependent upon the GP being willing to prescribe for them, and it is sometimes difficult to obtain a referral to an appropriate headache neurologist. As stated earler, sufferers are often misdiagnosed and misprescribed for.
8. Is there an unmet need for patients with this condition?	Rapid access to a headache neurologist. Sometimes the patient suffers months of pain before seeing a headache neurologist. So far, only St Thomas Hospital offers a rapid access service. Also acceptance by doctors that we are an expert patient group, and that the medications we tell sufferers about are appropriate for the condition and they can prescribe them, particularly with regard to high flow oxygen which is a first line abortive for the pain of the condition.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	If this trial of erenumab is successful in the treatment of cluster headache, this will mean that a high proportion of patients will received a medication that works, the needs prescribing only once a month and may change the need for preventive medications currently used. There will also be a cost saving to the NHS. Further if the trial in CH is successful, it will change sufferers lives completely giving them their lives back, knowing that the daily round of attacks while not totally eliminated is at least greatly reduced, removing the threat of losing employment and restoring their self-esteem.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We cannot say as yet as the technology is yet to complete trials for cluster headache.
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.	Certainly if the treatment is successful, chronic sufferers, some of whom have suffered attacks without respite for 25 years, will benefit far more than the episodic sufferers who experience bouts a couple of times a year over a period fo weeks or months, but with painfree respites in between.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Cluster headache is not gender or age specific**

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- organisation of sufferers of a rare and excruciatingly painful headache condition wish to see how this technology develops for migraine and hopefully will benefit our members.
- As trials are already started for cluster headache we feel it important to be as aware as possible of the likely benefits of this treatment
- That we are interested to follow the complete story of the development of this technology as it may have far-reaching benefits for our members.
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

PROFESSIONAL ORGANISATION SUBMISSION

ERENUMAB FOR PREVENTING MIGRAINE [ID1188]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	Dr Nicola Giffin
2. Name of organisation	Association of British Neurologists headache and pain advisory group

3. Job title or position	Consultant Neurologist, Chair ABN headache and pain advisory group
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):
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
Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	• To reduce the impairment and improve disability caused by migraine and improve associated disease-related quality of life for sufferers of migraine • To reduce the number of days affected by 'headache' or 'migraine' • To reduce the duration of migraine attacks • To reduce the impact of other associated functionally disabling "non-headache" symptoms associated with the disorder including aura

or prevent progression or disability.)	• To provide a preventative treatment that is well tolerated and safer than existing therapies • To reduce the need for additional acute medications to treat acute attacks
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.)	Both: 1.Reduction in 'headache load' (calculated by headache severity x duration) and/or days with migrainous associated symptoms by ≥ 50% in low frequency episodic (<10 days/month) migraine or >30% in high frequency episodic (10-14 days/month for >3 months) and chronic migraine (≥ 15 headache days/month for >3 months) 2.Significant reported change in patient quality of life measures e.g. a. HIT6 or MIDAS (validated quality of life measure in migraine) b. Functional sales (e.g. functional numeric analogue scale) c. Level of absenteeism from employment where relevant d. Patient reported efficacy e.g. functional numeric analogue scale)
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 • Significant 'iceberg' of patients with disabling migraine not accessing appropriate management and only a fraction seen in secondary care • Lack of recognition within healthcare systems of the impact and disability related to migraine • Lack of education in appropriate treatment options and therefore availability to these • Limited effective and targeted preventative pharmacological treatments where side effects do not limit compliance • 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

What is the expected place of the technology in current practice?	
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 usually referred to secondary care settings and those where the situation is refractory are seen within specialist services which are limited in number and location with often very long waiting lists Treatment is through: 1. Lifestyle, behavioural and psychological modification and education 2. A range of pharmacological options for both acute and preventative treatments. The latter preventative options being mostly re-purposed (betablockers, anti-epileptics, tricyclic anti-depressants and angiotensin converting enzyme inhibitors), having not been designed to target the underlying migraine biology with a range of side effects that are often limiting 3. For chronic migraine, those who remain refractory to standard oral prophylactic medication or drug intolerant the use of injectable techniques such as cranial nerve blocks and botulinum toxin A is an additional option. Neuromodulation devices e.g. vagal nerve stimulators and transcranial magnetic stimulation may be considered although their evidence base needs further growth before place in standard treatment established: use of these are variable with no routine funding in place
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Clinical Guideline 150 (2012 & updates) https://www.nice.org.uk/guidance/cg150 SIGN Guideline 155 - Pharmacological management of Migraine (Feb 2018) http://www.sign.ac.uk/sign-155-migraine.html British Association of Headache (BASH) Guideline – (2010 – in revision & update due to be published Feb 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. Often episodic migraineurs remain within the community or are managed by primary care. Whilst guidelines exist (NICE CG 150), the application of these are often not seen; for example many patients who should be accessing triptan therapy remaining triptan naïve.
• What impact would the technology have on the current pathway of care?	• Erunumab would bring a novel easily administered once monthly well tolerated treatment to the migraine pathway. The infrequent administration is expected to significantly improve patient compliance and potentially reduce the need for frequent GP review to (1) titrate treatments to their most effective and tolerated dose, and (2) monitor these drugs for commonly occurring and well known side effects (e.g. depression, suicidal ideation, personality change, weight gain, sedation, hypotension, renal calculi, cognitive dysfunction, teratogenic effects) associated with other preventative treatments • The use of new therapies such as Erenumab may reduce the burden on acute emergency hospital care by more successfully treating patients with headache disorders and preventing their need for emergency care, where patients with headache represent a high proportion of patients presenting at Accident and Emergency and Acute Medical Assessment Units • Erenumab opens up a new option for patients in secondary care. As the published studies have looked at episodic patients it is likely that a pool of patients who have failed to find suitable treatments will want to join the pathway which at present has limited resources. Introduction of a new agent that sits best within specialist services will lead to a bottleneck with current specialist resources and greater investment and manpower within these services may be needed.
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 increased compliance, ease of use and tolerability.

• How does healthcare resource use differ between the technology and current care?	It may need a better defined treatment pathway definition to determine 'starting' and 'stopping' criteria. However once treatment is established, Erenumab is self-administered and is likely to require less frequent follow up as opposed to treatments such as cranial botulinum toxin therapy which requires three monthly specialist contact.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The introduction of a new biologic agent sits best within specialist services to establish appropriate eligibility (starting criteria), access, monitoring to validate efficacy and safety for continued use and to establish those who no longer need the drug or do not benefit to discontinue therapy (stopping criteria).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• Injection training for patients • Useful to have digital platform e.g. electronic patient record with central monitored records of response accessible by clinicians • Facilities: specialist clinic expansion including staff (reception, specialist consultant and nurses, secretarial/admin support), clinic space
Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, especially in high frequency and chronic migraine populations and those migraine sufferers intolerant of, or with poor compliance to, conventional preventative treatments.
• 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, appeal of infrequent treatments, patient centred with less requirement for high intensity follow up.

Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Likely to be more effective in those with chronic migraine (≥ 15 headache days per month for >3 months) and high frequency episodic migraine (10-14 headache days per month for >3 months) as demonstrated in current clinical trials. Likely to be less appropriate in those with low frequency episodic migraine (<10 headache days per month).
The use of the technology	
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.)	Yes - probably easier. Compared to botulinum toxin for chronic migraine: it does not need the time needed for 31 botulinum toxin injections and the process of toxin disposal and associated consumables. It will still remain a problem for those who are needle phobic. Rapidity of treatment response within the first few months allows potential easier assessment of efficacy. Introduction may be benefited by a Headache nurse specialist led model of care to initiate, monitor and help in patient assessment.
Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting and stopping criteria would be advisable as this will be a high cost drug and need to safeguard targeted use to the appropriate population and insure outcome monitoring in place to determine suitability of continued treatment. Starting: i) failed 3 standard prophylactic mediation at sufficient dose and for at least 2 months unless reasonable tolerability concern ii) medication overuse addressed iii) compliant with diary monitoring

	iv) established migraine diagnosis with at least 10 headache days per month (i.e. high frequency episodic migraine and chronic migraine) or those with incapacitating low frequency episodic migraine 4-9 days per month v) if chronic migraine also failed cranial botulinum toxin unless contraindicated Stopping: i) assessment at 3 months after initiating treatment with treatment cessation in patients who do not meet the 30% responder rate in high frequency episodic/chronic state or >50% responder rate in those with low frequency episodic migraine and do not show significant reported change in patient quality of life measures/functional scales (e.g. HIT6, MIDAS). ii) re-evaluation at approximately1 year: consider discontinuation to assess need for ongoing treatment. Current lack of data on relapse rate after discontinuation of treatment to guide long term treatment decisions. No additional laboratory testing is required to implement these rules, but patient quality of life measures and headache diaries would need to be routinely monitored
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 initial data from an open label extension study showing 75-100% migraine frequency reduction a subset of responders is potentially a step change if sustained effects seen in published the data. This approaches the desires of patients to be “cured” of migraine.

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 offers the first preventative agent which is targeted at the underlying biology. It would appear to offer preventative treatment with limited side effects and with a dosing regimen that is far more attractive to patients and combined this will improve compliance and therein efficacy.
• Is the technology a 'step-change' in the management of the condition?	Potentially yes, although the clinical efficacy in the low frequency episodic migraine groups is similar to current preventive oral medications but tolerability is significantly better and adherence may be similarly good.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, this is a preventative treatment option which is not limited by side effects and daily dosing which restrict compliance.
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 very limited side effect profile reported (short term treatment) facilitates compliance and compared to current treatment options this in itself contributes to quality of life as days without headache are not blighted by side effects.
Sources of evidence	
Do the clinical trials on the technology reflect current UK clinical practice?	Not entirely - as in the clinical trials more than 50% of patients were completely treatment naïve (with exclusion criteria for the trials being more than 2 preventative options taken previously) and this would be unlikely in clinical practise - in practise high cost treatments would not be a 1st line treatment option. Also more data is required on whether medication overuse headache affects treatment outcome

• If not, how could the results be extrapolated to the UK setting?	Likely still applicable although anticipated treatment response may modestly fall as in practise it would be used in those whose migraine state was more resistant
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. Reduction in 'headache load' (calculated by headache severity and duration) and/or days with migrainous associated symptoms by ≥ 50% in low frequency episodic migraine or >30% in high frequency episodic and chronic migraine 2. Significant reported change in patient quality of life measures e.g. a. HIT6 or MIDAS (validated quality of life measure in migraine) b. Functional sales (e.g. functional numeric analogue scale) c. Level of absenteeism from employment where relevant d. Patient reported efficacy e.g. functional numeric analogue scale) 3. % of patients with sustained headache response 4. % of patients with 75% and 100% response rate In the two large reported Phase III trials (ARISE and STRIVE) % responder rate was reported based on headache days but we would emphasize, particularly in a chronic patient, often a more meaningful measure relates to the 'headache load' (cumulative severity x hrs) as attenuating and shortening headache episodes can have an enormous impact on ability to function. In the two large reported Phase III trials (ARISE and STRIVE) significant change in quality of life was reported on using the standard scales we use in practise, with modified scales that included measures of absenteeism and a newly developed functional scale (Migraine Physical Function Impact diary). Patient reported efficacy or satisfaction was not reported on. Preliminary data from an open label extension study has measured 75% and 100% responder rate and sustained response but final published results from these studies are awaited
• If surrogate outcome measures were used, do they adequately	N/A

predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge
Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Ongoing studies still occurring with Erunumab i.e. "LIBERTY" and "BECOME" and a trial looking at medication overuse headache may occur
Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA260]?	Yes - but no RCT data – all open label observational studies only 1. PREEMPT Severe headache days analysis 2017 https://link.springer.com/article/10.1186/s10194-017-0784-4 2. Real world usage in Europe of Onabotulinum toxin type A in Chronic migraine https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5734384 3. The REPOSE study – Still in preparation/press - Preliminary data 2017 https://link.springer.com/article/10.1186/s10194-017-0802-6 4. The COMPEL study 2018 https://link.springer.com/article/10.1186/s10194-018-0840-8
How do data on real-world experience compare with the trial data?	No real world data yet available on Erunumab as it is not yet licensed in the UK
Equality	
a. Are there any potential equality issues that should be	Access of patients not yet known to secondary care as previously self-managed in the community or primary care

taken into account when considering this treatment?	
b. Consider whether these issues are different from issues with current care and why.	Bringing a new treatment option for episodic migraine to a potential cohort of patients who are no longer under medical review will expose inequalities in access to specialist service.
Topic-specific questions	
Where in the treatment pathway for prophylaxis of migraine is erenumab likely to be used in clinical practice? After how many treatments?	For those with high frequency episodic migraine or chronic migraine or those with incapacitating low frequency episodic migraine and;- 1. Medication overuse addressed 2. Failed x3 sufficient prophylactic trials unless contraindicated 3. If chronic migraine also failed cranial botulinum toxin unless contraindicated
Does the treatment pathway differ according to whether people have chronic or episodic migraine?	Only in as much as with chronic migraine we would place treatment with cranial botulinum toxin A prior to treatment with erenumab
Would you expect any benefit with erenumab to be similar for people with chronic migraine and people with episodic migraine?	We would expect treatment response in both groups but anticipate that modifying chronic migraine will be more challenging than episodic migraine and hence the recommended responder rate which is clinically significant would be less in chronic migraine than low frequency episodic. In our experience preventive treatments in chronic migraine do not always achieve headache day reduction but can attenuate migraine severity and limit duration and hence improve QoL outcomes
How long would you expect patients to receive treatment with erenumab for?	For 3 months and then if sufficient response continue for a further 9 months and re-evaluate on a yearly basis

Would you expect the benefit of treatment with erenumab to continue after treatment has been stopped, and if so, for how long?	Uncertain. There is no published data so far for an ongoing benefit of Erenumab after discontinuation of treatment. There is also very little evidence for the ongoing benefit of standard migraine prophylactic treatment after treatment is discontinued, some patients can remain well controlled for some years but many relapse and need further courses of treatment. In patients responsive to cranial botulinum toxin A, a proportion remains stable when treatment is stopped and this can be for extended periods although the majority go on to need further management. For oral drug prophylactics, a study on the use of topiramate (Pascual et al 2007) showed that 50% will maintain treatment response for a further 6 months after 6 months of treatment.
If patients experience migraine again once treatment has been stopped, would re-treatment be considered?	Yes – it previously been an effective treatment and considered a responder If reproducibly there is a fast trajectory to reverting to higher frequency on cessation on more than 2 occasions, more prolonged treatment without treatment hold would be anticipated

Key messages

- **29. 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
- Adherence to injectable treatments is much higher than oral medications
- Side effects of Erenumab are much less than with oral preventative treatments and treatment is more tolerable than botulinum toxin
- Potentially high levels of high response rate to Erenumab in a subset of patients
- Novel mode of action targeting underlying pathogenesis of migraine

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Erenumab for preventing migraine [ID1188]

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- 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	
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 (BASH) is a professional body that represents Neurologists and Primary Care Physicians with interest in headache disorders. The organisation is funded through membership and is heavily involved in education and research in headache disorders all over the UK. BASH is a member of the International Headache Society (IHS) and European Headache Federation (EHF) representing views of the UK members in research, education at a global level.**
5b. 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,	The aim of this treatment is to: a) Reduce the frequency and severity of headache in migraine sufferers. b) Improve the quality of life to help migraine sufferers have less disability. c) To have a positive impact in patients' work life and in other activities of daily living.

or prevent progression or disability.)	d) To reduce the need of acute medications as a result of reduction in the frequency and severity of a migraine attack. e) Provide a preventive treatment with better tolerance and less side effects.
7. 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.)	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. Many studies report on average headache day reduction in comparison to placebo that does not reflect on actual therapeutic gain of the drug. 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 (QoL) 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?	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. The research in headache disorders is massively under-resourced. 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.

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Many patients with infrequent migraines do not consult and those seen in primary care are managed with simple analgesics. Those with frequent and disabling attacks are often referred to secondary care managed by a general neurologist with little understanding on headache disorders. The dedicated headache services are few and patchy in the UK and have a very long waiting time. There are handful of General Practitioners with interest in headache disorders (GPwSI) overwhelmed with the referrals. Those that are lucky to receive appropriate attention may get early diagnosis and treatment advice, although vast majority do not have access to headache specialist. The pharmacological options for both acute and preventive treatment are limited. There is no migraine-specific preventive treatment and medications currently used include antidepressants, anti-hypertensive and anti-convulsants. Many are either less effective or poorly tolerated with range of side effects often worse than the migraine itself. For Chronic Migraine there are injectable treatments such as Botox that are expensive and is only available to those that have failed to respond to three other treatments. Neuromodulation devices such as gammacore, cephaly, transcranial magnetic stimulation have been appraised positively by NICE but are not funded on the NHS unless pursued through exceptional treatment requests. Around 20% of migraine patients are refractory to all available options and are referred for intravenous dihydroergotamine or invasive procedures that are only available in one or two centres in London as very little in-patient headache services exist in the remainder of the UK. These are expensive options with huge cost-implications to the CCG. Lifestyle and general advice is helpful but time consuming and are often delivered by the specialist headache nurses, although there are only around 30 nurses in the UK. Behaviour and cognitive therapy are often helpful although psychology services linked with headache clinics do not exist in the UK.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are a range of guidelines available for management of migraine including those from American Headache Society, International Headache Society, European Headache Federation, European Federation of Neurological Sciences etc. However, in the UK many healthcare professionals follow NICE Guidelines CG 150 (2012 updated in 2015), SIGN Guidelines 155 (February 2018), BASH Guidelines 2010 (currently being updated)
• 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 care on headache and migraine varies across the country determined by the availability of either primary or secondary healthcare professional with interest in headache disorders. In general there is lack of expertise among many primary care healthcare professionals and many general neurologists lack detailed understanding on the disorder. Hence they vary from being extremely good to very poor based on the availability of special headache services. The approach to management of migraine depends whether you are a GP, Neurologist or headache specialist. The availability of guidelines are of little use if there is lack of expertise in making a proper diagnosis and management plan. Most of the infrequent and episodic headaches remain in the primary care.
• What impact would the technology have on the current pathway of care?	Erenumab is the first ever migraine-specific preventive treatment for both episodic and chronic migraine. The side effect profile of the drug is very similar to placebo. The drug can be self administered by the patient subcutaneously once a month that empower the patient to manage his/her own care. This will reduce the need for frequent GP or specialist consultation and treatment visits and with the current efficacy data will reduce the number of acute visits to the Accident and Emergency Department. The studies with Erenumab and its impending arrival is already widely known in the general public. Many patients will ask their general practitioner for the treatment that is likely to sit best with the specialised headache services considering not everyone will be suitable or responsive to the treatment. 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	This will add to the currently available treatment options. The positioning of the new treatment will depend on the cost.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The treatment pathway needs to be specifically defined for the new technology including: • Who will be eligible for the treatment? • What would be the start and stop criteria for the treatment? • How long the treatment be continued? • How and when the treatment is re-initiated once stopped? • How the treatment response will be monitored? • What follow up arrangement will be required considering the drug is self-administered? • How frequently the patient will need to be followed up. • Who will be training the patient as this is an injection treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment will be best suited to be commenced in the specialist headache centre albeit primary or secondary care although once started this could be monitored at a primary care level.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	With the publicity the new treatments often receive, there will be a massive increase in the demand for the treatment by the patient through their primary care physician. This will need to be considered before recommending on the NHS. In our opinion a headache nurse will be able to handle many of such referrals and would be able to train on injections. However, this will mean expansion of the specialist headache nurses in headache centres to be able to cope with the influx of new referrals.
11. Do you expect the technology to provide clinically	The main issue with current treatment is tolerability and side effects. 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 a real life data is available.

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – due to lack of side effects and better tolerability
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In our opinion the treatment will be equally effective in both episodic and chronic migraine. Currently there is more clinical need for better treatment in chronic migraine considering many patients refractory to the first line are treated with Botox. The fact that chronic migraine carries a very high disability and severely compromise the quality of life, it will be used more in chronic than episodic migraine.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare	The current treatment is a monthly subcutaneous injection that can be self-administered and has side effect comparable to placebo. This will be more acceptable to the patient and practically easier to administer.

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.)	For example treatment with Botulinumtoxin requires three monthly clinic visit to a specialist and involves 31 injections.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As this is likely to be a high cost technology, appropriate start and stop criteria will need to be established. Its placement with the current treatment will really be based on the cost of the technology. If similar to botulinumtoxin (for example) a suggestion to use the technology following failure of the first line drug (three preventive treatment) will be reasonable. Its use before or after botulinumtoxin will depend on the cost of the technology although home treatment, self-administration and lack of frequent follow up will be potentially cost savings. Careful monitoring for compliance, therapeutic response and adverse events will be required.

	As with other preventive treatment, treatment be given for three months and stopped if there is lack of therapeutic response. If effective, it will be reasonable to continue for 6-12 months following which attempts be made to withdraw the treatment. Medication overuse need to be evaluated as this may blur the response rate.
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?	The studies indicate some patients to show 100% improvement. This would obviously enhance their productivity; reduce GP and hospital visit and absenteeism. Often the indirect costs are difficult to measure in the QALY assessment.
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	The treatment is a first ever migraine specific preventive treatment for migraine (both episodic and chronic). The treatment after an initial consultation and training is self administered through monthly subcutaneous injection that may only need an infrequent telephone or email consultation by a specialist headache nurse. This certainly will reduce cost of care to the patient and the hospital/primary care. The side effect profile is better than existing treatment improving compliance, drop-out rates and quality of life.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes Better tolerability and side effect profile Self administered monthly subcutaneous injections.
• Does the use of the technology address any particular unmet need of the patient population?	A significant number of patients are not able to tolerate the currently available preventive medications or are not able to take it because of contra-indications. The new treatment would be a valuable addition as iit has a novel mode of action and a very low side effect profile.
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 trials have shown the side effect profile to be similar to placebo. This would improve compliance .
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Many patients in the clinical trials were patient naïve. We do not feel this treatment will be used as first line treatment, considering the cost may not be as low as the currently available treatments.

• If not, how could the results be extrapolated to the UK setting?	Those refractory to treatment could be offered the treatment following failure of first line drugs.
• What, in your view, are the most important outcomes, and were they measured in the trials?	-Reduction in frequency and severity of headache (50% in episodic and 30% in chronic) -Improvement in quality of life as measured by validated tools like HIT6, MIDAS, EQ5D Both phase III trials (Strive and Arise) show 50% improvement to be around 43-50% based on migraine days. There is no comment on reduction in severity and duration of an attack. Both studies report improvement in the quality of life scores.Preliminary results from open-label extension study (unpublished) are encouraging. The studies do not comment on the difference in outcome in those with two or less than two preventive treatment prior to enrolment in the study.The study excludes patients with medication overuse and in real life nearly two third of patients with chronic migraine have co-existing medication overuse.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials	There is no real life data available

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA260]?	There are many real life studies published for OnabotulinumtoxinA since the double-blind placebo controlled study (PREEMPT) in 2010. These include: Khalil et al J Headache Pain 2014;15:54, Ahmed et al Springerplus 2015;4: 589, Negro et al Springerplus 2015;4: 826, Cernuda-Morollon E et al Cephalalgia 2015;35:864-68, Negro et al J Headache Pain 2016;17:1, Blumenfield et al Compel Study J Headache Pain 2018;19:13, Matharu et al Cephalalgia 2017;37:1384-97
21. How do data on real-world experience compare with the trial data?	The product is not marketed so no real life data is available for Erenumab
Equality	
22a. Are there any potential equality issues that should be	Migraine is more common in women (22% versus 8% in men)

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	No
Topic-specific questions	
23. Where in the treatment pathway for prophylaxis of migraine is erenumab likely to be used in clinical practice? After how many treatments?	Assuming the cost of the technology being higher than the currently available oral prophylaxis and similar to Onabotulinumtoxin treatment, we feel: -Patients with episodic migraine and high frequency episodic migraine (10-14 days) be given the treatment following failure of at least three preventive treatments unless there are tolerability issues and contra-indications to the use of the existing treatments. -Patients with Chronic Migraine are given Erenumab following failure of three conventional preventive treatments and may be used ahead or after onabotulinumtoxin depending on the QALY assessment. -All patients must be addressed for medication overuse problem -The assessment and suitability of the treatment be done by a headache specialist either in primary or secondary care.

24. Does the treatment pathway differ according to whether people have chronic or episodic migraine?	Onabotulinumtoxin treatment involves attendance to the hospital with treatment administration by a specialist nurse or doctor and involves 31 intramuscular injections. Erenumab will not require hospital visit as it is self administered and involves a single subcutaneous injection every month.
25. Would you expect any benefit with erenumab to be similar for people with chronic migraine and people with episodic migraine?	We anticipate the benefit being high and cost-effective in chronic migraine as the condition is associated with more disability
26. How long would you expect patients to receive treatment with erenumab for?	3 months initially following which it should be stopped if there is no response Those that respond be given treatment for one year following which gradual withdrawal is attempted.
27. Would you expect the benefit of treatment with erenumab to continue after treatment has been stopped, and if so, for how long?	Uncertain as there is no real life data available.

28. If patients experience migraine again once treatment has been stopped, would re-treatment be considered?	Yes if it was effective However, this will require clear guidelines on who should be recommenced and for how long.

Key messages

29. In up to 5 bullet points, please summarise the key messages of your submission.

- This is the first ever migraine specific treatment for prevention
- The side effect profile of the drug is much better than currently available treatments
- The treatment is self-administered hence reducing cost to patient and healthcare provider
- Novel mode of action
- Better compliance than existing treatment because of better tolerability.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Erenumab for preventing migraine [ID1188]

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	**Primary Care Neurology Society**

3. Job title or position	**Clinical Lead East Kent Headache Service**
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 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).	Primary Care and Community based multidisciplinary organisation involved in education, production of clinic tools and a platform for exchange ideas and networking.
5b. 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,	Migraine prevention. There may be potential to intervene in Episodic Migraine and prevent progression to chronic migraine but as yet no supporting evidence

or prevent progression or disability.)	
7. 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.)	50% of subjects in the active arm achieving at least a 50% reduction of migraine days is regulatory milestone however improvement in quality of life is the patient clinical goal but it is hard to define (quite individual) and measure. There are suggested tools – MIDAS and HIT.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Particularly because existing systemic drug options struggle to achieve the 50% reduction in 50% of subject response and often cause significant side effects
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Migraine is mostly treated by patients in the community with no consultation with health professionals. If approximately 15% of the population have migraine, GPs normally only have 1-3% of their lists having a migraine diagnosis. Specialist Headache services are not uniformly available in England and Wales. A minority of hospitals have a Headache Clinic and most headache sufferers are seen by general neurologists, physicians or others. There are increasing numbers of Community based clinics. Only a small proportion of migraneurs are ever referred to a Specialist clinic by their GP. Most of those seeing a GP will not enjoy management as set out in the NICE guidance which is better followed by specialist services. Most specialists will offer Botox with its specific NICE TAG conditions.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	IHS Classification original 1988, several updates now ICHD 3 2018 SIGN NICE Headache Guidance– several updates since 2012 but last opportunity not taken up as no significant changes to incorporate NICE TAG re Botox British Association for the Study of Headache Migraine in Primary Care Advisory Group
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Reasonably defined re NICE for Drs and nurses but many areas require more evidence. Generally for Episodic Migraine management focussed of rescue (<1 attack a week or 2 days a week affected) whereas

state if your experience is from outside England.)	prevention the key in high frequency episodic and chronic migraine (rescue still used for exacerbations but great care re analgesic overuse) Many other professionals see and advise migraneurs and their opinions may differ – physical therapy, maxillofacial etc
• What impact would the technology have on the current pathway of care?	Not known with current evidence
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This depends on the detail in the evidence. Not used currently. The current key study suggests 50% reduction in 50% of patients starting with a mean of 4 days migraine, albeit with very few side effects. There is less convincing evidence that those who have failed several preventative drugs still have a similar response and reports of 5-10% having a dramatic response to the first injections. Predicted cost in the US $15-20,000 per year. Botox Pre-empt data started with a mean of migraine days of 19 and achieved a reduction of 8.2 days active versus 6.2 placebo. It appears that in a higher burden group, who had to failed to respond to 3 preventative drugs (given at correct dose and for a long enough trial) there is a 2 day advantage over

	placebo. The cost of a new patient being commenced and having 3 additional Botox injection series (4 injection visits in all) is £2282 per year in East Kent. Propranolol achieved a 50% reduction in 42% of patients as the active comparator in the registration study for Topiramate and at minimal cost. It appears that the outcome may be similar to existing options but with less side effects (apart from similar side effects to Botox). The key is if there is better response in refractory patients and identifying the rapid responders and when to stop in less impressive responders. I see no alternative to more evidence required. Direct comparator studies where non response is defined and non responders randomly allocated to treatment groups and efforts made to identify characteristics predictive of rapid response.
• How does healthcare resource use differ between the technology and current care?	Not known. First injection possibly to be supervised but there is no real training requirement needed and certainly secondary and tertiary centres not needed. Key is assessing outcome and ongoing treatment use, likely be face to face assessment and be subject to guidance but not with a large training need.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Optimally general practice but cost is likely to mean Specialist Centres all ie those in primary care as well as intermediate care and hospital based.
• What investment is needed to introduce the technology? (For	Very little. Challenge is the patchy provision of services nationally.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Possibly in refractory patients and those who have immediate responses.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Probably 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?	Possibly in refractory patients there may be responders.

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 than Botox but once trained Botox is a 5-minute simple procedure. There may be difficulty if rules are imposed re need for follow up. Attendance in clinic and observation after 1st and/ or 2nd etc injection may require resource not needed for some of the systemic/tablet options
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	With the proposed cost I think there inevitably will be rules. Failure of Botox (in itself, Botox has rules re failure of 3 preventative drugs) Rules around minimum starting migraine days and minimum reductions to merit ongoing use. The current evidence may not represent the migraine group that needs this option most (Chronic Migraine refractory to Botox)

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?	Reduction of work, chore and social activity days lost and days affected are often minimised in QALY calculations
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?	Potentially yes but I am not sure the current evidence supports the notion compared to existing options
• Is the technology a 'step-change' in the management of the condition?	Potential yes but specific evidence base needed to demonstrate this
• Does the use of the technology address any	Potential yes but specific evidence base needed to demonstrate this

particular unmet need of the patient population?	
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 low side effect reporting is of interest. MABs used in other conditions do have flu like symptoms and malaise reported that appear reduced with Erenumab
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No
• If not, how could the results be extrapolated to the UK setting?	No
• What, in your view, are the most important outcomes, and were they measured in the trials?	Academically the 50% reduction re license. But this does not assist clinical practice.
• If surrogate outcome measures were used, do they adequately predict	No

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA260]?	N/A
21. How do data on real-world experience compare with the trial data?	Need to be high quality but will be key

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23. Where in the treatment pathway for prophylaxis of migraine is erenumab likely to be used in clinical practice? After how many treatments?	After Botox unless cost is much lower than predicted

24. Does the treatment pathway differ according to whether people have chronic or episodic migraine?	Yes. Triptans are mostly affective with NSAIDs and prokinetics in EM. If refractory to rescue, there is a role for prevention – but other tablet options eg supplements, candesartan, propranolol, topiramate would be first line. Its hard to see how Erenumab would be cost effective in EM.
25. Would you expect any benefit with erenumab to be similar for people with chronic migraine and people with episodic migraine?	Very hard question. Those with lower numbers of migraine days tend to less refractory. CM is usually a mix of migraine and featureless headache days ie 8+ migraine within 15+ of some sort of headache per month. Suspicion is that the migraine drives disability and treatment response – this means at 8 migraine plus 8 tension type headache may not be equivalent to 16 migraine but both appear similar within CM.
26. How long would you expect patients to receive treatment with erenumab for?	An option is to use once. If responder, it may be that the pattern has reset and no need for more or that ongoing use is required to maintain. Rules need to be created. Different rules re number of injections allowed failure to reach responder status, otherwise have to stop Refractory to other treatment patients may require development of other rules.
27. Would you expect the benefit of treatment with erenumab to continue after	Not known.

treatment has been stopped, and if so, for how long?	Impression is that generally reduction of migraine less likely to reset the migraine pattern than a complete response.
28. If patients experience migraine again once treatment has been stopped, would re-treatment be considered?	If a responder yes.
Key messages	
29. In up to 5 bullet points, please summarise the key messages of your submission. • Current data has headline efficacy rates that can be seen as similar to existing preventative options • Side effect profile appears to be better than systemic options and similar to Botox • Likely position in treatment pathway is after Botox • Likely setting specialist headache clinics • More targetted research is needed	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

migraine - erenumab [ID1188]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation: The National Hospital for Neurology and Neurosurgery

Please indicate your position in the organisation:

- Department of Health or Welsh Government in general?
- commissioning services for the Department of Health or Welsh Government specific to the condition for which NICE is considering this technology?
- responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)?
- **a specialist in the treatment of people with the condition for which NICE is considering this technology?**
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- other (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

migraine - erenumab [ID1188]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Migraine is the commonest neurological disorder and affects approximately 1 in 8 people. Preventative treatment is appropriate for those suffering frequent and disabling headaches, with the general consensus being to consider preventative treatment when headaches occur more than 4 days a month. The most commonly used preventatives are oral medications, and there are guidelines available (such as from NICE Clinical Guidance CG150). For chronic migraine (15 or more days per month for more than 3 months) which has been refractory to 3 or more oral preventatives and medication overuse has been addressed, Botox is also used.

The principal advantages of current therapies over erenumab include:

1) Affordability. Many oral agents are off-patent and available generically. Erenumab is likely to be very costly
2) Fine control over dosage, with the ability to titrate according to response.
3) The potential to use a single agent to treat comorbid medical problems (e.g. beta-blockers or candesartan to help with both blood pressure and migraine).
4) In the case of Botox, the dosage frequency is three monthly, rather than monthly.

The disadvantages of current treatments compared with erenumab include:

1) Tolerability. Many oral agents in particular can result in significant side-effects which may be dose-limiting or necessitate withdrawal, whereas erenumab appears to be very well tolerated in the studies.
2) Oral preventatives require daily administration, often with multiple doses per day. Erenumab is given by injection once per month.
3) Botox requires administration in a specialist neurology or headache clinic setting, whereas erenumab, as a single subcutaneous injection, can be administered in primary care or potentially by the patient themselves, similar to insulin. The out of hospital administration potentially freeing up clinical capacity and easing patient burden of hospital visits
4) Lack of good evidence base for several of the preventive treatments commonly used. In fact, Nice Guidance CG150 was only able to recommend a few preventive treatments (Topiramate, Propranolol, Amitriptyline, Riboflavin)

To what extent and in which population(s) is the technology being used in your local health economy?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

migraine - erenumab [ID1188]

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

Erenumab is not currently licensed or available in the UK.

Given the likely cost of treatment (not yet confirmed), it is highly unlikely that erenumab will be cost-effective in episodic migraine (low frequency episodic migraine or high frequency episodic migraine). Its utility in the NHS is likely to be limited to chronic migraine

Erenumab may have a role similar to that currently occupied by Botox, i.e. for use in patients with a high headache burden who have failed to respond to several previous agents. Erenumab should ultimately be easier to administer and monitor than Botox, but the overall cost will dictate whether the treatment is considered as an alternative to Botox or used in those cases where Botox has been unhelpful. It is likely that the cost-effectiveness studies will suggest that Erenumab should be administered after failure to respond to Botox

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

Given there are limited randomised trial/evidence-based treatments for chronic migraine, Erenumab would be a potentially useful addition. The infrequent dosing, favourable side effect profile and unique mechanism on action will all appeal to patients. Erenumab may enable us to offer tolerable treatment to patients who have failed or been unable to tolerate previous treatments. Clinical studies currently suggest that 50% of patients may experience useful improvement, so this would offer a potentially attractive option for those patients who have not benefited from (or been able to tolerate) currently available treatments.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

It would probably be best to initiate the treatment in a secondary care setting, possibly in specialist clinics, given the novel nature of drug and lack of long term follow up (combined with issues of other monoclonal antibodies used in neurology) . Although ongoing monitoring of response would probably be similar to existing treatments, the administration of erenumab would be less resource-intensive than

required by Botox (which requires specialist injection of head and neck muscles).It may be inappropriate to expect primary care to do the monitoring hence shared-protocol will likely need to be developed

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

It is very difficult to make any useful forecast without knowing the price of the medication, though it is reasonable to assume, given the drug is a monoclonal antibody, that it will be costly. I would assume that the likely cost of erenumab would make it impractical to use in patients with episodic migraine but this would require modelling. I am not aware of any currently available data on the clinical outcomes following cessation of erenumab treatment and whether the requirement for treatment is likely to be ongoing or for a defined period – some assumptions about the likely duration of treatment will also guide estimate of budget impact.

Other issues may have impact on budget – may allow reduction in acute (triptan) use, may require less intensive follow up when established as compared to Botox, free up clinical setting as administered at home, and there may be potential for shared care protocols with primary care

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

This will depend in part on how the treatment is deployed. If used in episodic migraine, then there will be major cost implications regards expense of drug, potentially very large group of patients who would be suitable to use it and current lack of capacity in neurology. For patients with a high headache burden (chronic migraine) currently being treated, if erenumab were used instead of Botox, it may lessen demand for the latter. If used in those patients who have failed Botox (and hence would not be attending a Botox clinic anyway), there may not be much impact on existing clinic workload. Given the likely cost of treatment, it is unlikely that the potential advantages of Erenumab would put it above Botox in the treatment pathway

It is possible that the availability of a new treatment may result in the referral of people who had not otherwise been utilising secondary care resources, though this is perhaps less likely for patients with higher headache burdens as they are more likely to be “in the system” already.

Given treatment may lessen number of hospital visits patient would need to attend as compared to Botox this may be advantage as often travel can worsen migraine severity and also the day to day variation in symptoms can make it difficult to attend clinics.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

migraine - erenumab [ID1188]

Would there be any need for education and training of NHS staff?

Yes. If, as seems likely, the treatment would be initiated and monitored in secondary care but administered in primary care, then staff will need to be educated about the likely outcomes of treatment, as well as side-effects, though the latter do not appear to be a significant problem. As a simple subcutaneous injection, the administration will be no different to, say, the current requirements with insulin or low-molecular-weight heparin.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

I do not foresee any equality implications, although it is worth pointing out that women are three times more likely than men to be affected by migraine in general.

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology?

Chronic migraine still hugely under-recognised in terms of disability

A large number of headache experts in UK have conflicts of interest as they have been actively working with pharma developing CGRP monoclonal antibodies. Imperative that the experts on the appraisal committee include headache experts who don't have relevant conflicts of interest

NICE National Institute for Health and Care Excellence

Patient expert statement

Erenumab for preventing migraine [ID1188]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

- 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	**Sarah Broderick**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Migraine Trust
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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 didn't submit one, I don't 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. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Migraine has a massive impact on my life, even though I am lucky in that I do not suffer with vomiting with my migraines. When I am experiencing symptoms, it affects my vision, causes dizziness, slows my processing and affects my memory and speech. All of this affects my day to day life at home and my work as a teacher. I can struggle to keep my home clean and tidy. I often feel tired even on migraine free days due to the medications which adds to the problem. I can't always play with my son, running about in the garden, as I am frightened of falling due to dizziness. He understands, but I feel guilty that I'm not there for him. I work part-time and am unable to return to full time hours as I fear I would have unacceptable levels of absence if I did. I have already had an absence review meeting and it will not take many more days illness off work to trigger the next phase where I could be issued a warning. I rest on my off days to enable me to cope with working just two days. There are times at work when I know I cannot process changes quickly.

	This can make it difficult to adapt within the classroom and has an impact on my ability as a teacher which has been noticed during classroom observations. I go into work when I am not at my best, knowing it will affect my but also knowing that if I have a sick day then I feel I am letting everyone down and that there will be the further risk of a warning on my record. You can't win! How migraine affects you is not understood by everyone either – they just think it's a bad headache – but it can affect me for a few days after an attack too. I take each day as it comes because of all this and sometimes need to cancel plans with friends as I do not feel well enough to go out. I see how I am before suggesting a short trip out to the park, for example, so as not to disappoint.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Medication currently on the NHS has not been developed specifically for migraines. I have tried a few medications, but none work very well for me or I did not tolerate them well. The medication I am currently taking has been developed for epilepsy and the list of possible side effects is immense. I suffer with a few of these, but they are better than having migraines in the short term, although I have worries about being on it because of the possible long term effects.
10. Is there an unmet need for patients with this condition?	There is definitely an unmet need for patients with migraines in my opinion. We need a medication developed for this condition available to patients.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	This medication is designed for migraines and specifically targets them. In my case, it was very successful and completely removed the auras I was getting which were particularly troublesome. I had an injection every month which meant I didn't even need to take a tablet. No worrying about taking medication after food (a real problem if you feel sick or are a patient who is sick with migraines and so doesn't want to eat) or at particular times of day. I can take a tablet and instantly forget if I have taken it too, so I find myself constantly counting tablets and calculating to see if I have or have not taken medication to prevent taking too much or too little. The injection was great for me – relief from migraines and no tablet regime to worry about. I had gone from being a chronic migraine sufferer to being migraine free. I noticed no side effects

	which is so much better than the other treatments I have tried. It changed my life whilst I was on it.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Although I have a slight problem with needles, I am fine if I can see the needle. This is why I couldn't go for the Botox treatment! Patients will need to be shown how to self-inject though.
Patient population	
13. 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.	People like me, who have found that other treatments are not suitable or don't work and who are chronic sufferers. People in rural areas with limited access to doctors. Self-injecting monthly means you are not having to keep going back for treatments and medications.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Migraine can be classed as a disability under the Equality Act 2010 Women more likely to be affected by migraine and therefore women who already face inequality in the work place are further disadvantaged by migraine.

Other issues	
15. Are there any other issues that you would like the committee to consider?	In my experience, it is hard to see the specialist at the headache clinic. Routine 3 month appointments (ie going back to see how treatments are going) can take 6 – 12 months to be given a date. This means that there is not the access to these clinics. Therefore I would like to see how this medication would be available for the patients that really need it, like myself.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- First treatment specifically developed to prevent migraine and helps with chronic migraines
- Injections once a month with little other medication needed
- I had no side effects!
- It changed my life for the better when I was on it
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Erenumab for preventing migraine [ID1188]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- 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	**Wendy Thomas**
2. Are you (please tick all that apply):	**x**☐ a patient with the condition? **x**☐ a carer of a patient with the condition? x☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	The Migraine Trust
4. Did your nominating organisation submit a submission?	**x**☐ yes, they did ☐ no, they didn't ☐ I don't know
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)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't 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. How did you gather the information included in your statement? (please tick all that apply)	x☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The condition can have a profound impact on your quality of life including disabling symptoms and inability to make plans confidently. It is distressing to see other family members trying to manage this condition with limited success.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Most patients have limited success with current treatments. In addition there are insufficient specialists and clinics around the country for such a common disabling health condition.
10. Is there an unmet need for patients with this condition?	Definitely …a large unmet need.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	This is the first preventive medicine specifically developed for migraine has rapid onset action. It has a good side effect profile.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Patients are concerned that this will not be widely available.
Patient population	
13. Are there any groups of patients who might benefit	People who have more frequent attacks including those with chronic migraine may benefit most.

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Migraine can be a disability under the Equality Act and three times more women as men suffer from the condition.**
Other issues	
15. Are there any other issues that you would like the committee to consider?	No
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • Migraine is common and disabling and needs this new treatment. • It is the first preventive specially developed for migraine	

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-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Erenumab for preventing migraine

Produced by

Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout 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 HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Sabine Grimm, Xavier Pouwels, Willem Witlox, Svenja Petersohn, Nigel Armstrong and Dhwani Shah acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Shelley de Kock critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse events
BASH	British Association for the Study of Headache
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CGRP	calcitonin gene-related peptide
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effect
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
EQ-5D-5L	European Quality of Life-5 Dimensions, five-level scale
ERG	Evidence Review Group
FDA	Food and Drug Administration
HFEM	High-frequency episodic migraine
HIT-6	Headache impact test
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
HUI	Health utilities index
ITC	Indirect treatment comparison
ICER	Incremental cost effectiveness ratio
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
ITT	Intention to treat
IV	Intravenous
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LFEM	Low-frequency episodic migraine
LSM	Least square method
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
Mg	Milligram
MHD	Monthly headache days
MHRA	Medicines and Healthcare Products Regulatory Agency
MIDAS	Migraine disability assessment
MMD	Monthly migraine days
MPFID	Migraine physical function impact diary
MSQ	Migraine-specific quality of life questionnaire
NA	Not applicable
NHS	National Health Service
NHWS	National health and wellness survey

NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
ONS	Office of National Statistics
OR	Odds ratio
ORR	Overall response rate
PAS	Patient access scheme
PRESS	Peer review of electronic search strategies
PRO	Patient-reported outcome
PROMIS	Patient-reported outcomes measurement information system
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q4W	Every four weeks
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse events
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-6D	Short-form six-dimension
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SNRI	Serotonin and norepinephrine reuptake inhibitor
SPC	Summary of product characteristics
STA	Single technology appraisal
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
UK	United Kingdom
VAS	Visual analogue scale
WHO	World Health Organisation
WPAI	Work productivity and activity impairment

Table of Contents

Table of Tables

Table of Figures

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the NICE scope is people with migraine. Erenumab has received marketing authorisation from the European Medicines Agency (EMA) for the prophylaxis of migraine in adults who have at least four migraine days per month. However, the population in the company's submission represents a subset both of the population in the NICE scope and in the marketing authorisation. The targeted population is adult patients with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed. The population addressed is likely to reflect the expected use of erenumab in the NHS as it targets those with the highest unmet need. Furthermore, erenumab would not be expected to be used in treatment-naïve patients due to the low cost of oral prophylactics. The submission relies, primarily, on four randomised, placebo-controlled trials of erenumab, of which three were conducted in patients with episodic migraine and one in patients with chronic migraine. For all four trials, the data used in the submission were derived from *post-hoc* subgroup analyses of patients for whom ≥3 prior prophylactic treatment categories had failed.

The intervention (erenumab) is in line with the scope. The recommended dosage is 70mg every four weeks administered as a subcutaneous injection using a pre-filled pen for self-injection, although some patients may benefit from a dosage of 140mg every four weeks (Q4W), which is administered as two consecutive injections of 70mg each. The company's model assumed that 50% of patients would receive 70mg and 50% of patients 140mg. However, logically, if not all patients would receive the same dose then there must be variation in those patients such that some would benefit more from one dose than another. This would imply two different populations but the company did not explicitly differentiate any such populations and neither were such populations described in the scope. Therefore, it follows that both doses are indicated for the same population and therefore should be considered as comparators to each other. The implications of this are discussed in the economic modelling sections of this report.

The description of comparators in the NICE scope is: "Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies". For the main comparator, best supportive care (BSC), the company considered the placebo arms of the main erenumab trials to be representative of BSC and provided full details of concomitant treatment. No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus BSC. Although these comparators are appropriate for the patients addressed in the company's submission (for whom ≥3 prior prophylactic treatment categories had failed), any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s).

Relevant outcomes were described in the submission, although it is noted that the double-blind phases of the included trials are only up to 24 weeks. Data from open label phases of the trials are available up to 52 weeks but the effectiveness of erenumab as a long-term prophylaxis of migraine requires extrapolation from the data available.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company's submission (CS) included four key erenumab studies. Study 295 was the only erenumab study conducted in patients with chronic migraine. Three studies (STRIVE, ARISE and LIBERTY) were conducted in patients with episodic migraine. Across the four trials, a total of 2,445 patients were included (full intention-to-treat [ITT] population). Of these only 515 are directly relevant to the decision

problem as they had failed ≥3 prior prophylactic treatments. All erenumab trials were randomised, double-blind, placebo-controlled, parallel-group studies and all trials had open-label or active treatment extensions. Double-blind phases were either 12 or 24 weeks in duration. Eligible patients were adults, defined as 18 to 65 in all trials. The trials were international and, with the exception of the ARISE trial, all had a small number of UK sites. Overall, [redacted] patients from the UK were included across the four trials. Although all trials compared erenumab to placebo, dosages varied (70mg and/or 140mg). All outcomes related to change in the number of migraine days as a primary outcome but this was measured differently and at different time points across the trials.

In Study 295 (chronic migraine) the optimised population (≥3 prior prophylactic treatments have failed) had statistically significantly better outcomes in the erenumab 70mg and 140mg groups than in the placebo group. More specifically, at week 12 patients experienced approximately two and a half fewer migraine days whilst taking erenumab 70mg and four fewer whilst taking erenumab 140mg than on placebo. In total, 34.8% of patients taking 70mg of erenumab and 38.5% of patients taking 140mg erenumab achieved a ≥50% reduction in monthly migraine days (MMDs) from baseline, compared to 15.3% of patients on placebo. In studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. With the exception of change in MMDs in the LIBERTY trial, these effects were statistically significant. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed for any of the outcomes assessed.

Across all four trials, the vast majority of adverse events experienced by patients in the erenumab treatment arms were of mild or moderate severity and very low numbers of patients experienced any serious adverse events.

In the absence of direct evidence comparing erenumab to botulinum toxin, the company conducted three indirect treatments comparisons (ITCs) using erenumab data from Study 295 and botulinum toxin data from PREEMPT. In the optimised population (≥3 prior prophylactic treatments have failed) there was no significant difference between erenumab 70mg and botulinum toxin for ≥50% responder rate (based on monthly headache days) with an OR = [redacted]), this result was similar when using the full trial population (OR [redacted]). There were also no significant differences between erenumab 140mg and botulinum toxin in either the optimised population (OR [redacted]) or full trial populations (OR 1.19, 95% CI 0.74 to 1.92). The indirect comparison results also showed no significant differences between treatments when the outcome of ≥50% responder rate was calculated from monthly migraine days and monthly headache days (MHDs).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company conducted a systematic review to identify studies reporting the efficacy and safety of erenumab and botulinum toxin (as the only active comparator) for the prophylaxis of migraine in adults. The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches. A wide range of databases were searched, and additional searches of conference proceedings, HTA websites and a trials register were conducted. Relevant systematic literature reviews (SLRs) and

network meta-analyses (NMAs) identified through database and grey literature searches were also reference checked. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.

The ERG notes that the evidence for erenumab is based on four international RCTs investigating patient-relevant outcomes. However, only one trial was conducted in patients with chronic migraine and the number of trial participants for whom ≥3 prior prophylactic treatments had failed is relatively low (approximately 20% of the total studied population). Furthermore, three of the four studies had a double-blind phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was mean monthly migraine days. It is certainly inadequate to show the effect on a condition that would be expected to last far beyond this period, thus the long-term effectiveness of erenumab treatment remains unknown.

The ERG also questions the use of the more stringent (≥50% reduction in MMDs vs. ≥30% reduction in MMDs) definition of responder; it seems unlikely that patients in this population would consider a reduction in their MMDs of between 30 and 49% to be not clinically meaningful. Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <30% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 20% reduction in MMDs which they considered to be beneficial.

Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented. This observation applies to both the whole study populations and to the subgroups which are relevant to this submission. There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

With respect to the definitions of chronic and episodic migraine used in the included studies, there is a potential population group (≥15 headache days per month of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population.

With respect to the ITC of erenumab versus botulinum toxin in the chronic migraine population, the ERG notes that there is a lack of evidence to support the company's assertion that the difference in the time point at which the primary outcome was measured, between the erenumab and botulinum toxin studies used in the ITC, would be likely to favour botulinum toxin. The effect of this difference is unclear. The ERG does not have any concerns about the methods or results of the ITC analyses.

1.4 Summary of cost effectiveness evidence submitted by the company

The company developed a decision-tree plus state transition model. The decision tree represented the assessment period. At the end of the assessment period, the probability of treatment response was estimated. Thereafter, responders and non-responders were modelled as separate health states in the post-assessment period using a state transition model. The costs and quality-adjusted life years (QALYs) associated with these health states were calculated conditional on the MMD frequency distributions.

Erenumab, as per marketing authorisation, is indicated for the treatment of all migraine patients who experience ≥4 MMDs. However, the company assessed the cost effectiveness of erenumab in adults with migraine with ≥4 MMDs for whom ≥3 prior prophylactic treatments have failed. This subgroup was further separated into three populations:

- Whole population base-case (patients with ≥4 MMDs)
- Episodic migraine population (patients with <15 MHDs and ≥4 to <15 MMDs)
- Chronic migraine population (patients with ≥15 MHDs and ≥8 MMDs)

The whole population was based on a weighted average of chronic and episodic migraine (66% and 34% respectively; based on market research from the UK). In addition, the high-frequency episodic migraine (HFEM) (8-14 MHDs) subgroup was considered.

As per the licensed posology, the recommended dose for erenumab (self-administered subcutaneously) is 70mg Q4W. However, some patients may benefit from the higher 140mg Q4W dosage (given as two injections of 70mg). The company therefore assumed in their base-case that 50% of patients started treatment on erenumab 140mg and the remaining 50% starting on erenumab 70mg (named blended dose). Erenumab was modelled to be used in combination with BSC.

BSC was defined as continued treatment with acute medication and healthcare resource use in line with the MMD frequency being experienced. The company stated that the placebo arms in Study 295, STRIVE, ARISE and LIBERTY can be considered as reasonably representative of BSC in the UK.

Botulinum toxin was modelled as a comparator for patients having chronic migraine for whom ≥3 prior prophylactic treatments have failed, in line with its recommended use.

The analysis took an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was 12 weeks with a 10-year time horizon and a half-cycle correction was applied.

Clinical parameters were mainly derived from the subgroup of patients for whom ≥3 prior treatments had failed in the pivotal trials (i.e. Study 295 for chronic migraine and ARISE, STRIVE and LIBERTY for episodic migraine). The main treatment effectiveness parameters were the proportion of responders, the MMD frequency distributions (at baseline, after response and after non-response), treatment discontinuation and general population mortality (no excess mortality was assumed). The treatment effectiveness was extrapolated by assuming that the transition probabilities (i.e. probability of treatment discontinuation) as well as the MMD frequency distributions would be constant over time.

Adverse events were accounted for in terms of treatment discontinuation, but the impact on costs and health-related quality of life (HRQoL) was not explicitly modelled.

For the company's base-case analysis, treatment independent utility values for each MMD frequency were estimated based on Study 295, STRIVE, and ARISE. Utility values were estimated using multilevel models depending on the MMD frequency distributions. For this purpose, Migraine-Specific Quality of life questionnaire (MSQ) mapped utility values were used. The company stated that the advantage of the MSQ over the European Quality of Life-5 Dimensions (EQ-5D) is its recall period of four weeks, which makes it more likely to capture the impact of experiencing migraine on quality of life than with the European Quality of Life-5 Dimensions, three-level scale (EQ-5D-3L), which was collected in LIBERTY.

The cost categories included in the model were treatment costs and costs of disease management. Treatment costs included drug costs, administration costs and initiation costs. Costs for disease management contained visits to the emergency department, general practitioner, nurse practitioner and neurologist, hospitalisations, migraine-specific medication (assumed to be represented by triptan use) and other medication (assumed to be represented by analgesics). Unit prices stemmed from the

manufacturer, the British National Formulary (BNF) 2017, the National Health Service (NHS) Tariff 2017 and the Personal Social Services Research Unit (PSSRU) 2017. Resource use data from the National health and wellness survey (NHWS) of 2017 and 2018 were used.

The company presented their base-case results separately for the whole migraine, the chronic migraine and the episodic migraine populations, within the subgroup of patients for whom ≥3 prior prophylactic treatments had failed; and separately for the blended dose (50% of patients receiving erenumab 70mg and 50% erenumab 140mg), the 140mg dose and the 70mg dose. The deterministic base-case cost effectiveness results of erenumab (with patient access scheme [PAS]) compared with BSC for the blended dose amount to an incremental cost effectiveness ratio (ICER) of £22,446 per QALY gained in the whole migraine population, to £18,893 per QALY gained in the chronic migraine population, and to £35,787 per QALY gained in the episodic migraine population.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

Cost effectiveness searches in the CS and in the response to clarification were well documented and easily reproducible and were carried out in line with the NICE guide to the methods of technology appraisal. Searches were reported for a wide range of databases and additional searches of conference proceedings, grey literature sources and reference checking were also reported.

The model structure proposed by the company did not fully capture natural progression of migraine. The ERG believes the justification provided by the company, not to model natural progression of migraine, is reasonable. However, the impact of this simplification is not fully known and hence increases the uncertainty regarding the cost effectiveness results. The exact definition of response to treatment might be another source of uncertainty. The company used a ≥50% reduction in baseline MMDs to define response, however, guidelines state that a ≥30% reduction can be clinically meaningful in patients with chronic migraine. For NICE TA260 on botulinum toxin in chronic migraine the committee stated that a 30% (MHD) response rate was the most clinically relevant and reasonable negative (due to no response) stopping rule on which to base its decision.

Patients with ≥15 MHDs and ≥4 to <8 MMDs were not included in either the pivotal trials on chronic migraine or those on episodic migraine. However, these patients are included in the definition of the overall model population (migraine patients with ≥4 MMDs). The company assumed that data from chronic and episodic patients will be applicable to this patient group. As no justification was provided for this assumption and the characteristics of the excluded population are unknown, the ERG finds this assumption not well-founded and considers the evidence for the cost effectiveness of erenumab in patients with ≥15 MHDs and ≥4 to <8 MMDs to be lacking.

The base-case presented by the company used a blended dose of erenumab 70mg and erenumab 140mg for the intervention arm, assuming a dose mix of 50% and 50%, respectively. The use of the blended dose and the 50%/50% distribution are not appropriately justified. Therefore, the ERG included erenumab 70mg and erenumab 140mg separately in its base-case analysis (instead of the blended dose).

In their base-case, the company used a 10-year time horizon for the cost effectiveness analysis of erenumab versus BSC and botulinum toxin, which is not in accordance with the NICE reference case. To adhere to the NICE reference case, the ERG extended the time horizon to a lifetime horizon in their ERG base-case analysis.

There is a lack of evidence related to the extrapolation of (comparative) treatment effectiveness. Although the company provided data from open-label extension studies, these studies did not provide comparative effectiveness data and the follow-up of these studies was also limited (52 weeks for chronic

migraine and 64 weeks for episodic migraine). After this period there was no evidence to inform the extrapolation of treatment effectiveness.

Regarding adverse events, the main concerns of the ERG relate to not explicitly modelling the impact of adverse event on costs and HRQoL.

Whilst treatment effectiveness was based on the population with ≥3 prior prophylactic treatments failed, utility values in the model were informed by the full trial population. According to the company, using the population with ≥3 prior prophylactic treatments failed, the number of patients available in the analysis would be significantly reduced, particularly for STRIVE and ARISE. In response to clarification question B14.b, the company implemented a scenario using utility values estimated from the population with ≥3 prior prophylactic treatments, but only for the whole migraine population (not separately for chronic and episodic migraine) due to small sample sizes. Since the company only provided this analysis in the whole migraine population, the ERG maintained the company's base-case analysis using the full trial population in the ERG base-case. This ensures consistency in the derivation of utilities and resource use, but results in inconsistencies between utility and effectiveness estimates.

Similarly, all estimates of resource use and costs were obtained from patient populations not specified to have ≥3 prior failures of prophylactic treatment. The company provided no evidence that prior treatment failure does not impact the costs of migraine treatment. Hence, the ERG cannot rule out that the estimates presented are subject to bias. Additionally, the company assumed sumatriptan injections to have the same price as oral sumatriptan, without appropriate justification.

The main concerns related to the results presented by the company were the lack of full incremental analyses separately including both the erenumab 140mg and 70mg doses, and the failure to include all important parameters in the probabilistic sensitivity analyses.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The searches in the CS were well presented and easily reproducible. A good range of databases and grey literature sources were searched and reference checking was also undertaken. Recognised study design filters were applied to all clinical effectiveness searches and searches for costs, resource use and HRQoL. Furthermore, relevant terms were added to the study design filters to increase sensitivity. Reference checking was also undertaken by the company in order to identify additional studies not retrieved by the main searches. The clinical evidence is based on four multinational RCTs in a relevant patient group. Relevant outcomes are assessed.

The model developed by the company provides granularity with respect to MMD frequency. By reproducing the patient distributions across MMDs for each treatment for multiple time-points, the economic model retains a strong faithfulness to the trial data and captures information that would otherwise be lost through grouping patients.

1.6.2 Weaknesses and areas of uncertainty

The evidence for erenumab in the submission population (adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed) is based on *post-hoc* subgroup analyses of data from four RCTs involving approximately 20% of the total studied population (n=515). Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented in the erenumab studies, both with respect to the whole study population and to the subgroup relevant to this submission. There is also a lack of

evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age. Given the definitions of chronic (≥15 headache days per month, of which ≥8 were migraine days) and episodic (≥4 and <15 migraine days per month with <15 headache days per month) migraine used in the included studies, there is a population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population.

There is a lack of long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, for either the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed or the wider population covered by the marketing authorisation.

The ERG is concerned that a separate search for adverse events (AEs) was not undertaken. In response to clarification the company reported that AEs were identified by screening the results of database searches. However, clinical effectiveness searches applied a study design filter to identify randomised clinical trials (RCTs) and guidance by the Centre for Reviews and Dissemination (CRD) recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure AEs that are long-term, rare or unanticipated are not missed. It is possible that some relevant evidence may not have been identified as a consequence of this.

There is no direct evidence to compare the effectiveness of erenumab to botulinum toxin.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has incorporated various adjustments to the company base-case. The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that erenumab 140mg was cost effective at willingness to pay thresholds higher than £16,905 and £38,[illegible] per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period respectively (erenumab 70mg was dominated). For the episodic population the probabilistic ERG base-case results indicated that erenumab 70mg would be cost effective at willingness to pay thresholds as higher than £10,047 per QALY gained, when assuming a constant treatment effect over time (erenumab 140mg is dominated). When assuming treatment effect waning over a five-year period, this was [illegible]95,227 per QALY gained for erenumab 70mg (erenumab 140mg became cost effective at a willingness to pay threshold of £267,487 per QALY gained).

It should, however, be noted that the increased effectiveness (in terms of QALYs) of erenumab 70mg versus erenumab 140mg (when assuming constant treatment effectiveness), in the episodic migraine population, is inconsistent with the clinical effectiveness evidence presented in chapter 4 (Table 4.9). In Section 4.2.3, the ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed. Indeed, there is a numerically larger difference vs. placebo in change from baseline MMD for 140mg than for 70mg; only the former is statistically significant, and this only in the STRIVE trial. The favourable cost effectiveness of erenumab 70mg for the episodic population seems driven by the MMD frequency distribution for non-responders that is lower than for erenumab 140mg and BSC. It is questionable whether, given the above results for all patients, there would be an advantage for 70mg vs. 140mg for those patients who do not respond. It is also questionable whether extrapolating this benefit for non-responders (or any benefit in MMD frequency distribution for responders) is plausible given the changing response over time. This is to some extent mitigated in

the treatment waning scenarios given benefits in terms of MMD frequency distributions are decreased over time.

In conclusion, the cost effectiveness of erenumab in the chronic and episodic migraine populations largely depends on the assumptions related to the extrapolation of treatment effectiveness. Based on willingness to pay thresholds of £20,000 and £30,000 per QALY gained, erenumab 140mg and erenumab 70mg may be cost effective for the chronic and episodic migraine populations respectively if a constant treatment effect over time is assumed. However, as mentioned above, the plausibility of this assumption may be questionable. The estimated ICERs for erenumab increased above these willingness to pay thresholds of £20,000 and £30,000 per QALY gained if a treatment effect waning with a five-year period is assumed. Finally, it is unclear whether these results can be extrapolated to the population with ≥15 MHDs and ≥4 to <8 MMDs as no cost effectiveness evidence is provided for this population.

2. BACKGROUND

In this section, the Evidence Review Group (ERG) provides a review of the background evidence submitted by Novartis in support of erenumab, trade name Aimovig®, for the treatment of migraine. We outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken mainly from Chapter B.1 of the company's submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem.

The underlying health problem, addressed by this appraisal, is migraine. Migraine is a serious chronic neurological disorder It has been ranked as the third leading cause of disability in under 50's worldwide,[2] and classified among the most disabling illnesses by the World Health Organisation (WHO), comparable to dementia and active psychosis.[3] Migraine has a high burden of disease; attacks may last for up to 72 hours, with patients experiencing a variety of symptoms, including severe throbbing pain in the head, nausea and vomiting, dizziness, fever and visual disturbances.[4, 5]Around 25% of migraine suffers also experience an aura phase, which usually lasts for under an hour and is characterised by visual disturbances, numbness or weakness, slurred speech and sensitivity to light and sound.[1, 5] In addition to the clinical burden, migraine is the second most frequently cited cause of short-term absence from work, accounting for an estimated 43 million days of work lost each year in the UK.[1, 6]

Migraine is a spectrum disorder with migraine patients distributed across a continuum of monthly migraine and headache day frequencies.[7-10] Some guidelines, e.g. National Institute for Health and Care Excellence (NICE) and International Headache Society (IHS), classify patients as having either chronic or episodic migraine.[4, 11] The International Classification of Headache Disorders (ICHD-III) defines episodic migraine as 0–14 headache days per month, and chronic migraine as 15 or more headache days per month, of which eight or more have features of migraine (with or without aura).[4] Episodic migraine patients may be further categorised into low-frequency episodic migraine (LFEM) and high-frequency episodic migraine (HFEM); the CS (Section B.1.2.1) states that the latter group are "recognised as having a higher burden of migraine more in line with patients who would be classified as having chronic migraine."[1, 12] The CS (Section B.1.2.1) states that "these definitions are used to distinguish patients who have a higher frequency of headaches and migraines, and are likely to suffer more severely from their condition,"[1] but notes that they are not used in all guidelines, e.g. the British Association for the Study of Headache (BASH) guidelines do not clearly define separate chronic and episodic populations,[13] nor are they consistently applied in practice. Patients can experience changes in the frequency of their migraines and hence move between these classifications over time.[7, 14, 15] The decision problem (CS Section B.1.1) considers patients with ≥4 monthly migraine days for whom ≥3 prior prophylactic treatments have failed as a single population of patients across the full spectrum of monthly migraine frequencies, the "whole population base case",[1] but also addresses patients with chronic migraine and episodic migraine, as separate subgroups.[1]

The CS (Section B.1.2.1) states that: "Unpredictable variation in individual responses to prophylactic treatments, currently prescribed in the UK, results in around 30% of patients failing to respond to any particular prophylactic medication, and evidence suggests that up to 20% of migraine patients do not respond to more than three different prophylactic treatment options."[16, 17] Based on Novartis market research data (not provided in the CS): "It is estimated that around 100,000 migraine patients in England and Wales fall under this category, which represents a large and continued unmet clinical need."[1]

ERG comment:
The ERG checked the references cited by the company to support the statements made above and considered the company to have provided an appropriate description of the underlying health problem. However, the estimate of 100,000 migraine patients in England and Wales expected to be eligible for erenumab treatment (based on failure of ≥3 prior prophylactic treatments) was not adequately supported; this estimate was based on unpublished company data, which were not included in the CS. It should also be noted that the article cited in support of the statement that "around 30% of patients fail to respond to any particular prophylactic medication" concerns triptans only. The statement that "up to 20% of migraine patients do not respond to more than three different prophylactic treatment options" is solely supported in un-published Novartis survey of 40 neurologists; summary data provided suggest that the 20% estimate applies specifically to chronic migraine patients.[16]

2.2 Critique of company's overview of current service provision

The company states that the optimised positioning of erenumab within the care pathway is for the prophylaxis of migraine in patients for whom ≥3 prior prophylactic therapies have failed. This optimised positioning reflects the expected use of erenumab in the National Health Service (NHS), given the high burden of disease, the context of the availability of low-cost oral prophylactics as initial treatment options and the high unmet need for these patients; the only currently recommended treatment option at this point in the pathway is botulinum toxin, which is recommended only for chronic migraine patients who have not responded to ≥3 prior prophylactic treatments.

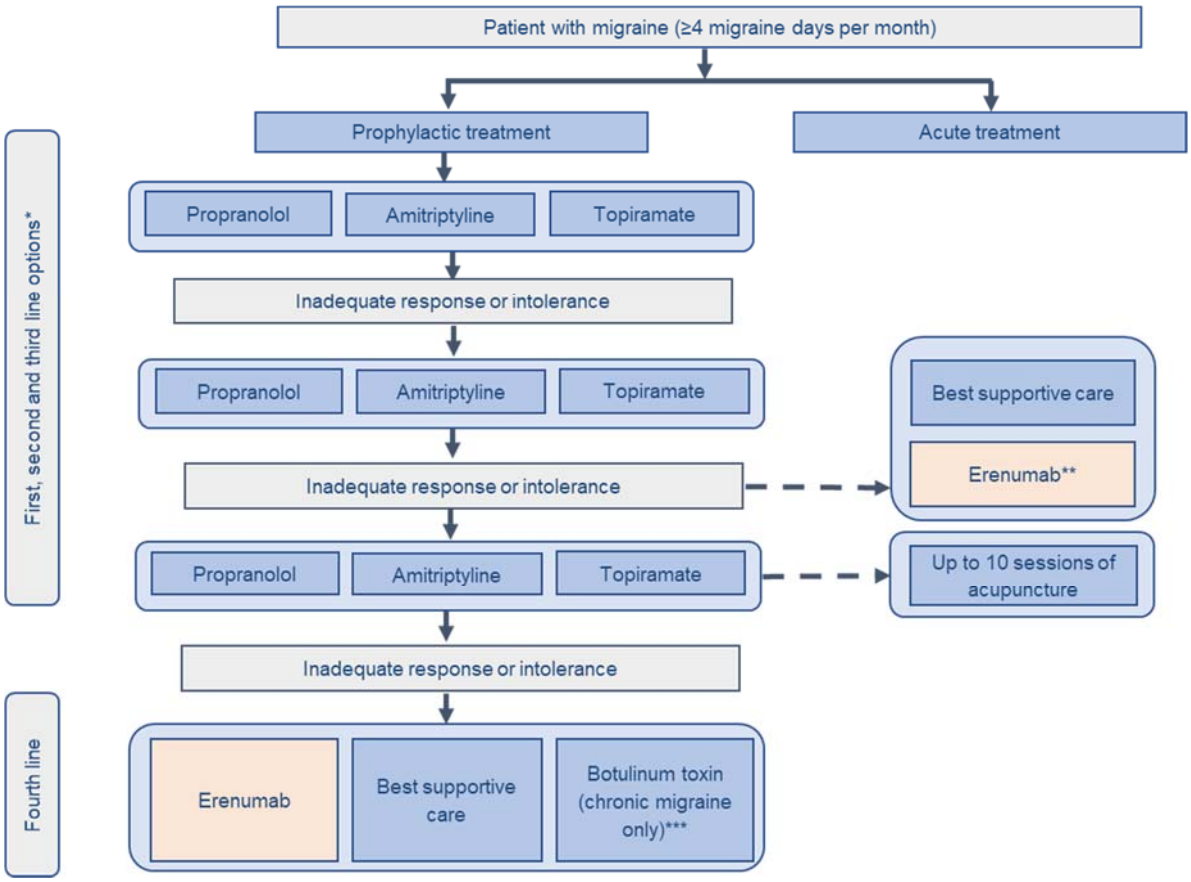
Current NICE clinical guidelines (CG150) recommend oral prophylactic treatments (typically topiramate, propranolol or amitriptyline) in the first instance for migraine patients.[11] However, these treatments are poorly tolerated, with patients frequently switching, discontinuing or delaying therapies due to a lack of efficacy or adverse events (AEs); reported adherence rates range from 17–20% after one year.[18-20] The CS (Appendix C: Health conditions and position of the technology in the treatment pathway) states that, once patients reach a point where ≥3 prophylactic therapies have failed for them, there are no further treatment options for the majority of patients and these patients therefore receive best supportive care (BSC). For some patients, contraindications, special warnings and precautions mean that this point is reached after fewer than three prophylactic therapies have failed. The exception is treatment with botulinum toxin, which is the only NICE-recommended therapy for the prophylaxis of migraine. However, botulinum toxin is only available for patients who have not responded to ≥3 prior prophylactic treatments and who meet the definition of chronic migraine specified in the NICE guidance (TA 260).[21]

ERG comment:

NICE clinical guidelines on diagnosis and management of headaches in over 12s (CG150)[11] include a statement about the possible use of acupuncture in relation to tension-type headache: "Consider a course of up to ten sessions of acupuncture over 5–8 weeks for the prophylactic treatment of chronic tension-type headache." No recommendations about acupuncture are included in the section of the guideline dealing with prophylactic treatment of migraine. Recommendations of the prophylactic treatment of migraine include the following statement on vitamin B2 supplementation: "Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people." The following special consideration is also noted, with respect to women and girls experiencing menstrual-related migraine: "For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) on the days migraine is expected."

Figure 2.1 shows the amended treatment pathway for patients with ≥4 migraine days per month, provided by the company in response to clarification question A14.[22] In the original proposed pathway, the company submission (CS) specified erenumab as fourth-line treatment.[1] The CS (Section B.1.2.2) states that the pathway was based on the NICE clinical pathway for the management of headaches in over 12s (CG150),[11] the section on migraine prophylaxis in BASH guidelines for the diagnosis and management of migraine, tension-type, cluster and medication-overuse headaches,[13] NICE TA260: botulinum toxin type A for the prevention of headaches in adults with chronic migraine,[21] and expert opinion obtained from an advisory board of eight UK neurologists.

Figure 2-1: Proposed treatment pathway for migraine patients with ≥4 migraine days per month



Source: Response to clarification question A14[22]

*If treatment at its maximum tolerated dose in the first-line is ineffective or poorly tolerated, the other two treatment classes may be considered for second-line. The same applies in moving from second-line to third-line treatment. No treatment should be tried twice in the pathway. **There may be clinical desire to use erenumab at an earlier point in the treatment pathway: in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions. This represents the minority of patients for whom ≥2 prior prophylactic treatments have failed. These patients would otherwise receive BSC in clinical practice. ***Botulinum toxin is recommended only for patients classified as having chronic migraine as per the NICE guidance for this therapy.[21]

ERG comment:

The company's description of the treatment pathway and options was based on existing NICE guidance and BASH guidelines, which is appropriate and relevant to the decision problem addressed by their submission. The pathway provided in the CS specified erenumab as fourth-line treatment. However, the proportion of patients in whom erenumab may be considered a treatment option before the fourth-line (e.g. due to contraindications for one or more oral prophylactic treatments) was unclear. The

company were asked to provide an amended pathway (Figure 2.1 above), with an indication of the proportions of patients who may be eligible for treatment with erenumab at each line. The company's response also stated that: "There may be clinical desire to use erenumab at an earlier point in the treatment pathway: in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions. The exact proportion of patients who would meet this definition is unclear. However, most patients will receive a third oral prophylactic therapy before they reach the point at which BSC is their only option, and therefore the population anticipated to receive treatment with erenumab at this point in the pathway is expected to be small."

The company were also asked to provide further detail on what BSC, in the UK, includes, to elaborate on why the company believes that placebo in the erenumab trials is a good proxy for BSC in the UK, and to provide details of concomitant medication received in the four main trials (Study 295, STRIVE, ARISE and LIBERTY). The company's response stated that:

"The only option for the majority of patients for whom ≥3 prophylactic treatments have failed is BSC, which consists of continued treatment with acute medication. The relevant NICE guideline (CG150), recommends combination therapy with an oral triptan and a non-steroidal anti-inflammatory drug (NSAID), or an oral triptan and paracetamol, as first-line acute treatment options for patients with migraine.[11] Similarly, the British Association for the Study of Headache (BASH) guidelines recommend a stepped management programme comprising NSAIDs, including aspirin and ibuprofen, and triptans as required.[13] Patients in the placebo arms of Study 295, STRIVE, ARISE and LIBERTY were prescribed any treatments deemed necessary to provide adequate supportive care for the duration of the studies (full details are provided in Appendix 1). The majority of patients used acute medications during these trials, with triptan-based migraine medications and non-opioid acute headache medications being the most frequent treatment categories used by patients across all arms of these trials. As these treatment categories align with the acute treatment options recommended in clinical guidelines, the placebo arms of these trials are considered to adequately reflect BSC in UK clinical practice. This is supported by the NICE appraisal for botulinum toxin for chronic migraine (TA260),[21] in which "standard management" (i.e. BSC) was accepted as an appropriate comparator, and was modelled based on the placebo arm of the PREEMPT trials which formed the clinical evidence base for the botulinum toxin appraisal. Similar, to the erenumab studies, patients in both the botulinum toxin and placebo arms were treated with rescue medications such as analgesics and triptans during attacks."

The ERG agrees that the placebo arms of the erenumab trials provide a reasonable proxy for BSC in the UK.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with migraine	Adults with migraine with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed. This represents an optimised use of erenumab in clinical practice. Specifically, this submission will address this decision problem by considering three populations: 1. Patients with ≥4 migraine days per month ["whole population base case"] 2. Patients defined as having chronic migraine (≥15 headache days a month of which at least eight are migraine) ["chronic migraine population"] 3. Patients defined as having episodic migraine (4–14 headache days per month) ["episodic migraine population"]	• Migraine is a spectrum disorder with patients distributed across a continuum of monthly migraine day frequencies; it is therefore appropriate to consider the population of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed as a whole • Some guidelines actively classify two populations of migraine (chronic and episodic) by frequency of monthly migraine or headache days,[4, 11] despite difficulties in distinguishing between these patients in practice.[23] It should be noted that these definitions are not universally represented in guidelines, and are of limited relevance in clinical practice. • The clinical trials for erenumab were also conducted in separate chronic and episodic populations in line with clinical trial guidelines, although the licence for erenumab does not distinguish between them as	The population addressed falls within the broader population specified by the scope and is likely to reflect the expected use of erenumab in the NHS. However, it does not fully reflect the final scope, and does not represent the whole population for which erenumab has received marketing authorisation from the EMA (prophylaxis of migraine in adults who have at least 4 migraine days per month when initiating treatment with erenumab).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			these trials showed efficacy in both populations and provided a simplified treatment algorithm • It was thus considered relevant to present evidence for the chronic and episodic migraine populations both together ("whole population base case") and separately	
Intervention	Erenumab	Erenumab 70mg or 140mg once every 4 weeks	NA – in line with NICE final scope	In line with scope
Comparator(s)	Established clinical management for migraine prophylaxis without erenumab	• BSC (for all three populations) • Botulinum toxin (for chronic migraine population only as per NICE recommendation[21])	• For the majority of patients for whom ≥3 prior prophylactic treatments have failed there are no further treatment options. Therefore, these patients would receive BSC • The exception to this is the availability of botulinum toxin, which is the only NICE-recommended therapy in the prophylaxis of migraine indication (and then for prophylaxis of chronic migraine only). Botulinum toxin is therefore a relevant comparator, though it is only recommended in a subset of patients who meet the definition of chronic migraine specified in the NICE guidance. Furthermore, it should	The specified comparators are appropriate for the 'optimised population' addressed in the company submission. However, any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			be noted that the availability of botulinum toxin for these patients is restricted, and must be performed by trained expert physicians with specialist equipment, with only [redacted]% of NHS trusts in the UK estimated to be performing the procedure.[24]	
Outcomes	The outcome measures to be considered include: • 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 • Adverse effects of treatment	Frequency of migraine days per month Change from baseline in mean monthly migraine days (MMDs) Proportion of patients with ≥50% reduction in mean MMDs from baseline Frequency of headache days per month Change from baseline in mean MHDs Severity of headaches and migraines Change from baseline in monthly average severity of migraine pain Change in pain interference with daily activities and migraine-specific impact from baseline, as measured by PROMIS (chronic migraine only)	NA – in line with NICE final scope	In line with scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• Health-related quality of life	Change from baseline in cumulative monthly headache hours Change from baseline in monthly acute migraine-specific treatment days Adverse effects of treatment Health-related quality of life (EQ-5D-5L, HIT-6, MSQ v2.1, MIDAS and WPAI)		
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.	• As per the NICE reference case, the cost-effectiveness of erenumab is expressed in terms of incremental costs per QALY, and costs have been considered from the perspective of the NHS and PSS. • A time horizon of ten years is employed in the base case analysis, as this was considered an appropriate duration over which to fully capture the costs and benefits of erenumab, and is consistent with the time horizon used when evaluating biologics for other chronic diseases.[25-27]	N/A – in line with NICE final scope	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• Costs will be considered from an NHS and PSS perspective.			
Subgroups to be considered/ exploratory analyses	Not specified in final scope	The decision problem includes a subgroup analysis of the episodic migraine population, that considers only those patients within this population who have high frequency episodic migraine (8–14 MHDs). In addition, the submission presents exploratory analyses that consider the use of erenumab at an earlier line of therapy in patients for whom ≥2 prior prophylactic treatments have failed, and who face BSC as their only remaining treatment option due to contraindications, special warnings or precautions precluding use of a third oral prophylactic. As per the analyses in the ≥3 prior treatments population, results of this exploratory analysis are presented for the whole population, the episodic migraine population and the chronic migraine population.	The justification for the subgroup and exploratory analyses included in the submission is as follows: • HFEM is a recognised subgroup of episodic migraine, who are considered to have a clinical burden similar to those classified as having chronic migraine. However, these patients are unable to access botulinum toxin in line with its licensed indication and NICE recommendation, and therefore face a particularly high unmet need • Subgroup analyses are also presented in patients for whom ≥2 prior prophylactic treatments have failed, and who face BSC as their only remaining treatment option due to contraindications, special warnings or precautions precluding use of a third oral prophylactic, following feedback from UK clinicians, which has indicated that there would be clinical desire to use erenumab	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
		Finally, analyses are presented in all three populations where all patients start treatment on the 140mg dose of erenumab. The base case models a 50/50 split between patients receiving the 140mg and 70mg dose on initiation, which represents an assumption in the absence of long-term clinical experience of erenumab dosing in UK NHS clinical practice.	at an earlier point in the treatment pathway • In the absence of long-term UK NHS clinical experience with erenumab, a conservative assumption, whereby 50% of patients would initiate treatment on erenumab 140mg, and the remainder on erenumab 70mg, is made in the base case analysis. However, the 140mg dose may be more appropriate for patients for whom ≥3 prior prophylactic treatments have failed, as there is a trend towards better efficacy with the 140mg dose in these more severe patients (see Section 4.2.3). Analyses in which all patients initiate treatment on erenumab 140mg are therefore also presented. Analyses in which all patients initiate treatment on erenumab 70mg are presented in Appendix Z for completeness	

Source: CS, Table 1, page 9
AE: adverse event; BSC: best supportive care; EQ-5D: EuroQol 5 dimensions; HFEM: high-frequency episodic migraine; HIT-6: Headache Impact Test; MHD: monthly headache day; MIDAS: Migraine Disability Assessment; MMD: monthly migraine day; MSQ-v2.1: Migraine-Specific Quality of Life Questionnaire Version 2.1; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PROMIS: Patient-Reported Outcomes Measurement Information System; PSS: Personal Social Services; QALY: quality-adjusted life year; WPAI: Work Productivity and Activity Impairment

3.1 Population

The population defined in the scope is people with migraine and the population in the submission is a subset of this population.

The submission focuses on adult patients with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed (CS, Section B.1.1).[1] The specification of patients with ≥4 migraine days per month is in line with the marketing authorisation from the European Medicines Agency (EMA), issued on 26 July 2018, for the "prophylaxis of migraine in adults who have at least 4 migraine days per month when initiating treatment with erenumab."[1] The CS (Section B.1.1) states that "The optimisation to patients for whom ≥3 prior prophylactic treatments have failed is relevant and appropriate in the context of clinical practice within the National Health Service (NHS); erenumab would not be expected to be used in treatment-naïve patients due to the low cost of oral prophylactics. As such, at this position in the pathway, erenumab targets patients facing the highest unmet need and a lack of treatment options."[1] The population in the submission is likely to reflect the expected use of erenumab in the NHS. However, it does not fully reflect the final scope, and does not represent the whole population for which erenumab has received marketing authorisation from the EMA.

The submission relies primarily, on four randomised, placebo-controlled trials of erenumab, of which three were conducted in patients with episodic migraine (STRIVE,[28] ARISE,[29] and LIBERTY[30]) and one, Study 295,[31] was conducted in patients with chronic migraine. For all four trials, the data used in the submission were derived from *post-hoc* subgroup analyses of patients for whom ≥3 prior prophylactic treatment categories had failed. With regard to the episodic migraine studies, the submission focuses on LIBERTY. The CS (Section B.2.6) states that: "the number of patients who had received ≥3 prior prophylactic treatments in STRIVE and ARISE was small (n=[redacted] and n=[redacted], [redacted]% and [redacted]% of the study populations, respectively). Analyses across all outcome measures in these subgroups are not therefore considered to be meaningful, and are presented in this section for completeness. LIBERTY provides more relevant clinical evidence in this subgroup as this was a study specifically designed to assess the efficacy and tolerability of erenumab in patients who have failed 2–4 previous migraine prophylactic treatments."[1]

The CS (Section B.2.12.2) reports that the trial populations included patients from [redacted] UK sites ([redacted] patients) in Study 295, [redacted] ([redacted] patients) in STRIVE and [redacted] ([redacted] patients) in LIBERTY,[1] however, it is unclear how many (if any) UK patients were included of patients for whom ≥3 prior prophylactic treatment categories had failed; the ARISE study had no UK sites. The CS (Section B.2.12.2) states that: "The study populations were deemed generalisable to the UK migraine population, as validated by expert clinicians at a UK advisory board,"[23] however, the cited report of this advisory board does not include any discussion of the generalisability of trials to the UK population.

Although migraine affects three times as many women as men,[32] and there is also some evidence that migraine prevalence may be lower in non-white populations,[33] both males and non-white populations appear to be under represented in the erenumab trials (See Tables 4.4 and 4.5 in Section 4.2.1 of this report for an overview of all baseline characteristics, for the relevant subgroup, in the four studies). There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

ERG comment:

The company were asked to provide clarification on whether erenumab is expected to be used in patients under 18 or over 65 years of age. The following response was provided:

"Erenumab is not expected to be used in patients under 18 years of age as the licence is for the prophylaxis of migraine in adults, classified as ≥18 years. Erenumab is expected to be used in patients over 65 years. Although this age group were not included in the clinical trials reported in the submission, the licence does not provide an upper age restriction. The Summary of Product Characteristics[34] states:

Aimovig has not been studied in elderly patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age.

However, as migraine most commonly affects people in their 30s–50s, it is anticipated that few patients over 65 years will be initiated on treatment in clinical practice."

3.2 Intervention

Erenumab is a monoclonal antibody calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is a pro-inflammatory vasodilating neuropeptide involved in migraine pathophysiology.[35] Erenumab binds to the CGRP receptor complex. It is designed to specifically inhibit CGRP biological activity through CGRP receptor signal transduction, irrespective of circulating CGRP levels. Therefore, the efficacy of erenumab is not affected by CGRP release or concentration. Binding to the receptor is competitive and can be reversible. By blocking the CGRP receptor, erenumab reduces the frequency and intensity of migraines experienced by patients.[1]

The intervention (erenumab) is in line with the scope. Regulatory approval by the EMA for the prophylaxis of migraine in adults who have at least four migraine days per month when initiating treatment with erenumab was granted on 26 July 2018. The recommended dosage is 70mg Q4W, administered as a subcutaneous injection using a pre-filled pen for self-injection, although some patients may benefit from a dosage of 140mg Q4W, which is administered as two consecutive injections of 70mg each.

ERG comment:

The company were asked to provide clarification on which patients are expected to benefit from the 140mg Q4W dose and how these patients can be identified before initiating treatment with erenumab. The following response was provided:

"The licence for erenumab does not indicate the specific patient population expected to benefit from the 140mg dose of erenumab. However, as discussed in Document B, Section B.2.6 of the CS, numerically superior clinical outcomes were observed for patients treated with erenumab 140mg compared to erenumab 70mg in the subgroup of patients for whom ≥3 prior treatments have failed. Additionally, there is no difference in the safety profiles of the 70mg and 140mg doses. The 140mg dose may therefore be most appropriate for the patient population for whom ≥3 prior treatments have failed: the optimised population considered in this submission. This is supported by feedback from six expert UK neurologists, who considered that starting patients on the 140mg dose may be the most efficient treatment approach for those patients with the greatest unmet need.[23] This patient population can be identified through their usage of prior prophylactic treatments, and it is estimated that overall 19% of patients classified as having chronic migraine and 10% of patients classified as having episodic migraine are in the category of patients for whom ≥3 prior treatments have failed (see Budget Impact Assessment document, Section 3.2)."

The ERG does not consider that this statement provides adequate clarification, since it implies that the whole of the optimised population considered in this submission are expected to benefit from the 140mg Q4W dose.

3.3 Comparators

The description of comparators in the NICE scope is: "Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies."

The company included BSC as a comparator for all populations considered and botulinum toxin as a comparator for chronic migraine population only, in-line with NICE guidance (TA260).[21]) These comparators are appropriate for the population addressed in the company submission (patients for whom ≥3 prior prophylactic treatment categories had failed). However, any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s).

For the main comparator, BSC, the company considered the placebo arms of the erenumab trials to be representative of BSC and provided full details of concomitant treatments, by study arm, for the optimised population (patients for whom ≥3 prior prophylactic treatment categories had failed) and for the exploratory analysis population (patients for whom ≥2 prior prophylactic treatment categories had failed), see Appendix 1 of this report. Hence, the STRIVE, ARISE, LIBERTY and Study 295 studies provided direct head-to-head evidence against this comparator.

ERG comment:

The ERG agrees that the placebo arms of the erenumab trials provide a reasonable proxy for BSC in the UK (see Section 2.2).

No direct head-to-head comparisons of erenumab versus Botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus BSC. Estimates of the clinical effectiveness of Botulinum toxin, in patients for whom ≥3 prior prophylactic treatment categories had failed, were taken from pooled data from two randomised placebo controlled trials (PREEMPT 1 and PREEMPT 2).[36] Full details of the baseline characteristics, including concomitant treatments, of the relevant population (patients with chronic migraine for whom ≥3 prior prophylactic treatment categories had failed) were provided for the erenumab study used in the ITC (Study 295[31]). For PREEMPT,[36] these data were unavailable for the subgroup (patients for whom ≥3 prior prophylactic treatment categories had failed); these patients were assumed to be similar to the whole study population and data were provided for the whole population.

3.3 Outcomes

The NICE final scope lists the following outcome measures:

- 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
- adverse effects of treatment
- health-related quality of life (HRQoL)

With the exception of HRQoL, all outcomes were reported, for the relevant population (patients who did not respond to ≥3 previous prophylactic treatments), in at least one of the three erenumab studies

conducted in patients with episodic migraine (STRIVE, ARISE and LIBERTY); HRQoL outcomes were only reported for the whole study populations. There were no safety, tolerability or quality of life outcomes reported in the subgroup who did not respond to ≥3 previous prophylactic treatments for either botulinum toxin (PREEMPT study) or for erenumab in the chronic migraine population (Study 295).

The CS includes response rate, defined as the proportion of patients with ≥50% reduction in mean MMDs from baseline as a primary outcome measure (used in economic modelling).[1] The company were asked to provide justification and supporting references for this definition, and provided the following response:

"The definition of a responder as achieving a ≥50% reduction in MMDs from baseline in the company submission was informed by the definition of responder used in the clinical trials for erenumab. The responder rate defined as a ≥50% reduction in MMDs from baseline was the primary endpoint in LIBERTY, and a key secondary endpoint in Study 295, STRIVE and ARISE. This definition of a responder aligns with the International Classification of Headache Disorders (ICHD) guidelines for controlled trials of drugs in migraine, which state that the proportion of patients with a 50% reduction in number of migraine days (i.e. responder rate), as compared to baseline values, is an important efficacy outcome.[37] Whilst it is acknowledged that the choice of a ≥50% reduction is arbitrary, it is considered to be clinically relevant as most patients with migraine value a ≥50% improvement in headache frequency as the most important attribute of an effective migraine preventive drug.[37] Similarly, International Headache Society (IHS) guidelines for conducting clinical trials in migraine state that responder rates in migraine have traditionally been defined as a ≥50% reduction in MMDs.[37] Whilst these guidelines state that a ≥30% reduction can be clinically meaningful in patients with chronic migraine, the more stringent ≥50% definition was considered to be more appropriate for this submission, where patients across the entire spectrum of migraine patients with ≥4 MMDs are considered, as per the licence for erenumab.[34] Finally, EMA guidelines suggest that the responder rate, where a 'responder' is defined as "*a patient with a 50% or greater reduction in attack frequency during treatment compared to baseline*", is collected as an endpoint in trials of migraine prophylactic therapies.[22]

This is supported further by feedback from six expert UK neurologists who recommended that clinical trials should capture the percentage responder rates rather than MMD frequencies. The advisors considered it more helpful to tell patients the chance of a therapy working, or how many migraine patients usually respond to a therapy, rather than how many fewer MMDs they could expect to experience.[23]"

ERG comment:

The ERG questions the use of the more stringent (≥50% reduction in MMDs vs. ≥30% reduction in MMDs) definition of responder; it seems unlikely that patients in this population would consider a reduction in their MMDs of between 30 and 49% to be not clinically meaningful. Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <30% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 20% reduction in MMDs which they considered to be beneficial.

3.5 Other relevant factors

The company argues that erenumab is innovative because: "it is the only licensed treatment to have been developed specifically for the prophylaxis of migraine, based on an understanding of the

underlying pathophysiology of the disease, and represents a major breakthrough as the first targeted therapy for the prophylaxis of migraine. Erenumab is a highly potent and selective antagonist of the CGRP receptor pathway, which plays a key role in mediating the pain of migraine. This novel mechanism of action compared to current therapies is a 'step change' in the management of migraine, and if recommended, erenumab will provide the first targeted prophylactic migraine therapy recommended for use in the UK."[1]

The company argues that: "The prophylaxis of migraine with erenumab has a potential wider societal value, as a reduction in migraine symptoms may mean that patients are able to return to work, reducing productivity loss from migraine. This would also have a positive impact on the UK economy, with absenteeism due to migraine costing the UK economy approximately £4.4 billion per year."[1]

With respect to the higher (140mg) erenumab dose, [redacted] A simple PAS (confidential discount), making erenumab available at a fixed net price of £[redacted] per 70mg dose was approved by the NHS England Commercial Medicines and Devices Investment Group on 1 May 2018.

[redacted]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify studies reporting the efficacy and safety of erenumab and botulinum toxin (as the only active comparator) for the prophylaxis of migraine in adults. The population defined by the inclusion criteria for this systematic review (see Table 4.1) was broader than the optimised population specified in the company's definition of the decision problem (adults with migraine with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed); it is unclear whether any studies conducted in the broader population were excluded. The systematic review did not search for studies on BSC, as the company considered the placebo arms of the erenumab trials (where acute treatment for migraine attacks was allowed) to be representative of BSC and hence to provide a direct comparison. The systematic review is described, in detail, in Appendix D of the CS.[38]

This section of the ERG report critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis of erenumab and comparator studies.

4.1.1 Searches

The following contains summaries and critiques for all searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidenced based checklist for the peer review of electronic search strategies (PRESS) was used to inform the critique.[39] The submission was checked against the single technology appraisal (STA) specification for company/sponsor submission of evidence.[40]

A SLR was undertaken to identify clinical evidence from RCTs, SLRs and NMAs of erenumab and onabotulinumtoxin A in February 2018 and then updated in July 2018. Searches were reported for Medline, including In-Process, Daily and Epub Ahead of Print, Embase, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effect (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) and the Health Technology (HTA) database. Further searches of congresses, HTA websites and ClinitalTrials.gov were also conducted. Relevant SLRs and NMAs were reference checked. All searches were clearly reported and reproducible, the database name, database date span, and date searched was provided. No language or date limits were applied except for congress searches which were restricted to the previous two years as high-quality studies reported before this time would be expected to have been published. Database searches in Embase and Medline databases included an RCT filter based on one provided by Scottish Intercollegiate Guidelines Network (SIGN) with some adaptions to increase sensitivity.[41]

ERG comment:

- Database searches were clearly structured and documented and contained a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation.
- The ERG noted that the inclusion of the Emtree term for erenumab would have helped make Embase searches more thorough. Some additional synonyms and the use of adjacency for onabotulinumtoxin A would have also helped to increase sensitivity. For example "onabotulinum toxin A" or "botulinum toxin adj2 A".
- Section B.2.9 of the CS states that the safety and tolerability of erenumab was evaluated within Study 295, STRIVE, ARISE and LIBERTY.[1] No separate literature searches to identify other AE data were undertaken. The ERG queried this and in the response to clarification the company stated that results from database searches were screened for AEs.[22] However, the clinical effectiveness searches incorporated a study design filter intended to limit to RCTs.

Guidance by the Centre for Reviews and Dissemination (CRD) [42] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that AEs that are long-term, rare or unanticipated are not missed. The ERG considers that it was possible that some relevant safety data may not have been identified as a consequence of the study design limits applied to the database searches.

4.1.2 Inclusion criteria

The inclusion criteria specified in the systematic review conducted by the company (CS, Appendix D[38]) are provided in Table 4.1.

Table 4.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Domain	Inclusion criteria	Exclusion criteria
Patient population	Adult humans with chronic or episodic migraine	• Non-humans • Humans without migraine • ≥50% children
	Studies with mixed populations (e.g. where some patients have migraine and some have non-migraine headaches, or where both adults and children were included) were included if all or most (≥50%) patients were relevant (i.e. had migraine and were adults), or if separate relevant results were reported for relevant patients.	
Intervention	• Erenumab (Aimovig), previously known as AMG 334 or AMG334 • Onabotulinumtoxin A (also known as botulinum toxin [type] A or Botox)	• Interventions other than erenumab and onabotulinumtoxin A • Non-pharmacological interventions • Acute treatments (i.e. treatments providing symptomatic relief) • Herbal remedies, such as butterbur or feverfew
Comparator	Any	-
Outcomes	• Efficacy outcomes, including but not limited to: o CFB in migraine episodes o CFB in monthly migraine days o CFB in monthly headache days o CFB in monthly migraine-specific acute medication days o Proportion of responders (e.g. participants with ≥50% improvement in migraine	Studies that did not report any outcomes of interest, such as studies reporting only costs or resource use

Domain	Inclusion criteria	Exclusion criteria
	attacks, or any other reported threshold or definition) • Safety and tolerability o All-cause discontinuation o Discontinuation due to AEs o Discontinuation due to lack of efficacy o Adherence o Persistence o Treatment-emergent AEs o Treatment-related AEs o Serious AEs o Serious treatment-related AEs o Specific AEs, including but not limited to: o Depression o Dizziness o Fatigue o Dry mouth o Nausea o Parasthesias o Sleep disturbance o Vomiting o Weight gain • HRQoL o Any generic measures (e.g. SF-36 or EQ-5D) o Any disease-specific measures (e.g. MSQ) o HIT scores o MIDAS score o MPFID score, including "Impact on physical activities" and "Physical impairment" domain scores o Headache severity (VAS)	
	Publications reporting study protocols or baseline characteristics only, without any outcomes of interest, were included at title/abstract review. At full-text review, they were linked to other publications reporting on the same study. If there was at least one publication reporting relevant outcomes (efficacy, safety or HRQoL) for the trial, the protocol or baseline characteristics were included as	

Domain	Inclusion criteria	Exclusion criteria
	a secondary publication for the trial. However, if there were no publications with relevant outcomes, the protocol or baseline characteristics were excluded.	
Study design	RCTs	• Interventional non-randomised controlled trials (non-RCTs), including single-arm studies • Narrative review articles, editorials and letters • Observational studies • Economic analyses or models • Case studies
	SLRs, meta-analyses or NMAs of relevant RCTs were included at title/abstract review for the purpose of identifying any additional studies not identified in the database searches, but were subsequently excluded at full-text review.	
Other	• Full-text or abstract in the English language • If the full-text was non-English, the abstract had to report enough data to be eligible for inclusion in its own right	Non-English abstract

Source: Table 6, Appendix D of the CS

CFB: change from baseline; AE: adverse event; HRQoL: health-related quality of life; EQ-5D: European Quality of Life-5 Dimensions, five-level scale; SF-36: 36-item Short form survey; MSQ: Migraine-Specific Quality of life questionnaire; HIT: Headache Impact Test; MIDAS: Migraine Disability Assessment; MPFID: Migraine Physical Function Impact Diary; VAS: visual analogue scale; RCT: randomised controlled trial; SLR: systematic literature review; NMA: network meta-analysis

ERG comment: Recommended methods were used for inclusion screening: two reviewers independently assessed studies for inclusion in the SLR and any disagreements were resolved through discussion and consensus.

The company were asked to provide clarification on the definition of 'adult patients' and whether erenumab is expected to be used in patients under 18. The following response was provided: "Erenumab is not expected to be used in patients under 18 years of age as the licence is for the prophylaxis of migraine in adults, classified as ≥18 years."

Only English language studies, or studies with an English language abstract reporting sufficient data for inclusion, were included. Although this is widely accepted by NICE within STAs, it is not good practice for systematic reviews, since relevant studies, published in other languages, may be missed. The company were asked to clarify how many papers/studies were excluded solely on the basis of not having an English abstract or full text. The following response was provided: "At the full-text review

stage, one paper was excluded solely on the basis of not having an English full text: *Blumenkron D, Rivera C, Cuevas C. Efficacy of botulinum toxin type A in patients with migraine. Medicina Interna de México. 2006;22(1):25-3.* This paper considered the efficacy of botulinum toxin in patients with migraine. However, the study involved only 30 patients and all patients were recruited from a single hospital in Mexico, limiting generalisability to the UK migraine patient population. In addition, the trial does not specifically state the frequency of migraine attacks, instead characterising patients as mild, moderate, severe and very severe, therefore it is unclear whether results are in patients classified as either chronic or episodic migraine."

The ERG considers that the inclusion criteria for the SLR were in line with the NICE scope, as applied to the optimised population (adult patients with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed) covered by this submission. The full population specified in the scope (people with migraine) would require the SLR to include studies of oral prophylactic treatments for migraine, as well as studies of erenumab and onabotulinumtoxin A.

4.1.3 Critique of data extraction

The CS does not provide any details of how data were extracted from the erenumab studies and the comparator study of botulinum toxin, or how many reviewers were involved in the process. It is therefore not clear whether the data extraction process was adequately designed to minimise error and bias during data extraction.

4.1.4 Quality assessment

No formal, validated quality assessment or risk of bias tools were used to assess the quality of included studies. A seven-question checklist, adapted from CRD's guidance for undertaking systematic reviews in health care,[42] was used to provide quality assessments of the studies included in the submission (erenumab studies and the botulinum toxin study). The checklist adequately covers the key risk of bias issues for randomised controlled trials (randomisation, allocation concealment, blinding, baseline equivalence of treatment groups, drop-outs, selective outcome reporting and missing data). The full results of the quality assessment process, with supporting information, are provided in Appendix D of the CS (Tables 18 and 23).[38] The ERG has assessed the trials included in this report against the criteria provided, and agrees with the quality assessment and supporting information provided in the CS.

4.1.5 Evidence synthesis

The STRIVE, ARISE, LIBERTY and Study 295 studies, individually, provided direct head-to-head evidence for the comparison to BSC. The CS (Section B.2.8.1) states that: "Throughout these trials, patients were prescribed any treatments deemed necessary to provide adequate supportive care, meaning that the placebo arms were considered to be representative of BSC."[1]

The SLR did not identify and direct head-to-head comparisons of erenumab to botulinum toxin in patients with chronic migraine, for whom ≥3 prior prophylactic treatments have failed. The company conducted an ITC, using the methods of Bucher et al.,[35] for change from baseline in mean MMDs, change from baseline in mean MHDs and ≥50% responder rate. Data for erenumab were taken from Study 295 and data for botulinum toxin were taken from PREEMPT (pooled data from the PREEMPT 1 and PREEMPT 2 trials). The ITC is described in Section B.2.8 of the CS[1] and in Appendix D of the CS.[38]

ERG comment: A meta-analysis of erenumab studies was not performed. The CS (Section B.2.7 states that: "Study 295 used a different definition for a "migraine day" and a "headache day" to that of the

studies in episodic migraine (STRIVE, ARISE and LIBERTY), therefore rendering any pooling of these trials inappropriate as outcomes cannot be interpreted as equivalent across trials."

Table 4.2: Definitions of migraine used in erenumab studies

	Study 295	**STRIVE, ARISE and LIBERTY**
Definition of migraine	A qualified migraine headache was determined by the following criteria: • A migraine without aura, lasting for **≥4 continuous hours** and having met criteria a) and/or b): a) ≥2 of the following pain features: o Unilateral o Throbbing o Moderate to severe o Exacerbated with exercise/physical activity b) ≥1 of the associated symptoms: o Nausea and/or vomiting o Photophobia and phonophobia **OR** • A migraine with aura having met criteria c) and d) below, defined as: c) Meeting ≥1 of the following aura symptoms o **Visual** o **Sensory** o **Speech and/or language** o **Retinal** o **Brainstem** d) Aura accompanied, or followed within 60 minutes, by headache lasting for ≥4 continuous hours If the patient took an acute migraine-specific drug on a calendar day, then it was counted as a migraine day regardless of the duration and pain features/associated symptoms.	A qualified migraine headache was defined as a migraine with or without aura, lasting for ≥**30 minutes**, and meeting at least one of the following criteria: • ≥2 of the following pain features: o Unilateral o Throbbing o Moderate to severe o Exacerbated with exercise/physical activity • ≥1 of the following associated symptoms: o Nausea and/or vomiting o Photophobia and phonophobia If the patient took a migraine-specific medication during aura or to treat headache on a calendar day, then it was counted as a migraine day regardless of the duration and pain features/associated symptoms.
Source: CS, Table 7		

STRIVE, ARISE and LIBERTY evaluated different doses of erenumab (STRIVE, 70mg and 140mg Q4W; ARISE, 70mg Q4W; LIBERTY, 140mg Q4W), and STRIVE assessed primary outcomes at 24 weeks, whereas ARISE and LIBERTY had a study duration of 12 weeks. Pooled patient-level data from STRIVE, ARISE and LIBERTY were used to inform the economic analyses.

A critique of the analysis methods used for the ITC is provided in Section 4.4 of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS (Section B.2.1) stated that the SLR identified nine RCTs of erenumab; however, only eight studies were listed. Four main trials (Study 295, STRIVE, ARISE and LIBERTY) were included in the CS clinical effectiveness Section (B.2),[1] two further studies (NCT20130255, a long-term follow-up study of patients enrolled in Study 295, and NCT01952574,[43] a phase II study cited in support of the model assumptions regarding long-term maintenance of erenumab efficacy) provided supporting evidence and were summarised in Appendix L of the CS,[38] Two phase I studies (NCT01688739 and NCT01723514)[44] were identified and excluded from the submission, because they were conducted in healthy individuals and patients with migraine.[1]

ERG comment:

The company was asked to clarify the discrepancy in the number of erenumab studies reported. The following explanatory text was provided:

"Two studies identified in the SLR were omitted in error from Table 4 of the original submission. These are listed below. Neither of these studies informed the clinical evidence base for the economic model.

NCT02630459[45] – this study is ongoing, specific to Japan, and no results are available. The estimated study completion date is 3rd June 2019.

NCT03333109[46] – the EMPOWER study – study of safety and efficacy in episodic migraine patients ongoing in countries other than the US, Europe and Japan. The estimated completion date is 7th February 2020.

In addition, study NCT02174861[47] was included – this study was a long-term follow-up of patients enrolled in Study 295. Results are presented in Section B.2.9 of the CS (long-term safety data). This study is the same as study NCT20130255 originally listed in Table 4, which refers to the additional study ID number for this trial. This study was incorrectly described as NCT20130255, when the actual study ID is NCT02174861 (20130255 is the Novartis study number for this open-label extension). Results have recently been presented at a congress (Tepper et al., Assessment of long-term safety and efficacy of erenumab during open-label treatment of subjects with chronic migraine. Presented at: AHS, San Francisco, CA, USA, June 28–July 1 2018).[48]

It should be noted that that the total number of studies of erenumab in Table 4 when adding these studies is ten."

The ERG agrees that all relevant studies were included in the submission and that the ongoing studies identified could not have been used in the submission.

4.2.1 Details of included erenumab studies

The CS includes four key erenumab studies (see Table 4.3), which are the focus of this report. Study 295 was the only erenumab study conducted in patients with chronic migraine. Three studies (STRIVE, ARISE and LIBERTY) were conducted in patients with episodic migraine. Because the LIBERTY trial included only patients who had failed two to four previous migraine prophylactic treatments, this study contributed the majority of the data on patients with episodic migraine included in this submission (optimised population for whom ≥3 prior prophylactic treatments have failed); the STRIVE and ARISE studies included only small numbers of patients in this subgroup (see Table 4.5). No two studies evaluated the same erenumab dose in comparable populations, with similar outcome measures and follow-up times (see Table 4.3).

Across the four trials, a total of 2,445 patients were included (full ITT population): Study 295 n=667; STRIVE n=955; ARISE n=577; LIBERTY n=246. Of these only 515 are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments: Study 295 n=236; STRIVE n=74; ARISE n=56; LIBERTY n=149.

All erenumab trials were randomised, double-blind, placebo-controlled, parallel-group studies and all trials had open-label or active treatment extensions. Double-blind phases were either 12 or 24 weeks in duration. This report will present data from the blinded phases of the trials only. Eligible patients were adults, defined as 18 to 65 in all trials. The trials were international and, with the exception of the ARISE trial, all had a small number of UK sites. Overall [redacted] patients from the UK were included across the four trials. Although all trials compared erenumab to placebo, dosages varied. Study 295 in patients with chronic migraine and STRIVE in patients with episodic migraine allowed patients to receive 70 or 140mg doses. However, in ARISE patients could only receive the 70mg dose and in LIBERTY only the 140mg dose was given. All outcomes related to change in the number of migraine days as a primary outcome but this was measured differently and at different time points across the trials.

Table 4.3: Clinical effectiveness evidence for erenumab in patients with migraine

Study	Study 295	STRIVE	ARISE	LIBERTY
Study design	Phase II	Phase III	Phase III	Phase IIIb
	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study			
Study duration	≤3-week screening phase, 4-week baseline phase			0–2 weeks screening, 4-week baseline phase
	12-week double-blind phase 52-week open-label phase	24-week double-blind phase 28-week active treatment phase	12-week double-blind phase 28-week open-label treatment phase	12-week double-blind phase 52-week open-label
	Subsequent 12-week safety follow-up			
Study location	International: 69 sites UK (four sites, [redacted] patients)	International: 121 centres UK (six sites, [redacted] patients)	International: 69 centres UK 0	International: 68 locations UK (five sites, [redacted] patients)
Population	Adults aged 18–65			
	History of chronic migraine, with or without aura (≥15 headache days per month, of which ≥8 were migraine days)	History of episodic migraine (≥4 and <15 migraine days per month with <15 headache days per month) with or without aura for ≥12 months		History of episodic migraine (4–14 baseline migraine days) with <15 days per month of headache symptoms who have failed 2–4 previous migraine prophylactic treatments
Intervention	Erenumab 70mg or 140mg Q4W		Erenumab 70mg Q4W	Erenumab 140mg Q4W
Comparator	Placebo			
Primary outcome	Mean change in MMDs from baseline to final four weeks of 12-week double-blind phase	Change from baseline in mean MMDs using the MMDs from each of the last three months of 24-week double-blind phase	Mean change in MMDs from baseline to final four weeks of 12-week double-blind phase	At least 50% reduction from baseline in MMDs in Month 3 (the final month) of the double-blind phase

Source: CS Tables 5 and 6

Mg = milligrams; MMD = monthly migraine day; Q4W = every four weeks; UK = United Kingdom

As the population of interest in this submission is patients for whom ≥3 prior prophylactic treatments have failed, we will not describe or comment in detail on the baseline characteristics of the whole study populations in the four included studies, but will focus on the information provided for the relevant subgroups. Baseline characteristics for the population for whom ≥2 prior prophylactic treatments have failed, used in exploratory economic analyses, were provided in Appendix E of the CS and are not reproduced in this report.[38]

ERG comment:

The ERG notes that the evidence for erenumab is based on international RCTs investigating patient-relevant outcomes, however, only one trial was conducted in patients with chronic migraine and the number of trial participants for whom ≥3 prior prophylactic treatments had failed is relatively low (approximately 20% of the total studied population). Furthermore, three of the four studies had a double-blind phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was mean monthly migraine days; evidence is lacking about the long-term effectiveness of erenumab treatment.

Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented (see Tables 4.4 and 4.5); this observation applies to both the whole study populations and to the subgroups which are relevant to this submission. There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

With respect to the definitions of chronic and episodic migraine used in the included studies (see Table 4.3), there is a potential population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population. This was confirmed in the company's response to clarification questions: "Given the definitions of chronic and episodic migraine used in the clinical trial programme, which were based on clinical guidelines, patients falling outside of these definitions were not included in the clinical trials. However, the license for erenumab covers all patients that have ≥4 MMDs, therefore under the terms of this license, erenumab could be used in patients with ≥15 MHDs, and ≥4 to <8 MMDs."[22]

Studies evaluated different doses of erenumab; Study 295 and STRIVE evaluated 70mg and 140mg Q4W, ARISE evaluated 70mg Q4W, and LIBERTY evaluated 140mg Q4W. The company were asked to provide clarification on which patients are expected to benefit from the 140mg Q4W dose and how these patients can be identified before initiating treatment with erenumab. The following response was provided: "The licence for erenumab does not indicate the specific patient population expected to benefit from the 140mg dose of erenumab. However, numerically superior clinical outcomes were observed for patients treated with erenumab 140mg compared to erenumab 70mg in the subgroup of patients for whom ≥3 prior treatments have failed. Additionally, there is no difference in the safety profiles of the 70mg and 140mg doses. The 140mg dose may therefore be most appropriate for the patient population for whom ≥3 prior treatments have failed: the optimised population considered in this submission."

No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus Botulinum toxin, in patients with chronic migraine (see Section 4.4). For the main comparator, BSC, the company considered the placebo arms of the erenumab trials to be representative of BSC and provided full details of concomitant treatments, by study arm, for the optimised population (patients for

whom ≥3 prior prophylactic treatment categories had failed), see Appendix 1 of this report. The ERG agrees that the placebo arms of the erenumab trials provide a reasonable proxy for BSC in the UK (see Section 2.2).

Study 295 (Chronic migraine population)

The company reported that overall baseline characteristics were comparable between the ITT population and the patients for whom ≥ 3 prior prophylactic treatments have failed. Patients in the erenumab 140mg arm were slightly older in the optimised population than in the whole ITT population (44.1 vs. 42.9 years respectively). The age at onset of migraine was slightly lower in the optimised population, for all arms, however, baseline MMDs were comparable.

Additional data from the company indicated that [redacted] of the optimised population subgroup from study 295 had a diagnosis of migraine with aura, at baseline.[22] Information about which medications were used to treat acute migraine, during the study, was requested in the clarification letter and is provided in Appendix 1 of this report.

Table 4.4: Baseline characteristics of patients for whom ≥ 3 prior prophylactic treatments have failed in Study 295

Characteristic	Placebo [redacted]	Erenumab 70mg [redacted]	Erenumab 140mg [redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Women	[redacted]	[redacted]	[redacted]
Men	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]
Age at migraine[b] onset, years (SD)	[redacted]	[redacted]	[redacted]
Disease duration, years (SD)	[redacted]	[redacted]	[redacted]
Previous use of preventative drug topiramate, n (%)	[redacted]	[redacted]	[redacted]
Previous use of botulinum toxin, n (%)	[redacted]	[redacted]	[redacted]
Previous prophylactic treatment failures, n (%)			
Divalproex sodium, sodium valproate	[redacted]	[redacted]	[redacted]

Characteristic	Placebo [redacted]	Erenumab 70mg [redacted]	Erenumab 140mg [redacted]
Topiramate	[redacted]	[redacted]	[redacted]
Beta-blockers	[redacted]	[redacted]	[redacted]
Tricyclic antidepressants	[redacted]	[redacted]	[redacted]
Flunarizine or verapamil	[redacted]	[redacted]	[redacted]
SNRI	[redacted]	[redacted]	[redacted]
Lisinopril or candesartan	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Acute headache medication use, n (%)			
Migraine specific[c]	[redacted]	[redacted]	[redacted]
Non-migraine specific	[redacted]	[redacted]	[redacted]
Baseline period, mean (SD)			
Monthly migraine days	[redacted]	[redacted]	[redacted]
Monthly headache days	[redacted]	[redacted]	[redacted]
Monthly migraine attacks	[redacted]	[redacted]	[redacted]
Monthly acute migraine-specific drug use days	[redacted]	[redacted]	[redacted]

Source: CS Table 32 and additional information provided in response to clarification questions
Footnotes: [a]Other includes American Indian or Alaska native, multiple, native Hawaiian or other Pacific Islander and all other races. [b]Migraine with or without aura. [c]During the baseline phase, 557 patients (58.5%) used triptan-based medications and four patients (0.4) used ergotamine-based medications (safety analysis set).
BMI = body mass index; SD = standard deviation; SNRI = Serotonin and norepinephrine reuptake inhibitor.

ERG comment:
The ERG agrees with the company's statement that the overall baseline characteristics were comparable between the ITT population and the optimised population, for whom ≥3 prior prophylactic treatments have failed. However, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations.

Although all patients in described in Table 4.4 have failed ≥3 prior prophylactic treatments, it is not clear that the treatments failed correspond to the treatments or treatment classes indicated in the care pathway (Figure 2.1), i.e. not all patients have failed to respond to treatment with a beta-blocker, an anti-convulsant and a tricyclic antidepressant.

STRIVE, ARISE and LIBERTY (Episodic migraine population)

As these trials are all in episodic migraine, we present the baseline characteristics of patients for whom ≥ 3 prior prophylactic treatments have failed together in the table below.

The CS (Section B.2.6 states that: "It should be noted that the number of patients who had received ≥3 prior prophylactic treatments in STRIVE and ARISE was small (n=[redacted] and n=[redacted], [redacted]% and [redacted]% of the study populations, respectively). Analyses across all outcome measures in these subgroups are not therefore considered to be meaningful, and are presented in this section for completeness. LIBERTY provides more relevant clinical evidence in this subgroup as this was a study specifically designed to assess the efficacy and tolerability of erenumab in patients who have failed 2–4 previous migraine prophylactic treatments."

For STRIVE, the company reported that baseline characteristics were comparable between the ITT population and the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, but notes that a higher proportion of patients in this subgroup is white, and patients in the subgroup have slightly higher MMDs at baseline. For ARISE, the company reported that baseline characteristics for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed were consistent with those in the full trial population, both in terms of patient demographics and baseline disease characteristics. For both studies, fewer details of the baseline characteristics were provided for the subgroup population than for the whole population, e.g. age at onset of migraine and disease duration were not provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. In addition, baseline data for the secondary outcomes, mean monthly headache days (MHD) and acute migraine-specific drug use outcomes, were not provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in either STRIVE or ARISE.

For LIBERTY, the company reported that baseline characteristics for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed were consistent with those in the full trial population, both in terms of patient demographics and baseline disease characteristics.

Additional data from the company indicated that [redacted] of the optimised population subgroup, from STRIVE, ARISE and LIBERTY respectively, had a diagnosis of migraine with aura, at baseline.[22] Information about which medications were used to treat acute migraine, during the studies, was requested in the clarification letter and is provided in Appendix 1 of this report.

Table 4.5: Baseline characteristics of patients for whom ≥ 3 prior prophylactic treatments have failed in STRIVE, ARISE and LIBERTY

Characteristics	STRIVE			ARISE		LIBERTY	
	Placebo [redacted]	E70mg [redacted]	E140mg [redacted]	Placebo [redacted]	E70mg [redacted]	Placebo [redacted]	E140mg [redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)							
Women	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Men	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)							

Characteristics	STRIVE			ARISE		LIBERTY	
	Placebo	E70mg	E140mg	Placebo	E70mg	Placebo	E140mg
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at migraine[b] onset, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of previous prophylactic treatment failure							
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Details of previous prophylactic treatment failures							
Divalproex sodium, sodium valproate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blockers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tricyclic antidepressants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flunarizine or verapamil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SNRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril or candesartan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute headache medication use, n (%)							
Migraine specific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-migraine specific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline period, mean (SD)							
Monthly migraine days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monthly headache days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monthly acute migraine-specific drug use days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	STRIVE			ARISE		LIBERTY	
	Placebo [redacted]	E70mg [redacted]	E140mg [redacted]	Placebo [redacted]	E70mg [redacted]	Placebo [redacted]	E140mg [redacted]
Acute migraine-specific drug use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: CS Tables 33, 34 and 35, and additional information provided in response to clarification questions Footnotes: [a] Other includes Native American, Pacific Islander, unknown and all other races; [b] Migraine with or without aura BMI = body mass index; E = erenumab; kg = kilogrammes; MMD = mean monthly migraine days; SD = standard deviation; NA = not applicable; NR = not reported							

ERG comment:
The ERG agrees with the company's statement that the overall baseline characteristics were comparable between the ITT populations and the optimised populations, for whom ≥3 prior prophylactic treatments have failed. However, it should be noted that some baseline data were not provided, for whom ≥3 prior prophylactic treatments have failed, in STRIVE and ARISE. In addition, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations.

Although all patients in described in Table 4.5 have failed ≥3 prior prophylactic treatments, it is not clear that the treatments failed correspond to the treatments or treatment classes indicated in the care pathway (Figure 2.1), i.e. not all patients have failed to respond to treatment with a beta-blocker, an anti-convulsant and a tricyclic antidepressant.

4.2.2 Risk of bias assessment for included erenumab studies

Full risk of bias assessments, including supporting information for each criterion, were provided in Appendix E of the CS.[38] Table 4.6 provides a summary of the risk of bias assessments conducted for the four included erenumab studies.

Table 4.6: Overview of risk of bias assessments for studies of erenumab

Trial number (acronym)	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT NCT02483585)	LIBERTY (NCT03096834)
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors	Yes	Yes	Yes	Yes

Trial number (acronym)	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT NCT02483585)	LIBERTY (NCT03096834)
blind to treatment allocation?				
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	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	No
Source: CS Table 14				

ERG comment:
The ERG agrees with the risk of bias assessment provided in the CS.

4.2.3 Clinical effectiveness results for included erenumab studies

This section focuses on the key clinical effectiveness outcomes, reported in the CS and used to inform economic modelling, change in MMD/MHD from baseline to week 12 and responder rate (proportion of patients achieving ≥50% reduction in MMD/MHD from baseline week 12). As the population of interest in this submission is patients for whom ≥3 prior prophylactic treatments have failed, results are reported for this population rather than for the whole study ITT population; results are also provided for the two populations used in exploratory economic analyses (patients for whom ≥2 prior prophylactic treatments have failed, and patients with HFEM (defined as MMD eight to 14 in all three studies of erenumab for the prophylactic treatment of episodic migraine) for whom ≥3 prior prophylactic treatments have failed).

Table 4.7: Key clinical effectiveness results for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in Study 295

	Study 295		
	Placebo (n=[redacted])	**Erenumab 70mg (n=[redacted])**	**Erenumab 140mg (n=[redacted])**
Change from baseline in MMDs			
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change at Week 12 (SE)	[redacted]	[redacted]	[redacted]

	Study 295		
	Placebo (n=[redacted])	**Erenumab 70mg (n=[redacted])**	**Erenumab 140mg (n=[redacted])**
LSM difference versus placebo (95% CI)	NA	−2.53 (−4.27, −0.78)	−4.09 (−5.83, −2.33)
p-value	NA	0.005	<0.001
≥50% responder rate (MMDs)			
n (%)	15 (15.3)	23 (34.8)	25 (38.5)
Odds ratio (95% CI)	NA	3.0 (1.4, 6.3)	3.5 (1.6, 7.4)
p-value	NA	0.004	0.001
Change from baseline in MHDs			
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change at Week 12 (SE)	[redacted]	[redacted]	[redacted]
LSM difference versus placebo (95% CI)	NA	[redacted]	[redacted]
p-value	NA	[redacted]	[redacted]
≥50% responder rate (MHDs)			
n (%)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NA	[redacted]	[redacted]
p-value	NA	[redacted]	[redacted]

Source: CS Section B.2.6.1 and Table 32

CI = confidence interval; MHDs = mean headache days; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; LSM = Least square method

Table 4.8: Key clinical effectiveness results for the subgroup of patients for whom ≥2 prior prophylactic treatments have failed in Study 295

	Study 295		
	Placebo (n=141)	**Erenumab 70mg (n=90)**	**Erenumab 140mg (n=92)**
Change from baseline in MMDs			
Baseline, mean (SD)	18.2 (4.7)	17.9 (4.4)	17.8 (4.7)
Mean change at Week 12 (SE)	−2.68	−5.3 (NR)	−6.96 (NR)
LSM difference versus placebo (95% CI)	NA	−2.71 (−4.20, −1.21)	−4.28 (−5.75, −2.80)
p-value	NA	<0.05	<0.05
≥50% responder rate (MMDs)			
n (%)	17 (12.1)	24 (26.7)	32 (34.8)
Odds ratio (95% CI)	NA	2.81 (1.39, 5.67)	3.96 (2.01, 7.82)
p-value	NA	0.003	<0.001

Source: CS Table 36

CI = confidence interval; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; LSM = Least square method

ERG comment:

The ERG notes that in Study 295 (chronic migraine) the optimised population (≥3 prior prophylactic treatments have failed) had better outcomes in the erenumab 70mg and 140mg groups than in the placebo group. More specifically, at week 12 patients experienced approximately two and a half fewer migraine days whilst taking erenumab 70mg and four fewer whilst taking erenumab 140mg than on placebo. In total, 34.8% of patients taking 70mg of erenumab and 38.5% of patients taking 140mg erenumab achieved a ≥50% reduction in MMDs from baseline, compared to 15.3% of patients on placebo. Results were similar for the subgroup of patients for whom ≥2 prior prophylactic treatments had failed, however, response rates appeared slightly lower in this expanded population; 26.7% of patients taking 70mg of erenumab and 34.8% of patients taking 140mg erenumab achieved a ≥50% reduction in MMDs from baseline, compared to 12.1% of patients on placebo.

With respect to secondary outcome measures in the population for whom ≥3 prior prophylactic treatments have failed, neither erenumab dose was associated with a statistically significant reduction in monthly migraine severity relative to placebo; Patients in the erenumab 70mg and erenumab 140mg arms achieved mean reductions versus placebo of [redacted] (95% CI: [redacted]; [redacted]) and [redacted] (95% CI: [redacted]; [redacted]), respectively. At week 12, patients treated with either erenumab dose had a significantly greater reduction in the monthly acute migraine-specific treatment days from baseline, compared with placebo; patients achieved a mean reduction of [redacted] and [redacted] days in the erenumab 70mg and 140mg arms, respectively, compared to [redacted] days in the placebo arm. This was associated with an LSM difference versus placebo of [redacted] days (95% CI: [redacted]; [redacted]) for the erenumab 70mg arm, and [redacted] days (95% CI: [redacted]; [redacted]) for the erenumab 140mg arm. This finding is consistent with the greater reduction in MMD observed in patients on the higher dose of erenumab.

The CS did not include any data on the long-term (>12 weeks) effectiveness of erenumab compared to placebo in people with chronic migraine. The open-label extension of study 295 (NCT20130255),[47] described in Appendix L of the CS,[38] provides some information about the longer-term maintenance of the effects, relative to baseline, of erenumab. However, due to a protocol amendment that resulted in the dose of erenumab being altered from 70mg to 140mg, the results provided are averaged across the whole trial population consisting of patients who had received either erenumab 70mg, erenumab 140mg or erenumab 70mg/140mg over the open-label extension follow-up period, and there are no results for the subgroup of patients in whom ≥3 prior prophylactic treatments have failed. The mean (95% CI) change from Study 295 baseline in MMDs was –8.36 (95% CI: –8.92, –7.80) days at week 24 and –9.29 (95% CI: –9.96, –8.62) days at week 52. The group ending the study on the 140mg dose showed numerically higher ≥50% responder rates, with 67.1% achieving the response compared with 53.5% of those who finished the study on 70mg erenumab.

Table 4.9: Key clinical effectiveness results for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in STRIVE, ARISE and LIBERTY

	STRIVE			ARISE		LIBERTY	
	Placebo (n=27)	**Erenumab 70mg (n=24)**	**Erenumab 140mg (n=23)**	**Placebo (n=29)**	**Erenumab 70mg (n=27)**	**Placebo (n=72)**	**Erenumab 140mg (n=77)**
Change from baseline in MMDs							
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at Week 12 (SE)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus placebo (95% CI)	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
≥50% responder rate (MMDs)							
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
Change from baseline in MHDs							
Baseline, mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	[redacted]	[redacted]
Mean change at	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	STRIVE			ARISE		LIBERTY	
	Placebo (n=27)	**Erenumab 70mg (n=24)**	**Erenumab 140mg (n=23)**	**Placebo (n=29)**	**Erenumab 70mg (n=27)**	**Placebo (n=72)**	**Erenumab 140mg (n=77)**
Week 12 (SE)							
Difference versus placebo (95% CI)	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
≥50% responder rate (MHDs)							
n (%)	NR	NR	NR	NR	NR	[redacted]	[redacted]
Odds ratio (95% CI)	NR	NR	NR	NR	NR	NA	[redacted]
p-value	NR	NR	NR	NR	NR	NA	[redacted]

Source: CS Section B.2.6.1 and Tables 33, 34 and 35

*For STRIVE this is mean change to last three months of the double-blind treatment phase

CI = confidence interval; MHDs = mean headache days; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error

Table 4.10: Key clinical effectiveness results for the subgroup of patients for whom ≥2 prior prophylactic treatments have failed in STRIVE, ARISE and LIBERTY

	STRIVE			ARISE		LIBERTY*	
	Placebo (n=54)	**Erenumab 70mg (n=49)**	**Erenumab 140mg (n=58)**	**Placebo (n=49)**	**Erenumab 70mg (n=56)**	**Placebo (n=124)**	**Erenumab 140mg (n=119)**
Change from baseline in MMDs							
Baseline, mean (SD)	8.12 (2.49)	8.89 (2.04)	8.68 (2.51)	[redacted]	[redacted]	9.3 (2.71)	9.3 (2.58)
Mean change at Week 12 (SE)**	−0.24 (0.76)	−1.56 (0.74)	−2.95 (0.73)	[redacted]	[redacted]	−0.15 (0.41)	−1.76 (0.44)

	STRIVE			ARISE		LIBERTY*	
	Placebo (n=54)	**Erenumab 70mg (n=49)**	**Erenumab 140mg (n=58)**	**Placebo (n=49)**	**Erenumab 70mg (n=56)**	**Placebo (n=124)**	**Erenumab 140mg (n=119)**
Difference versus placebo (95% CI)	NA	−1.32 (−2.64, 0.00)	−2.70 (−3.97, −1.44)	NA	[redacted]	NA	−1.61 (−2.70, −0.52)
p-value	NA	0.051	<0.001	NA	[redacted]	NA	0.004
≥50% responder rate (MMDs)							
n (%)	6 (11.1)	13 (26.5)	21 (36.2)	[redacted]	[redacted]	17 (13.7)	36 (30.3)
Odds ratio (95% CI)	NA	2.89 (1.00, 8.33)	4.54 (1.66, 12.39)	NA	[redacted]	NA	2.73 (1.43, 5.19)
p-value	NA	0.045	0.002	NA	[redacted]	NA	0.002

Source: CS Tables 21 and 36

*For LIBERTY, the population of patients for whom ≥2 prior prophylactic treatments have failed is the same as the whole study ITT population

**For STRIVE this is mean change to last three months of the double-blind treatment phase

CI = confidence interval; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error

Table 4.11: Key clinical effectiveness results for the subgroup of patients with HFEM for whom ≥3 prior prophylactic treatments have failed in STRIVE, ARISE and LIBERTY

	STRIVE			ARISE		LIBERTY	
	Placebo (n=19)	**Erenumab 70mg (n=16)**	**Erenumab 140mg (n=17)**	**Placebo (n=19)**	**Erenumab 70mg (n=16)**	**Placebo (n=72)**	**Erenumab 140mg (n=76)**
Change from baseline in MMDs							
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	NR (NR)	NR (NR)	[redacted]	[redacted]
Mean change at Week 12 (SE)*	NR (NR)	NR (NR)	NR (NR)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]

placebo (95% CI)							
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
≥50% responder rate (MMDs)							
n (%)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]

Source: CS Section B.2.6.3
*Week 24 for STRIVE
CI = confidence interval; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error

ERG comment:

The ERG notes that in studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks, and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed (MMD or MHD, ≥50% responder rates, monthly severity of migraine pain, monthly acute migraine-specific treatment days, monthly cumulative hours of migraine. The ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed.

Results were similar for the expanded subgroup of patients for whom ≥2 prior prophylactic treatments had failed. The ERG notes that numbers of study participants were very small for the subgroup of patients with HFEM, for whom ≥3 prior prophylactic treatments have failed. The ERG also notes that, for the STRIVE trial, there is an inconsistency between the effect estimate for 140mg erenumab versus placebo in patients with HFEM for whom ≥3 prior prophylactic treatments have failed reported in the summary of key results box on page 80 of the CS (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]) and that reported in the main text (Section B.2.6.3 of the CS) and in Table 4.11 of this report (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]).

The CS does not include any long-term (beyond 24 weeks) data on the effectiveness of erenumab compared to placebo in people with episodic migraine. The open label extension of a phase II study (NCT01952574),[43] described in Appendix L of the CS,[38] provides some information about the longer term maintenance of the effects, relative to baseline, of erenumab (70mg, Q4W). At Week 64, patients achieved a mean reduction of 5.0 (SD: 4.2) MMDs from a baseline of 8.6 MMDs (SD: 2.6), with 65% of patients achieving a reduction of ≥50% in MMDs from baseline.[43] The double-blind phase of this study was not included in the clinical effectiveness section of the CS.

4.4.4 Health-related quality of life data for included erenumab studies

The erenumab studies included in the CS used a variety of instruments to assess the impact of erenumab treatment on health-related quality of life: Study 295, HIT-6, MSQ 2.1, MIDAS and PROMIS; STRIVE, HIT-6, MSQ 2.1, MIDAS and MPFID; ARISE, HIT-6, MSQ 2.1 and MPFID; LIBERTY, HIT-6, EQ-5D-5L and WPAI. All health-related quality of life results were for the full study populations; no health-related quality of life data were provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Economic modelling used utility values which were derived by mapping patient-level MSQ 2.1 data from Study 295, STRIVE and ARISE onto EQ-5D-3L (CS, Section B.3.4.1).[1] This approach is discussed in detail in Section 5.2.8 of this report.

4.4.5 Adverse events data for included erenumab studies

This section considers the information about AEs provided in the CS. Adverse events data reported in the CS were for erenumab studies only and for the whole study population. As the population of interest in this submission is patients for whom ≥3 prior prophylactic treatments have failed, the company was asked to provide AEs for this subgroup. The company's response to points of clarification included a summary of AEs, by grade, for this population (see Table 4.12). Table 4.13 shows the equivalent data for the whole trial safety analysis set of Study 295, STRIVE, ARISE and LIBERTY. Full details of individual AEs occurring in ≥2% of patients, AEs leading to discontinuation and SAEs in the safety analysis set of Study 295, STRIVE, ARISE and LIBERTY are provided in the CS (Tables 44 to 46).[1] However, these data are not available for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. For the whole trial safety populations, the most commonly observed AEs (of any grade) were consistent across all four studies (nasopharyngitis, nausea, fatigue, upper respiratory tract infection and arthralgia), and the most frequently reported adverse drug reactions for the 70mg and 140mg doses were injection site reactions (5.6% and 4.5%), constipation (1.3% and 3.2%), muscle spasms (0.7% and 2.0%) and pruritus (1.0% and 1.8%).[1]

The CS did not include any AE data for the PREEMPT study or any other AE data for botulinum toxin. Summary AE data for botulinum toxin, taken from Dodick et al. 2010,[49] are provided in Table 4.14. The most frequent treatment-related adverse events were neck pain (6.7%), muscle weakness (5.5%), eyelid ptosis (3.3%) and injection-site pain (3.2%).[49] No AE data are available for botulinum toxin the subgroup of patients for whom ≥3 prior prophylactic treatments have failed.

ERG comment:

The ERG agrees with the company's statement that: "Across all four trials, the vast majority of AEs experienced by patients in the erenumab treatment arms were of mild or moderate severity and very low numbers of patients experienced any SAEs."[1] This statement appears to be applicable to both the whole trial safety populations and to the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. However, given the small sample size it is not possible to draw firm conclusions regarding adverse events for patients for whom ≥3 prior prophylactic treatments have failed.

The rate of SAEs for botulinum toxin (4.8%) appears higher than that observed for the whole trial safety populations in the erenumab studies (see Table 4.13).

Table 4.12: Treatment-emergent AEs in patients for whom ≥3 prior prophylactic treatments have failed in Study 295, STRIVE, ARISE and LIBERTY (safety analysis set)

Total no. of patients (%)	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 140mg (n=[redacted])
With AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With AEs leading to discontinuation of investigational product	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 6, Response to clarification[22]
AE: adverse event; SAE: serious adverse event

Table 4.13: Treatment-emergent AEs in the safety analysis set of Study 295, STRIVE, ARISE and LIBERTY

Total no. of patients (%)	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=282)[a]	Erenumab 70mg (n=190)[a]	Erenumab 140mg (n=188)[a]	Placebo (n=319)[b]	Erenumab 70mg (n=314)[b]	Erenumab 140mg (n=319)[b]	Placebo (n=289)	Erenumab 70mg (n=283)	Placebo (n=124)	Erenumab 140mg (n=119)
With AEs	110 (39.0)	83 (43.7)	88 (46.8)	201 (63.0)	180 (57.3)	177 (55.5)	158 (54.7)	136 (48.1)	67 (54.0)	65 (54.3)
With SAEs	7 (2.5)	6 (3.2)	2 (1.1)	7 (2.2)	8 (2.5)	6 (1.9)	5 (1.7)	3 (1.1)	1 (0.8)	2 (1.7)
With Grade ≥2[c]	[redacted]									
With Grade ≥3[c]	[redacted]						8 (2.8)	6 (2.1)		
With Grade ≥4[c]	[redacted]									
With AEs leading to discontinuation of investigational product	2 (0.7)	0 (0.0)	2 (1.1)	8 (2.5)	7 (2.2)	7 (2.2)	1 (0.3)	5 (1.8)	1 (0.8)	0 (0.0)

Source: Table 43, CS[1]

a: Number of subjects reporting at least one occurrence of a treatment-emergent adverse event

b: Number of subjects with non-missing values.

c: Grading categories determined using Common Toxicity Criteria for Adverse Events version 4.03.

AE: adverse event; SAE: serious adverse event

Table 4.14: Summary of overall AEs reported in the 24-week double blind phase for the PREEMPT program (PREEMPT-1 and PREEMPT-2)

Total no. of patients (%)	**OnabotulinumtoxinA 150 to 195 U (n = 687)**	**Placebo (n = 692)**
With AEs	429 (62.4)	358 (51.7)
With treatment-related AEs	202 (29.4)	88 (12.7)
With SAEs	33 (4.8)	16 (2.3)
With treatment-related SAEs	1 (0.1)	0 (0.0)
With AEs leading to discontinuation of investigational product	26 (3.8)	8 (1.2)
Deaths	0 (0.0)	0 (0.0)
Source: Dodick et al. 2010[49] AE: adverse event; SAE: serious adverse event		

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS (Section B.2.8.2) states that Study 295 and the pooled PREEMPT study were judged to be similar in terms of their study design and the patient baseline characteristics; details are provided in Appendix D of the CS.[38] The patient baseline characteristics, for both trials, are summarised in Table 4.15 and the results from each trial, used as inputs for the ITC, are provided in Table 4.16.

The CS (Section B.2.8.3) provides a full description of the uncertainties relevant to the ITC assumption of comparable patient populations, in summary:

- Baseline characteristics were not reported for the subgroup of patients for whom ≥3 prior prophylactic treatments had failed in PREEMPT. Because the baseline characteristics for the full trial populations in Study 295 and PREEMPT were similar, it was assumed that the subgroup populations were also similar.
- In both trials, patients were not stratified by previous prophylactic use when randomised. As a result, the analysis for the subgroup comparisons breaks randomisation and patient characteristics may therefore be imbalanced between treatment arms for measured and unmeasured variables.
- Least squares means were reported for each outcome, but the variables adjusted for in PREEMPT are not reported.
- The outcomes were reported at different time points with Study 295 reporting outcomes at 12 weeks while PREEMPT reported outcomes at 24 weeks.

ERG comment:
The CS did not include any AE data for the PREEMPT study or any other AE data for botulinum toxin.

Appendix D (Section D.1.4) of the CS notes that:

"Data for both trials in the patient population for whom ≥3 prior prophylactic treatments have failed were only available for the change from baseline in mean monthly migraine days, change from baseline in mean monthly headache days and the percentage of patients with a 50% reduction in mean monthly headache days. Therefore, the ITC was performed on these three efficacy outcomes. There were no safety, tolerability or quality of life outcomes reported in the subgroup who did not respond to ≥3 previous prophylactic treatments for either study."

Appendix D (Section D.1.4) of the CS notes that:

"There was a difference in the study duration, 12 weeks for Study 295 versus 24 weeks for PREEMPT. This difference in timepoint is likely to have an impact when comparing efficacy outcomes at the primary endpoint, as data from PREEMPT show that botulinum toxin was more effective compared to placebo at 24 weeks compared to 12 weeks [1] Any comparisons between erenumab and botulinum toxin using primary endpoint data would therefore be likely to favour botulinum toxin." The ERG notes that the study cited does not report a comparison of the effectiveness of botulinum toxin at 24 weeks compared to 12 weeks. Graphical representations of change in MMD and MHD over time indicate a significant treatment effect, for botulinum toxin versus placebo, from week four onwards; it is not clear whether the difference in follow-up time, 12 weeks for Study 295 versus 24 weeks for PREEMPT, for the primary endpoint comparison would be likely to favour botulinum toxin.

Table 4.15: Summary of the participants' baseline characteristics for studies used in the ITC

Study	Treatment	Age, years, mean (SD)	Gender, % female	Race, % white	Migraine days/month, mean (SD)	Headache days/month, mean (SD)	Acute medication days/month, mean (SD)	≥1 prior prophylaxis treatments, %
PREEMPT*	Botulinum toxin 155U –195U	41.1 (10.4)	87.6	89.7	19.1 (3.99)	19.9 (3.68)	14.6 (6.4)	61.8
	Placebo	41.5 (10.7)	85.2	90.5	18.9 (4.05)	19.8 (3.68)	14.9 (6.4)	65.2
Study 295 (NCT02066415) full trial population	Erenumab 70mg	41.4 (11.3)	86.9	92.1	17.85 (4.39)	20.49 (3.82)	8.76 (7.16)	72.3
	Erenumab 140mg	42.9 (11.1)	84.2	96.8	17.78 (4.72)	20.73 (3.83)	9.66 (7.02)	71.6
	Placebo	42.1 (11.3)	79.0	93.7	18.22 (4.73)	21.12 (3.93)	9.46 (7.58)	76.2
Study 295 (NCT02066415) ≥3 prior treatment failures subgroup**	Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100
	Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100

Source: Table 16, Appendix D of the CS

*Baseline characteristics for the subgroups of patients for whom ≥3 prior prophylactic treatments have failed were not available for PREEMPT.

** Baseline characteristics are for the subgroups of patients for whom ≥3 prior protocol-defined treatment categories have failed; for example, prior non-responders to a beta-blocker, a tricyclic antidepressant and topiramate

SD: standard deviation

Table 4.16: Summary of study results used in the ITC

Study	Treatment	Population	CfB mean monthly migraine days, mean (SE)	CfB mean monthly headache days, mean (SE)	Patients with a 50% reduction in mean monthly headache days, n/N (%)
PREEMPT	Botulinum toxin 155U –195U	Full trial population, 24 weeks	–8.2 (–8.69, –7.70)[a]	–8.4 (–8.90, –7.92)[a]	NR (47.1)
	Botulinum toxin 155U –195U	Full trial population, 12 weeks	–7.09 (0.13)	–7.15 (0.26)	339/688 (49.3)
	Botulinum toxin 155U –195U	≥3 previous prophylaxis treatments, 24 weeks	–7.1[b] (NR)	–7.4[b] (NR)	76/189 (40)
	Placebo	Full trial population, 24 weeks	–6.2 (–6.69, –5.68)[a]	–6.6 (–7.07, –6.08)[a]	NR (35.1)
	Placebo	Full trial population, 12 weeks	–5.59 (0.23)	–5.97 (0.23)	NR
	Placebo	≥3 previous prophylaxis treatments, 24 weeks	–4.3[b] (NR)	–4.7[b] (NR)	51/207 (25)
Study 295 (NCT02066415)	Erenumab 70mg	Full trial population, 12 weeks	–6.63 (0.45)	–6.43 (0.45)	[redacted]
	Erenumab 70mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Erenumab 140mg	Full trial population, 12 weeks	–6.53 (0.50)	–6.96 (0.52)	[redacted]
	Erenumab 140mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Placebo	Full trial population, 12 weeks	–4.24 (0.38)	[redacted]	[redacted]
	Placebo	≥3 previous prophylaxis treatments, 12 weeks	[redacted]	[redacted]	[redacted]

Source: Table 17, Appendix D of the CS and Response to clarification, question A17

[a]95% confidence intervals are reported instead of standard error; [b]Means reported for these outcomes are least-squares means, not absolute means. [c]Note that the ITC utilised data from patients who had failed on ≥3 prior prophylactic treatments irrespective of category, in order to most accurately reflect the decision problem

CfB: change from baseline; NR: not reported; SE: standard error

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The indirect comparison (ITC) compared erenumab 70mg and 140mg with botulinum toxin for the optimised population (≥3 previous prophylactic treatments had failed) using data from Study 295 and PREEMPT. As the two studies reported outcomes at different timepoints (12 weeks for Study 295 and 24 weeks for PREEMPT) three different analyses were performed.

1. Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison
2. Full trial population primary endpoint comparison (12 weeks for erenumab and 24 weeks for botulinum toxin
3. Full trial population, 12 weeks for both treatments

The ITC used the recommended statistical analysis method, the Bucher method[35] and the analyses performed were appropriate. Apart from the differences in the timepoints, the CS judged the two studies to be similar for most baseline characteristics and the baseline values of the outcomes included in the ITC. "It was therefore determined that there was no risk of bias due to the imbalances". The conclusions from the supporting ITC analyses using full trial data for the primary endpoint and 12 weeks were similar to those from the subgroup for whom ≥ 3 prior prophylactic treatments have failed, and none of the analyses found any statistically significant differences between erenumab 70mg or 140mg and botulinum toxin for ≥ 50% response, or change from baseline in mean monthly migraine days or mean headache days.

The ERG does not have any concerns about the methods or results of the ITC analyses. A summary of the results of the ITC analyses is provided in Table 4.17.

Table 4.17: ITC results for erenumab versus botulinum toxin

Group	Treatment 1	Treatment 2	Point estimate: Treatment 1 vs Treatment 2 (95% CI)[a]
≥50% responder rate (monthly headache days)			
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 140mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
≥50% responder rate (defined in terms of monthly migraine for erenumab and monthly headache days for botulinum toxin)			
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]

Group	Treatment 1	Treatment 2	Point estimate: Treatment 1 vs Treatment 2 (95% CI)[a]
Full trial population, primary endpoint comparison	Erenumab 140mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Mean monthly migraine days			
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=231	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70mg (12 weeks), n=178	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70mg (12 weeks), n=178	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=231	[redacted]
Full trial population, primary endpoint comparison	Erenumab 140mg (12 weeks), n=182	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140mg (12 weeks), n=182	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Mean monthly headache days			
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=231	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70mg (12 weeks), n=178	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70mg (12 weeks), n=178	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]

Group	Treatment 1	Treatment 2	Point estimate: Treatment 1 vs Treatment 2 (95% CI)[a]
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=231	[redacted]
Full trial population, primary endpoint comparison	Erenumab 140mg (12 weeks), n=182	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140mg (12 weeks), n=182	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]

Source: Tables 38 to 41 (CS Section B.2.8.2) and Tables 19 to 22 (CS Appendix D)

[a]A negative point estimate indicates that the comparison favours treatment A, n is number of patients at Week 12 of the trials

CI = confidence interval; NA = not applicable

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The NICE scope describes the clinical effectiveness of erenumab, within its marketing authorisation, for the prophylaxis of migraine. Erenumab has received marketing authorisation from the EMA for the prophylaxis of migraine in adults who have at least four migraine days per month when initiating treatment with erenumab. The submission focuses on a subgroup of adult patients, those with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed, who are considered likely to reflect the expected use of erenumab in the NHS. However, it does not fully reflect the final scope, and does not represent the whole population for which erenumab has received marketing authorisation from the EMA. The evidence for erenumab in the submission population (adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed) is based on *post-hoc* subgroup analyses of data from four RCTs involving approximately 20% of the total studied population. Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented in the erenumab studies, both with respect to the whole study population and to the subgroup relevant to this submission. There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

Given the definitions of chronic (≥15 headache days per month, of which ≥8 were migraine days) and episodic (≥4 and <15 migraine days per month with <15 headache days per month) migraine used in the included studies, there is a population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population.

The description of comparators in the NICE scope is: "Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies." The company included BSC as a comparator for all populations considered and Botulinum toxin as a comparator for chronic migraine population only, in-line with NICE guidance (TA260).[21]) These comparators are appropriate for the population addressed in the company submission (adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed). However, any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s). For the main comparator, BSC, the company considered the placebo arms of the erenumab trials to be representative of BSC; this assumption is supported by the details of on-study treatments acute migraine episodes, which were provided in the company's response to points for clarification submitted by the ERG.

There is a lack of long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, for either the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed or the wider population covered by the marketing authorisation. Furthermore, three of the four erenumab studies had a double-blind phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was mean monthly migraine days.

Studies evaluated different doses of erenumab; Study 295 and STRIVE evaluated 70mg and 140mg Q4W, ARISE evaluated 70mg Q4W, and LIBERTY evaluated 140mg Q4W. In Study 295 (chronic migraine) the optimised population (≥3 prior prophylactic treatments have failed) had better outcomes

in the erenumab 70mg and 140mg groups than in the placebo group. More specifically, at week 12 patients experienced approximately two and a half fewer migraine days whilst taking erenumab 70mg and four fewer whilst taking erenumab 140mg than on placebo. In total, 34.8% of patients taking 70mg of erenumab and 38.5% of patients taking 140mg erenumab achieved a ≥50% reduction in MMDs from baseline, compared to 15.3% of patients on placebo. In studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks, and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed.

The erenumab studies included in the CS used a variety of instruments to assess the impact of erenumab treatment on health-related quality of life: Study 295, HIT-6, MSQ 2.1, MIDAS and PROMIS; STRIVE, HIT-6, MSQ 2.1, MIDAS and MPFID; ARISE, HIT-6, MSQ 2.1 and MPFID; LIBERTY, HIT-6, EQ-5D-5L and WPAI. All health-related quality of life results were for the full study populations; no health-related quality of life data were provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Economic modelling used utility values which were derived by mapping patient-level MSQ 2.1 data from Study 295, STRIVE and ARISE onto EQ-5D-3L.

The rates of SAEs in the erenumab treatment arms were generally low, across all four studies. No adverse events data were provided for the active comparator, botulinum toxin, but data from the PREEMPT trials indicated that botulinum toxin may be associated with a higher rate of SAEs than erenumab.

No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus botulinum toxin, in patients with chronic migraine. The ERG does not have any concerns about the methods or results of the ITC analyses.

Overall, although the evidence for erenumab is based on international RCTs investigating patient-relevant outcomes, there is uncertainty about the effectiveness of the lower (70mg Q4W) dose for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, particularly for those patients with episodic migraine. There is also a lack of data for male patients, those over 65 years of age and for non-white populations. The long-term effectiveness of erenumab (beyond 24 weeks) is unknown.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

A combined SLR was performed with the objective to identify and select relevant literature on 1) Economic evaluations of pharmacological interventions for the treatment of chronic or episodic migraine (CS Appendix G[38]); 2) Health state utility values for chronic or episodic migraine patients (CS Appendix H[38]); and 3) Cost and resource use data for chronic or episodic migraine patients (CS Appendix I[38]). The initial search was performed in July 2017 and updated in January 2018. In response to clarification, the cost effectiveness searches were updated again in September 2018.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

A SLR was conducted to identify economic evidence to support the development of a cost effectiveness model for erenumab for the treatment of chronic or episodic migraine. The search strategies applied included terms to identify utility values as well as economic evaluations, resource use and costs. Searches were originally carried out in July 2017 and subsequently updated in January and September 2018. The following databases were searched: Medline, including Medline Daily, In-Process and Epub Ahead of Print, Embase, HTA Database, NHS Economic Evaluation Database (NHS-EED) and EconLit. The host provider for each database was listed, the date span of the databases and the date the searching was conducted was provided. In addition to electronic database searches, manual searches of major migraine and neurological congresses held over the past three years (2015-2018) were undertaken. High-quality abstracts from congresses before 2015 were expected to have been published in full-text so searches earlier than 2015 were not needed. Supplementary searches were also carried out in NICE, Scottish Medicine Consortium (SMC), All Wales Medicines Strategy Group (AWMSG), National Centre for Pharmacoeconomics (NCPE), Cost-effectiveness Analysis (CEA) Registry, University of Sheffield Health Utilities Database (ScHARRHUD), EQ-5D Publications Database and EconPapers at Research Papers in Economics (RePEc). Embase and Medline searches used recognised study design filters from SIGN for economic studies with some added extra terms to increase sensitivity. To identify health state utility studies, search terms were based on those proposed in the NICE Decision Support Unit's (DSU) Technical Support Document 9.[30] Reference lists of relevant SLRs, meta-analyses, HTA submissions and economic evaluations were also checked. The searches met the requirements detailed in the NICE guide to the methods of technology appraisal.[50]

ERG comment:

- A wide range of resources to identify published and unpublished literature were searched and searches were well-reported and reproducible.
- The database searches were clearly structured (population and study design), using a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation.

5.1.2 Inclusion/exclusion criteria used in the study selection

Inclusion and exclusion criteria for cost effectiveness studies, utilities, and costs and resource use studies are presented in Table 5.1.

Table 5.1: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with chronic or episodic migraine	Articles reporting populations without chronic or episodic migraine patients, and articles reporting populations with ≥50% children
Intervention	Prophylactic pharmacological interventions, see CS Appendix G [38]	• Non-pharmacological interventions • Acute treatments • Herbal remedies • Several prophylactic treatments, see CS Appendix G[38]
Comparator	Any comparator	None
Outcomes(s) 1 (Published economic evaluations)	Outcomes of relevant study designs, including: • Costs • Life years gained (LYG) • Quality-adjusted life years (QALYs) • Incremental costs and QALYs • Incremental cost effectiveness ratios (ICERs)	Studies not reporting relevant outcomes
Outcomes(s) 2 (Utility studies)	Original health state utility data, for example those measured using: • EQ-5D • SF-6D • HUI3 • Time trade-off • Standard gamble	
Outcomes(s) 3 (Cost/resource use studies)	Original costs or resource use data relevant to a cost-utility analysis from the perspective of the UK NHS and personal and social services (PSS) (or social work in Scotland) or the Health Service Executive in Ireland	
Study design 1 (Cost effectiveness analysis studies)	Original economic evaluations considering both the costs and benefits of alternative interventions: • Cost effectiveness • Cost utility	• Publications without original data • Comments • Letters • Editorials

PICOS	Inclusion criteria	Exclusion criteria
	• Cost benefit • Cost minimisation • Cost consequence • SLRs of economic reviews (for reference list search)	• Non-systematic/narrative reviews • Articles not in the English language • Studies not in human subjects Studies not conducted from a UK or Irish perspective (applicable to cost effectiveness studies and cost and resources use studies)
Study design 2 (Utility studies)	• Primary research publications on any study design • HTAs, or SLRs of relevant primary publications (for reference list search)	
Study design 3 (Cost/resource use studies)	• Primary research publications on any study design • HTAs, or SLRs of relevant primary publications (for reference list search)	

Source: CS Appendix Tables 35-37[38]
Abbreviations: EQ-5D: EuroQol 5-Dimensions; HTA: Health Technology Assessment; HUI3: Health Utilities Index; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHS: National Health Service; PSS: Personal and Social Services; QALYs: quality-adjusted life years; SF-6D: Short-Form Six-Dimension; SLR: systematic literature review; UK: United Kingdom

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. However, the ERG is concerned about the potential language bias arising from restricting searches to English language only; this is not in line with current best practice.

5.1.3 Included/excluded studies in the cost effectiveness review

The initial SLR related to cost effectiveness evidence identified 0 publications which met the inclusion criteria, 3,410 titles/abstracts and 205 full texts were reviewed. Six additional publications were found through handsearching of conference proceedings and websites. The 2018 update of the SLR resulted in additional six publications, the updated hand search resulted in one additional article. Hence, a total of six unique economic evaluations, and 19 unique cost/resource use studies were identified. Twenty-two unique utility studies were identified of which 13 reported EQ-5D utility values (see Appendix G of the CS Figure 5 for the PRISMA diagram).[38] The included cost effectiveness studies were summarised and critically appraised using the checklist of Drummond et al. (1996),[51] in Tables 40 and 41 of the CS Appendix.[38] Summaries of utility studies, and cost and resource use studies included were presented in Tables 42 and in Appendices G, H and I of the CS.[38]

ERG comment: The rationale for excluding cost effectiveness studies after full paper reviewing is considered appropriate given the defined inclusion and exclusion criteria. Nine publications identified in the SLR were not fully extracted because they did not report EQ-5D data and were thus not in line with the NICE reference case (Table 43 of the CS Appendix H[38]). Considering the potential limitations of the EQ-5D in migraine patients and the scarcity of utility data in migraine patients with ≥3 prior prophylactic treatment failures, as outlined in Section 5.2.8, the ERG is concerned that relevant HRQoL

studies may have been excluded. Furthermore, for utility studies, and cost and resource studies, the reasons for exclusion of articles and a quality assessment of included articles were not presented.

5.1.4 Conclusions of the cost effectiveness review

The CS and CS appendices provided an overview of the included cost effectiveness, health-related quality of life, and resource use and costs studies. None of the identified economic evaluations assessed the cost effectiveness of erenumab. No specific conclusion has been formulated for the HRQoL studies included in the review. Studies identified on costs and resource use did not report results by MMD frequency, therefore resource use was mainly informed by the 2017 and 2018 National Health and Wellness Surveys.[52, 53]

5.2 Summary and critique of company's submitted economic evaluation by the ERG

The company developed a de novo model. Relevant parameters are described in Table 5.2. A checklist comparing the model to the NICE reference checklist is given in Table 5.3.

Table 5.2: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Combined decision tree and state transition model	To represent the assessment period (decision tree) and the long-term post-assessment period (state transition model)	Section B.3.2.2
States and events	Decision tree endpoints: responder, non-responder state transition model health states: on treatment, discontinuation, death.		Section B.3.2.2
Comparators	BSC Botulinum toxin (chronic migraine population only).	There are no treatment options for episodic migraine patients (for whom ≥3 prior prophylactic treatments have failed). Thus, BSC is the most relevant comparator. Botulinum toxin has been recommended in patients classified as having chronic migraine (for whom ≥3 prior prophylactic treatments have failed). However, due to limited availability of botulinum toxin (as it must be administered by a trained specialist), BSC is also a relevant comparator for chronic migraine patients.	Section B.3.2.3
Population	Migraine patients for whom ≥3 prior prophylactic treatments have failed. This population consisted of episodic migraine patients (with <15 MHDs and	The population is a subpopulation of the population as defined in the	Section B.3.2.1

	Approach	Source/Justification	Signpost (location in CS)
	≥4 to <15 MMDs) and chronic migraine patients (with ≥15 MHDs and ≥8 MMDs).	NICE scope and the licence for erenumab.	
Treatment effectiveness	Treatment effectiveness was estimated based on the estimated response, MMD frequency and treatment discontinuation.	Treatment effectiveness was informed from the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in Study 295, STRIVE, ARISE and LIBERTY.	Section B.3.3
Adverse events	Adverse events were accounted for through treatment discontinuation, but the impact on costs and HRQoL was not explicitly modelled.	The company justified this approach based on expert advice from UK clinicians stating that adverse events associated with migraine prophylaxis are usually non-severe.	Section B.3.3.7
Health related QoL	Treatment independent utility values were estimated based on mapped MSQ data from Study 295, STRIVE, and ARISE for each MMD frequency. Treatment dependent health state utility values were estimated based on the MMD frequency distributions of each treatment.	The EQ-5D-5L data from LIBERTY were not used. The company states that the advantage of the MSQ over the EQ-5D is its recall period of four weeks, which makes it more likely to capture the impact of experiencing migraine than the EQ-5D.	Section B.3.4
Resource utilisation and costs	The cost categories included in the model were treatment costs and costs of disease management	Unit prices stemmed from the manufacturer, the British National Formulary (BNF) 2017, the National Health Service (NHS) Tariff 2017 and the Personal Social Services Research Unit (PSSRU) 2017. Resource use was mainly retrieved from the pivotal trials as well as the National Health and Wellness survey of 2017 and 2018.	Section B.3.5
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case.	Table 60
Subgroups	Patients with HFEM for whom ≥3 prior prophylactic treatments have failed (HFEM was defined as 8–14 MHDs).	The HFEM population is a recognised subgroup of episodic migraine patients who are considered to have a clinical burden similar to patients classified as having chronic migraine. However, unlike chronic migraine patients, patients with HFEM	Section B.3.2.1

	Approach	Source/Justification	Signpost (location in CS)
		at this line of therapy are unable to access botulinum toxin in line with its NICE recommendation. The subgroup of HFEM patients therefore face a particularly high unmet need.	
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses.		Section B.3.8

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	The company defines a narrower population (i.e. patients for whom ≥3 prior prophylactic treatments have failed).
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Yes	
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	No	Time horizon was restricted to ten years
Synthesis of evidence in outcomes	Systematic review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	No	Mapped utilities (from MSQ) were used in the base-case instead of EQ-5D-5L utilities.

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	No	Mapped utilities were used.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Partly	Important parameters were excluded from the sensitivity analyses
NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review			

5.2.2 Model structure

The company developed a decision-tree plus state transition model (named Markov model by the company) in Microsoft Excel (Figure 5.1). The decision tree represented the assessment period and the state transition model represented the post-assessment period. The costs and QALYs associated with the health states are calculated as a function of the MMD frequency distributions.

Assessment period

A 12-weeks assessment period was modelled for erenumab and BSC, justified by the company as the length of time deemed clinically appropriate to observe a change in MMDs. The assessment period was 24 weeks for botulinum toxin (chronic migraine population only), which is consistent with previous TA260 and NICE guidance.[21]

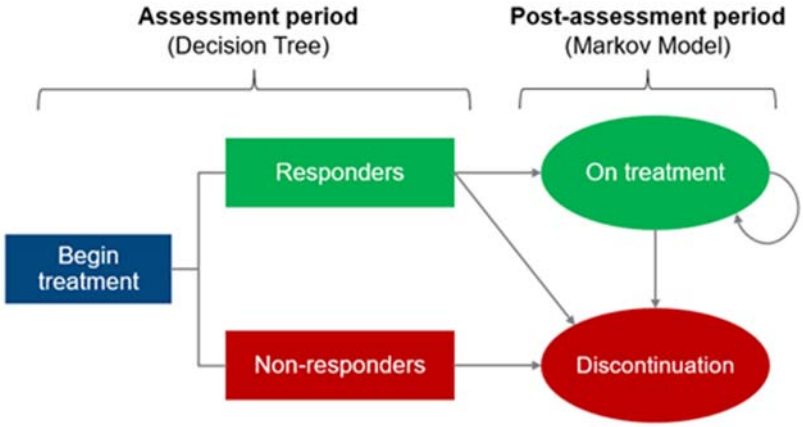
Response was assessed at the end of the assessment period and was defined as a ≥50% reduction from baseline MMD. Patients who discontinued treatment due to adverse events during the assessment period entered the 'discontinuation' health state in the state transition model and were assumed to rebound to the baseline MMDs distribution.

Post-assessment period

The state transition model consisted of three health states: on treatment, discontinuation and death. At the assessment time point, non-responders entered the discontinuation health state, discontinued prophylactic treatment and were assumed to receive only BSC (i.e. acute and background disease management). Non-responders maintained their non-responder MMD as measured at the assessment time point for the remainder of the model time horizon. From the assessment time point onwards (i.e. either 12 or 24 weeks), the post-assessment costs and utilities (depending on the MMD frequency distribution) were applied. Responders entered the on-treatment health state and were assumed to

remain on erenumab or the comparator treatment and hence maintain the responder MMD until treatment discontinuation.

Figure 5.1: Decision-tree plus state transition model (death not shown)



Source: Based on Figure 19 of the CS.[1]

ERG comment: The main concerns of the ERG relate to: a) the failure to fully capture natural progression of disease in the model; b) the 50% response threshold used to define response; c) the positive treatment discontinuation scenario (i.e. re-evaluating responders for continuation of treatment whereby positive discontinued patients maintain the responder MMD); d) the use of a discontinuation risk from 24 weeks onwards (as opposed to immediately following assessment) and; e) differential onset of responder/non-responder specific costs and utilities.

a) Based on the AMPP study (US), patients with migraine may over the course of one-year experience persistence of disease (84%), clinical remission (10%), partial remission (3%), and progression (3%).[54] This natural progression of migraine was not fully captured in the model. This was justified by the company by stating that it would require added complexity in the model, and noting the scarcity of natural progression evidence.[22] In clarification response, the company assumed that, when included in the model, the sum of temporary progressions and remissions would not lead to drastically different results. To illustrate this, the company explored three scenarios with: 1) decrease of respondent health state utility over time (to simulate progression in both arms; 2) the doubling of long-term discontinuation (to reflect remission) and; 3) a variation of scenario 6 (positive discontinuation scenario in the original CS) with an increased proportion of positive discontinuation (alternative scenario to reflect remission on erenumab). The estimated incremental cost-effectiveness ratios (ICERs) in these scenario analyses were lower than the ICER estimated for the company base-case. The ERG considers the company's justification for not modelling natural progression of migraine reasonable, wishes to point out that considerable uncertainty may arise from it (given that the impact and direction of this simplification is not fully known).

b) Based on expert opinion, the company defined a 50% reduction in MMDs as the criterion to determine treatment response. According to NICE TA260 on botulinum toxin in chronic migraine, treatment should be stopped in people whose condition is not adequately responding to treatment; defined as less than a 30% reduction in MHD after two treatment cycles.[21] The committee concluded that a 30% response rate was the most clinically relevant and reasonable negative (due to no response) stopping rule on which to base its decision. Given that the majority of the modelled population were patients with chronic migraine, the ERG considers the responder criterion defined

in TA260 clinically relevant, and presents a scenario analysis using a 30% reduction in MMD as response threshold.

c) According to NICE TA260 on botulinum toxin in chronic migraine, treatment should also be stopped in people whose condition has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.[21] To reflect the potential impact of this, the ERG adopted the positive discontinuation scenario (CS scenario 6) as a scenario analysis. This scenario assumed that continuously after a maximum of 64.5 weeks all patients on treatment discontinue treatment for a re-evaluation period of 12 weeks. In total, 20% of the re-evaluated patients experience positive treatment discontinuation i.e. they stop treatment and thus do not incur the cost of treatment, but continue to receive the benefit of treatment (i.e. the same MMD frequency distribution as responders that are on treatment). The ERG could not identify any evidence to support these assumptions, hence this scenario should be interpreted with caution.

d) The company included a long-term discontinuation probability to model all cause discontinuation in the post-assessment period. This probability was applied from week 24 onwards for erenumab and BSC, and from week 36 onwards for botulinum toxin. However, this should have been applied directly after the response assessment (i.e. 12 weeks for erenumab and BSC and 24 weeks for botulinum toxin). This was adjusted in the ERG base-case.

e) The timing of assessment of response was modelled dependent on the treatment arm, either after 12 weeks (erenumab and BSC) or after 24 weeks (botulinum toxin), whereby baseline utilities and costs were applied in the pre-assessment period and response-specific utilities and costs were applied in the post-assessment period. The ERG is concerned this approach is not reflective of the utility and cost benefits of response that are likely to manifest prior to this assessment point, especially regarding treatment with botulinum toxin where response-specific utilities and costs are only applied after 24 weeks. Hence, to explore the impact of this assumption the ERG applied the post-assessment costs and utility for botulinum toxin at 12 weeks in a scenario.

5.2.3 Population

Erenumab, as per the marketing authorisation, is indicated for the treatment of all patients with migraine who experience ≥4 MMDs (i.e. the licensed indication is not defined in terms of episodic or chronic migraine). In the final scope, issued by NICE, the population was defined as "all people with migraine". However, the company assessed the cost effectiveness of erenumab in adults with migraine with ≥4 MMDs for whom ≥3 prior prophylactic treatments have failed. Within this subgroup, three populations were considered, hereafter referred to as:

- Whole population base-case (patients with ≥4 MMDs)
- Episodic migraine population (patients with <15 MHDs and ≥4 to <15 MMDs)
- Chronic migraine population (patients with ≥15 MHDs and ≥8 MMDs)

In the model, patients had an average age of 42 years and 85% of the population was assumed to be female (based on the average from the pivotal trials, i.e. Study 295 for chronic migraine and ARISE, STRIVE and LIBERTY for episodic migraine). The whole population was based on a weighted average of chronic and episodic migraine (66% and 34% respectively; based on market research from the UK).

In addition, the HFEM (8-14 MHDs) subgroup was considered using subgroup specific clinical effectiveness data (e.g. proportion of responders, MMD frequency distributions). According to the company, this subgroup is considered to have a clinical burden similar to patients with chronic migraine. However, HFEM patients are not able to access botulinum toxin (NICE recommendation), and

therefore, this subgroup faces a particularly high unmet need. Finally, exploratory analyses modelled the population in whom ≥2 prophylactic treatments have failed and who are unable to receive further prophylactic treatment.

ERG comment: The main concerns of the ERG relate to: a) lacking evidence for patients with ≥15 MHDs and ≥4 to <8 MMDs; b) proportions of episodic and chronic migraine patients and; c) HFEM subgroup definition.

a) The ERG notes an inconsistency between the population of the main trials (Study 295, STRIVE, ARISE and LIBERTY) and the overall population as described in the model as well as the licensed indication. Patients with ≥15 MHDs and ≥4 to <8 MMDs were not included in either the trials on chronic migraine or the trials on episodic migraine (see also Sections 4.2.1 and 5.2.6). However, these patients are included in the definition of the whole population (migraine patients with ≥4 MMDs). The company assumed that data from chronic and episodic patients are transferable to this patient group.[22] As no justification was provided for this assumption and the characteristics of the excluded population are unknown, the ERG finds this assumption not well-founded and considers the evidence for the cost effectiveness of erenumab in patients with ≥15 MHDs and ≥4 to <8 MMDs to be lacking.
b) In the company base-case, it was assumed that chronic and episodic migraine patients make up the base-case population at a ratio of 66% and 34%. The company justified this assumption using their 2018 market research.[1] In response to clarification question B5, the company provided evidence from the BECOME trial and the literature supporting their assumption.[22] The ERG believes that the ratio of 66% and 34% is reasonable but that it is more informative to consider the chronic and episodic populations separately. This is in line with the pivotal trials and does not imply that all patients with ≥4 MMDs are covered (including the population with ≥15 MHDs and ≥4 to <8 MMD).
c) Throughout the CS, two definitions of HFEM were used (8-14 MHDs or 8-14 MMDs).[1] In response to clarification question B3, the company stated that in the LIBERTY trial, HFEM was defined as 8-14 MMDs, but in the economic mode, HFEM was defined as 8-14 MHDs.[22] This latter definition is more in line with definitions used in the literature, but assumes that data from patients with 8-14 MMDs can be used to inform outcomes in patients with 8-14 MHDs. Given that MMDs and MHDs are separate outcomes, this assumption may be invalid. The potential bias caused by this assumption is unclear. Additionally, other HFEM definitions can be found in the literature (e.g. 10-14 MHDs). To assess the impact of the definition used for the HFEM subgroup, the ERG presents a scenario using a 10-14 MHDs definition for HFEM.

5.2.4 Interventions and comparators

As per the licensed posology, the recommended dose for erenumab (self-administered subcutaneously) is 70mg Q4W. However, some patients may benefit from the higher 140mg Q4W dosage (given as two injections of 70mg). The company therefore assumed in their base-case that 50% of patients started treatment on erenumab 140mg and the remaining 50% started on erenumab 70mg. Erenumab was modelled to be used in combination with BSC.

BSC was defined as continued treatment with acute medication and healthcare resource use as a function of the MMD frequency being experienced. The company stated that the placebo arms in Study 295, STRIVE, ARISE and LIBERTY can be considered as reasonably representative of BSC in UK clinical practice, because patients were prescribed any treatments necessary to provide adequate supportive care in these trials.

Botulinum toxin was modelled as a comparator for patients having chronic migraine for whom ≥3 prior prophylactic treatments have failed, in line with its recommended use.

ERG comment: The main concern of the ERG relates to the use of the blended dose.

The base-case presented by the company used a blended dose of erenumab 70mg and erenumab 140mg for the intervention arm, assuming a dose mix of 50% and 50%, respectively.[1] The recommended and licensed dose of erenumab is 70mg, for which the results were presented in CS Appendix Z.2.[38] The use of the blended dose and the 50%/50% distribution were not appropriately justified. The employment of a blended dose is illogical because the purpose of the model is to estimate the cost effectiveness per patient of one mutually exclusive treatment compared to another: no patient will receive the blended dose. Put another way, the cost effectiveness analysis aims to inform a decision as to which single treatment to provide to a patient, which, if it is erenumab, can only be either one dose or the other. Although, in their clarification response letter, the company mentioned that "numerically superior clinical outcomes were observed for patients treated with erenumab 140mg compared to erenumab 70mg in the subgroup of patients for whom ≥3 prior treatments have failed", it did not specify which subgroup of patients would be most suitable for the 140mg dose of erenumab or how these patients should be identified.[22] Therefore, the ERG included erenumab 70mg and erenumab 140mg separately in its base-case analysis (instead of the blended dose).

ERG comment: The ERG questioned the use of placebo arms as a proxy for BSC in the UK. In their clarification response, the company elaborated that continued treatment with acute medication is the only treatment available in patients with ≥3 prophylactic treatment failures.[22] The company stated that "Patients in the placebo arms of Study 295, STRIVE, ARISE and LIBERTY were prescribed any treatments deemed necessary to provide adequate supportive care for the duration of the studies",[22] and provided information to show that the medications used were reflective of NICE guideline CG150 recommendations.[11] The ERG considers the evidence supportive of the assumption that BSC is adequately reflected by the studies' placebo arms (see also Section 3.3).

5.2.5 Perspective, time horizon and discounting

The analysis took an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was 12 weeks with a 10-year time horizon, and a half-cycle correction was applied.

ERG comment: In their base-case, the company used a 10-year time horizon for the cost effectiveness analysis of erenumab versus BSC and botulinum toxin, which is not in accordance with the NICE reference case. In scenario analysis 9 of the CS, this time horizon was extended to 15 years, causing the ICER of erenumab versus botulinum toxin to increase, and the ICER of erenumab versus BSC to decrease.[1] To adhere to the NICE reference case, the ERG extended the time horizon to a lifetime time horizon in their ERG base-case analysis. The ERG also noted that the company converted between weekly and annual results by using the factor 52, because the preferred method is to divide by 52.18 (365.25 divided by 7), the ERG amended this in their base-case.

5.2.6 Treatment effectiveness and extrapolation

Clinical parameters were mainly derived from the subgroup of patients for whom ≥3 prior treatments had failed in the pivotal trials: Study 295 for chronic migraine (i.e. patients with ≥15 MHDs and ≥8 MMDs) and ARISE, STRIVE and LIBERTY for episodic migraine (i.e. patients with <15 MHDs and ≥4 to <15 MMDs). The whole base-case population consisted of a weighted average of chronic and episodic migraine (66% and 34% respectively).

Response assessment (decision tree period)

In the model, response was defined as a ≥50% reduction from baseline MMD. This was implemented at week 12 for erenumab and BSC, and at week 24 for botulinum toxin. For botulinum toxin the proportion of responders was estimated using odds ratios of [redacted] and [redacted] versus erenumab 70mg and 140mg respectively. These odds ratios were obtained from an indirect comparison of erenumab (response based on MMD) versus botulinum toxin (response based on MHD), see Table 5.4 and CS Tables 40 and 41.[1]

Table 5.4: Proportion of responders (at 12- or 24-weeks response assessment)

Treatment	Chronic migraine	Episodic migraine
Erenumab 70mg (12 weeks)	[redacted]	[redacted]
Erenumab 140mg (12 weeks)	[redacted]	[redacted]
BSC (12 weeks)	[redacted]	[redacted]
Botulinum toxin (24 weeks)	[redacted]	NA
Source: Based on Table 52 of the CS[1] Abbreviations: BSC = best supportive care; NA = not applicable		

Treatment discontinuation for responders

All non-responders were assumed to discontinue treatment at the response assessment (continuing to receive BSC). At the response assessment, responders could discontinue treatment due to adverse events (see Table 5.5). Finally, after the response assessment, a 'long-term' treatment discontinuation probability of 2.38% per cycle was applied for responders (i.e. 9.9% annually).

Table 5.5: Proportion of responders discontinuing due to adverse events (at response assessment)

Treatment	Chronic migraine	Episodic migraine
Erenumab 70mg (12 weeks)	0.00%	[redacted]
Erenumab 140mg (12 weeks)	1.06%	[redacted]
BSC (12 weeks)	0.71%	[redacted]
Botulinum toxin (24 weeks)	3.40%	NA
Source: Based on Table 53 of the CS[1] Abbreviations: BSC = best supportive care; NA = not applicable		

Monthly migraine days frequency distributions

The MMD frequency distributions were incorporated in the economic model assuming a normal distribution with a range truncated between 0-28 migraine days per month. Table 5.6 provides an overview of the mean and standard deviations used to estimate the truncated normal distributions. The MMD frequency distributions were not available for botulinum toxin, hence the company assumed the same MMD frequency distributions for botulinum toxin as for erenumab.

The baseline MMD frequency distributions were used until the response assessment. Afterwards, treatment- and response-dependent MMD frequency distributions were used for the remainder of the time horizon. It should be noted that the company assumed that where discontinuation occurred for any other reason than non-response (either due to adverse events or due to long-term discontinuation), patients would return to their baseline MMD frequency distribution (i.e. not the MMD frequency distribution for non-responders).

Table 5.6: MMD frequency distributions used in the economic model

	Treatment	Chronic migraine	Episodic migraine
		Mean (standard deviation)	Mean (standard deviation)
Baseline	Treatment independent	[redacted]	[redacted]
Responders 12 weeks	Erenumab 70mg	[redacted]	[redacted]
	Erenumab 140mg	[redacted]	[redacted]
	BSC	[redacted]	[redacted]
Non-responders 12 weeks	Erenumab 70mg	[redacted]	[redacted]
	Erenumab 140mg	[redacted]	[redacted]
	BSC	[redacted]	[redacted]

Source: Based on Table 88 of the CS Appendices[38]
Abbreviations: BSC = best supportive care

Mortality

No excess mortality was assumed. Hence, general population mortality was included in the model based on the Office of National Statistics (ONS) National Life Tables in England and Wales (2014-2016).

Extrapolation of treatment effectiveness

The treatment effectiveness was extrapolated by assuming that the transition probabilities (i.e. probability of treatment discontinuation) as well as the MMD frequency distributions are constant over time. The company justified the extrapolation of treatment effectiveness by referring to two (non-comparative) open-label extension studies: NCT01952574[43, 55] (considering erenumab 70mg in episodic migraine patients) and the open-label extension of Study 295[47] (considering erenumab 70mg and 140mg in chronic migraine patients). It was stated (based on NCT01952574[43, 55]) that "At Week 64, patients achieved a mean reduction of 5.0 (SD: 4.2) MMDs from a baseline of 8.8 MMDs (SD: 2.6), with 65% of patients achieving a reduction of ≥50% in MMDs from baseline". Moreover, based on the open-label extension of Study 295 (NCT20130255[47]) it was stated that "the mean (95% CI) change from Study 295 baseline in MMDs was [redacted] days at Week 24 and [redacted] days at Week 52 for the [redacted] patients who received either erenumab 70mg, erenumab 140mg or a combination of erenumab 70mg followed by erenumab 140mg over the course of the OLE"

ERG comment: The main concerns of the ERG relate to: a) the extrapolation of treatment effectiveness up to 52/64 weeks; b) the extrapolation of treatment effectiveness beyond the open-label extension studies; c) the floor and ceiling effects related to the truncated normal distributions assumed for the MMD frequency distributions; d) inconsistency between the company submission and the economic model regarding MMD frequency distributions; e) difference in definition of response for erenumab and botulinum toxin; f) assumptions related to the MMD distribution after treatment discontinuation and; g) the method used to combine data from STRIVE, ARISE and LIBERTY.

a) In response to clarification question B9a, the company argued that whilst the open-label extension studies "did not contain a control arm as this may have raised ethical challenges, these results support the assumption that the reduction in MMDs in patients treated with erenumab 70mg and 140mg is maintained at 64 weeks". The ERG believes this is reasonable to assume up to 64 weeks. However, it is unclear this is similar for the comparative effectiveness of erenumab versus placebo (i.e. BSC). Particularly, given that based on Figure 7 in the clarification response, the change from

baseline MMD seemed to have plateaued at the end of the initial trial period for erenumab (weeks 8-12) while for placebo this was still decreasing.

b) Considering the extrapolation beyond the open-label extension studies (after 52 weeks for chronic migraine and after 64 weeks for episodic migraine) up to 10 years (model time horizon), the company argued, in response to clarification question B9b, that "Whilst no data are available from longer-term follow-up of patients treated with erenumab, the results of these [open-label extension] studies provide no indication of a waning in the treatment effect: in both studies, patients experienced numerical reductions in MMDs from the end of the double-blind treatment phase to Week 52 or Week 64". However, the ERG believes that, given the absence of evidence related to the long-term effectiveness, it is uncertain whether there is a treatment waning effect. In response to clarification question B9d, the company explored an alternative scenario for the long-term effectiveness by reducing the health state costs and health state utilities for erenumab and botulinum toxin linearly over time, to eventually reflect the health state costs and health state utilities associated with BSC non-responders. This scenario indicated that a treatment waning effect could substantially increase the estimated ICERs. The scenario presented by the company assumed a treatment waning period of 10 years; decreasing this period would be likely to further increase the estimated ICERs. Th[illegible] sc[illegible]nario, as well as a similar scenario with a five-year waning period is adopted by the ERG.

c) For the implementation of the MMD frequency distributions in the model, the company assumed normal distributions wit[illegible] a ra[illegible]ge truncated between 0-28 migraine days per month. This restricted range resulted in floor an[illegible] ceil[illegible]g effects (see for instance CS Figure 24), which the company acknowledged may introduce bias (response to clarification question B12c). Although the company argues that this bias is conservative, this is not completely convincing to the ERG given that no evidence was provided to support thi[illegible]

d) The MMD frequency distributions were s[illegible]mmar[illegible]se[illegible] in Table 88 of the CS Appendix S.[38] However, additional MMD distributions to those desc[illegible] be[illegible] in the CS were used for the episodic migraine. Specifically, 24-week MMD distributions were ad[illegible]ed [illegible] responders. Given that the rationale for only using 24-week MMD distributions for respon[illegible]s [illegible]ith [illegible]sodic migraine was lacking, this inconsistency was adjusted in the ERG base-case to be [illegible] line with the CS description as well as with the chronic migraine population.

e) For the indirect comparison the different timings of response [illegible] [illegible]nu[illegible] (based on 12 weeks MMD) and botulinum toxin (based on 24 weeks MHD) were (impli[illegible]tly) [illegible]ssumed to have no effect on the size of the response. This may have biased the estimated cost and effects of botulinum toxin. However, the direction and magnitude of this bias is unclear to the ERG (see Sections 4.3 and 4.4 for more details).

f) The company assumed that the nature of treatment discontinuation determines whether patients either return to the baseline MMD distribution (discontinuation *due to adverse events or long*-term discontinuation) or maintain the non-responder MMD as measured at week 12 (discontinuation due to non-response at week 12). In response to clarification question B10 the company argued that response status reveals heterogeneity within the patient population of interest and thus it was assumed that a different propensity to respond to treatment also means a different disease status when coming off treatment. The company argued that those who respond to treatment would hence have experienced a 'better' natural improvement in MMDs compared to non-responders. The ERG believes that this argumentation is inconsistent with the modelling approach adopted by the company, given that in chronic migraine non-responders actually have a [redacted] MMD frequency than the baseline MMD frequency and in episodic migraine [redacted]. (see Table 5.6). Therefore, the ERG assumed that all treatment discontinuers would have the week 12 non-responder MMD frequency.

g) In response to clarification question B11, the company indicated that the patient-level data from STRIVE, ARISE and LIBERTY were combined without adjustment or weighting. This assumes that there is no trial-level effect and that the trials sample from the same patient population with the same MMD frequency at baseline. It is unclear to the ERG to what extent this latter assumption is reasonable or may induce bias. Moreover, this assumption might result in discrepancies with the data presented in chapter 4.

5.2.7 Adverse events

Adverse events were accounted for in terms of treatment discontinuation, but the impact on costs and HRQoL was not explicitly modelled. The company justified this approach based on expert advice from UK clinicians, stating that adverse events associated with migraine prophylaxis are usually non-severe (serious adverse events occurred in 1%-3% in Study 295, ARISE, STRIVE and LIBERTY).

ERG comment: The main concerns of the ERG relate to not explicitly modelling the impact of adverse events on costs and HRQoL. When considering the population for whom ≥3 prior prophylactic treatments have failed (instead of the whole trial population), the proportion of serious adverse events may be [redacted]. According to the company's response to clarification question A9, the serious adverse events may be as high as [redacted] and [redacted] for erenumab 70mg and 140mg respectively. However, given the small sample size it is not possible to draw firm conclusions regarding adverse events for patients for whom ≥3 prior prophylactic treatments have failed.

5.2.8 Health-related quality of life

For the company base-case analysis, treatment independent utility values for each MMD frequency were estimated based on Study 295, STRIVE, and ARISE. Utility values were estimated based on the MMD frequency distributions.

Health-related quality of life data identified in the review

According to the CS, the SLR identified 25 publications meeting the inclusion criteria. Of these, 16 publications reported EQ-5D utility values. None of these studies reported EQ-5D values by MMD frequency, or by migraine subpopulation.[1] Hence, none of the studies identified in the SLR were used in the company base-case analysis.

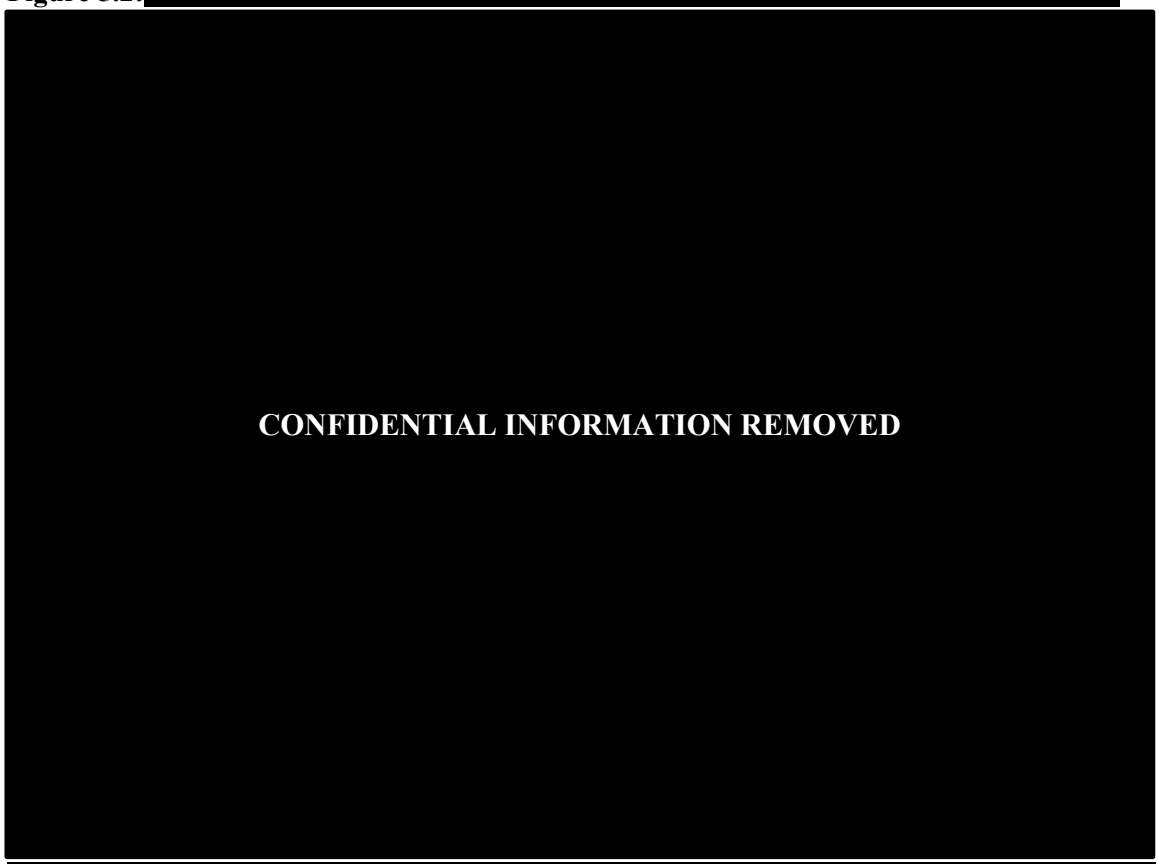
Health state utility values

The company stated that the advantage of the MSQ over the EQ-5D is its recall period of four weeks, which makes it more likely to capture the impact of experiencing migraine on quality of life than the EQ-5D-5L, which were collected in LIBERTY. For the base-case analysis, the company therefore mapped MSQ v2.1 utility data collected in Study 295, STRIVE, and ARISE trials to EQ-5D-3L utility values using the mapping algorithm described by Gillard et al. 2012.[56] MSQ data were not collected in LIBERTY.

The mapped MSQ utility values were used and multilevel models fitted to estimate disutility values associated with each MMD frequency. These multilevel models were fitted to all three studies combined for the whole migraine population analysis; and separately to Study 295 data and the pooled STRIVE and ARISE data for the indication specific (chronic and episodic migraine) analyses. The resulting estimated disutility values were re-converted into utility values by subtracting the disutilities from 1. Figure 5.2 provides an overview of the estimated utility values for each MMD frequency for the different populations. Health state utility values were obtained by multiplying the proportion of patients

in each MMD frequency by the utility values associated with each MMD frequency. A summary of all health state utility values used in the cost effectiveness analysis is provided in Table 5.7.

Figure 5.2: [redacted]



[redacted]

EQ-5D-5L data were collected during the LIBERTY trial but were (according to the company) not deemed suitable to inform the cost effectiveness analysis, because the utility elicitation took place on appointment days and asked the patients to rate their health at that moment. The company argued that most of the patients experiencing a migraine were likely to postpone their appointment and thus unlikely to experience a migraine during appointment days. Hence, utility values collected during LIBERTY do not represent the impact of experiencing migraine on quality of life. The utility values elicited in LIBERTY were used in a scenario analysis for the episodic migraine population (using the cross-walk from EQ-5D-5L to EQ-5D-3L[57]).

Based on expert opinion, disutilities associated with AEs and modes of administration were not included in the base-case analysis (see Section 5.2.7). A scenario analysis explored the influence of incorporating disutilities associated with mode of administration on the results. These disutilities were obtained from an unpublished vignette-based study including mostly general population respondents and some patients with migraine.[58]

Table 5.7: Health state utility values (conditional on MMD distributions; see Section 5.2.6)

	Treatment	Whole population	Chronic migraine	Episodic migraine
Baseline[a]	Treatment independent	0.577	0.466	0.688
Responders	Erenumab 70mg	0.743	0.735	0.769
	Erenumab 140mg	0.762	0.752	0.784
	BSC	0.746	0.731	0.770
Non-responders	Erenumab 70mg	0.601	0.491	0.695
	Erenumab 140mg	0.603	0.512	0.686
	BSC	0.592	0.495	0.685
On treatment (post-assessment period)[b]	Erenumab 70mg	0.741	0.735	0.760
	Erenumab 140mg	0.761	0.752	0.779
	BSC	0.741	0.731	0.756

[a] AE-related and long-term negative discontinuation have the same utility value as baseline

[b] See critique in 5.2.6 (ERG comment point d) regarding the addition of this time point for responders with episodic migraine only.

ERG comment: The main concerns of the ERG relate to a) the population in which the utility values were elicited, b) a lack of detail concerning the modelling of MMD specific disutilities, c) the exclusion of HRQoL impact of AEs, d) the use of EQ-5D data collected in LIBERTY, and e) the use of HIT-6 data mapped to EQ-5D.

a) Whilst treatment effectiveness was based on the population with ≥3 prior prophylactic treatments, utility values in the model were informed by the full trial population, as the company clarified in response to clarification question B14.b.[22] According to the company, using the population with ≥3 prior prophylactic treatments, the number of patients available in the analysis would be significantly reduced, particularly for STRIVE and ARISE. The ERG is concerned about this inconsistency in the evidence used. It is noteworthy that cost estimates were also derived from the full trial population. In response to clarification question B14.b, the company implemented a scenario using utility values estimated from the population with ≥3 prior prophylactic treatments, but only for the episodic and chronic migraine populations combined instead of for the indication-specific populations, due to small sample sizes. As the company indicated, the utility estimates estimated in the population with ≥3 prior prophylactic treatments reflect a greater increase in disutility associated with each MMD frequency, which improves the cost effectiveness of erenumab. This was supported by a decreased ICER for the blended dose of erenumab compared with placebo in the whole migraine population. Since the company only provided utility values estimated from the population with ≥3 prior prophylactic treatments for the episodic and chronic migraine populations combined (i.e. not indication-specific), the ERG maintains the company's base-case analysis using the full trial population in the ERG base-case. This ensures consistency in the derivation of utilities and resource use, but results in inconsistencies between utility and effectiveness estimates. Therefore, the ERG implemented the utility values estimated from the population with ≥3 prior prophylactic treatments in a scenario analysis.
b) The ERG is concerned about the lack of detail provided in the CS concerning the modelling of MMD frequency specific disutilities, in particular with regards to the pooling of studies, the handling of missing data and model selection. It should be acknowledged that the company provided most of the requested information in response to the clarification letter and most of the ERG's concerns have been addressed. One issue regarding missing data remains unresolved: the ERG notes that the number of missing observations in STRIVE (16.2%) was significantly larger than in Study 295 (3.9%) and ARISE (2.5%). It is not clear why this was the case and whether this may introduce any bias in the analyses. With regards to model selection, the ERG has further concerns. The linear model was chosen even though the company showed, in response to clarification question B14.a, that the cubic model made a better statistical fit. However, the ERG acknowledges that these models were very similar in terms of their statistical fit and agrees that the choice of linear model is likely to be appropriate. The alternative models, however, were not (correctly) implemented in the company's model (e.g. not all covariates were included), so any effect of this on the ICERs cannot be assessed by the ERG.
c) As was highlighted in Section 5.2.7, the ERG is concerned that HRQoL and costs associated with AEs are not reflected in the model (apart from causing treatment discontinuation). The ERG considers the impact of on-treatment AEs on HRQoL estimates to be relevant to this setting, in which patients will continuously receive prophylactic treatment with erenumab. In such a setting, even Grade 1/2 AEs may have an impact on patients' HRQoL. In response to clarification question B17, the company implemented a scenario including AEs. However, the ERG considers this to be potentially flawed, as the selection procedure for AEs was unclear, it assumed equal AE for erenumab 70mg and 140mg based on Study 295 only and the utility decrements relied on an unpublished vignette-based study[38] including mostly general population respondents and some

migraine patients, which is not in accordance with the NICE reference case.[50] It is further noteworthy that the company's results, presented in response to clarification question B17.e, also include a utility decrement for mode of administration associated with botulinum toxin (based on the same vignette-based study).

d) The company's argument that EQ-5D values did not capture the impact of migraine on HRQoL because they were elicited mostly during migraine-free days (and hence preferred mapped utilities from MSQ data over EQ-5D utilities), is plausible. However, using EQ-5D utilities from LIBERTY had a large impact on the ICER (increased from £35,787 in the CS base-case to £68,080 per QALY gained in the company's scenario, see CS Table 87). Since using EQ-5D utilities is in line with the NICE reference case, the ERG considers the use of LIBERTY EQ-5D data as a scenario analysis.

e) The company used mapped utilities from MSQ data, whilst mapped utilities from HIT-6 data could also have been used. In response to clarification questions B16, the company provided scenarios using the mapping algorithm by Gillard et al (2012)[56] to map HIT-6 data to EQ-5D utilities. In these scenarios, ICERs in all populations and comparisons increased by at least £10,000 per QALY gained (Tables 72-79 of response to the clarification letter).[22] However, the company pointed out that the HIT-6 instrument measures the impact of headaches, rather than that of migraines, on HRQoL. The ERG found that utility values per MMD frequency ranged from [redacted] using the HIT-6 instrument whilst they ranged from [redacted] using the MSQ instrument (whole migraine population). The latter are more aligned with utility ranges considered in the previous TA260,[21] which is likely to be because these were also based on MSQ data. The ERG considers that MSQ is likely to be a better source than HIT-6 for mapped utility data in this population.

5.2.9 Resources and costs

The cost categories included in the model were treatment costs and costs of disease management. Treatment costs included drug costs, administration costs and initiation costs. Costs for disease management included visits to the emergency department, general practitioner, nurse practitioner and neurologist, hospitalisations, migraine-specific medication (assumed to be represented by triptan use) and other medication (assumed to be represented by analgesics).

Unit prices stemmed from the manufacturer, the British National Formulary (BNF) 2017,[59] the National Health Service (NHS) Tariff 2017[60] and the Personal Social Services Research Unit (PSSRU) 2017.[61]

Resource use and costs data identified in the review

According to the CS, the SLR identified 22 publications reporting UK relevant resource use and costs, corresponding to 19 unique studies.[1] The company did not use these studies to inform resource use as none of them reported costs or resource use by MMD frequency. Instead resource use data from their National Health and Wellness survey (NHWS) of 2017 and 2018 were used.[52, 53]

Treatment costs (with PAS)

An overview of treatment costs is provided in CS Table 48.[1] Erenumab is either delivered per 70mg (1 × 70mg pre-filled pen) or per 140mg (currently two packs of 1 × 70mg pre-filled pen). The prices of the 70mg dose and 140mg dose are £[redacted] and £[redacted] respectively. Erenumab was administered three times per model cycle (of 12 weeks), the treatment cost per cycle were thus £[redacted] and £[redacted] for 70mg and 140mg respectively. Administration costs do not apply but a one-off initiation cost of £40.04 was incorporated to reflect training of the patient on how to use the injection (assumed to be the cost of one working hour of a Band 5 hospital nurse, applied in the first cycle only).[61]

No treatment costs for BSC were incorporated (besides the health state costs described below) given that both erenumab and botulinum toxin are used in conjunction with BSC. Botulinum toxin for chronic migraine was used at a list price of £276.40 per 200 IU vial, corresponding to the Summary of Product Characteristics (SmPC) recommended dose of 155 to 195 units, applied once per cycle. Administration costs of £116.00 were applied (assumed to be the tariff "WF01A Follow Up Attendance - Single Professional (code 400)" in the non-mandatory prices worksheet).[60] This resulted in treatment cost per model cycle (of 12 weeks) of £392.40.

Health state costs

Acute and background disease management costs were applied to all patients. This was solely dependent on the number of MMDs, i.e. independent of treatment status (see CS Table 51[1] for resource use frequency and cost per cycle by MMD frequency). Each model health state was associated with a different MMD frequency distribution (see Section 5.2.6 for more details). By combining these MMD frequency distributions with the costs per MMD frequency, average costs were calculated per health state.

The following components were included in the health state costs: emergency department (A&E) visits, hospitalisations, general practitioner visits, nurse practitioner visits, neurologist visits. Resource use by MMD frequency was informed by the NHWS 2017[52] and unit prices were taken from the NHS Tariff 2017[60] and the PSSRU 2017,[61] see CS Table 57.[1]

Migraine-specific medication use and other medication use per MMD frequency were also included. The company assumed migraine-specific medication could be represented by triptan use and other medication use could be represented by use of analgesics. The proportions of medications used were informed by the NHWS 2018,[53] unit prices and doses per migraine drug day/other medication day were taken from the BNF 2017.[59] A regression model based on pooled clinical data from Study 295, ARISE, LIBERTY and STRIVE informed the number of migraine drug days/other medication days per cycle by MMD frequency. Health state costs based on MMD distribution and MMD frequency-dependent healthcare utilisation are shown in Table 5.8.

Table 5.8: Health state costs per cycle (of 12 weeks)

Health state	Erenumab 70mg	Botulinum toxin[d]	Erenumab 140mg	Botulinum toxin[e]	BSC
Total population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Episodic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	Erenumab 70mg	Botulinum toxin[d]	Erenumab 140mg	Botulinum toxin[e]	BSC
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Model sheet 'Costs'[1]
Abbreviations: BSC: Best supportive care
[a] Patients with adverse event-related or long-term discontinuation in the post-assessment period are assumed to have baseline health state costs
[b] Referring to non-responders in the assessment period and patients off treatment in the post-assessment period due to initial non-response
[c] See critique in 5.2.6 (ERG comments point d) regarding the addition of this time point for responders with episodic migraine only.
[d] When compared to erenumab 70mg
[e] When compared to erenumab 140mg

Adverse event related costs
As described in Section 5.2.7., costs and resource use related to adverse events were not explicitly included in the cost effectiveness analysis.

ERG comment: The main concerns of the ERG relate to: a) the use of evidence from populations without ≥3 prior failures of prophylactic treatment, b) the merging of datasets related to migraine and other medication days, c) the inconsistency and representativeness of medication brands selected, d) assumptions related sumatriptan injections costs, e) patient grouping by MHDs for medication use per MMD and, f) the exclusion of the cost impact of AEs.

a) Due to the scarcity of data on patients with ≥3 prior failures of prophylactic treatment, all estimates of resource use and costs were obtained from patient populations not specified to have ≥3 prior failures of prophylactic treatment. The company provided no evidence that prior treatment failure does not impact the costs of migraine treatment.[22] Given that no evidence was provided, the ERG cannot rule out that the estimates presented are subject to bias.
b) The company pooled data on acute medication days and other headache medication days from Study 295, STRIVE and ARISE by merging datasets. This approach differs from the method used to pool QoL data (using a multi-level regression model) and assumes that there is no trial-level effect and that the trials sample from the same patient population with the same MMD frequency. It is unclear to the ERG to what extent these assumptions are reasonable or may induce bias.
c) To inform the prices of acute medication and other headache medication days, per medication item, a brand was selected to inform the price per medication dose. No specified criteria were used in the selection of the brand, causing inconsistency. It is unclear to what extent the brands chosen correspond with the brands predominantly used in UK clinical practice. The identified prices may therefore not be fully representative of the mix of brands used in UK clinical practice.
d) The company assumed sumatriptan injections (used in 18.4% of patients as headache medication,[22]) to have the same price as oral sumatriptan.[38] The justification for this assumption is unclear to the ERG. The ERG therefore amended the cost per triptan medication to reflect the costs of sumatriptan injections (instead of the costs of oral sumatriptan) in the ERG base-case analysis.
e) In their clarification response, the company amended a typographical error in Table 58 of the CS and clarified that patients were grouped by number of MHDs to estimate medication use by MMD.[22] The ERG considers the assumption of MHDs approximating MMDs to be questionable, given that

these are separate outcomes, and wishes to highlight that the estimates of resource utilisation may consequently be biased.

f) As was highlighted in Sections 5.2.7 and 5.2.8, the ERG is concerned that HRQoL and costs associated with AEs are not reflected in the model (apart from causing treatment discontinuation). The ERG cannot rule out that the exclusion of AE-related resource use and costs introduces bias in the cost effectiveness results.

5.2.10 Cost effectiveness results

The company presented their base-case results separately for the whole migraine, the chronic migraine population and the episodic migraine populations; and separately for the blended dose (50% of patients receiving erenumab 70mg and 50% erenumab 140mg), erenumab 140mg and erenumab 70mg (although the latter was only presented in Appendix Z.2). The deterministic base-case cost effectiveness results of erenumab (with PAS) compared with BSC for the blended dose amount to an ICER of £22,446 per QALY gained in the whole migraine population, to £18,893 per QALY gained in the chronic migraine population, and to £35,787 per QALY gained in the episodic migraine population. The results (including fully incremental results for the chronic migraine population, and the other doses) are shown in Tables 5.9-5.11.

Table 5.9: Company's deterministic base-case cost effectiveness results (blended dose)

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Fully incremental ICER (£/QALY)	ICER versus BSC
Company base-case whole migraine population						
BSC	[redacted]	[redacted]				
Erenumab 70mg/140mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£22,446
Company base-case chronic migraine population						
BSC	[redacted]	[redacted]			-	
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£15,953	£15,953
Erenumab 70mg/140mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,893	£17,212
Company base-case episodic migraine population						
BSC	[redacted]	[redacted]				
Erenumab 70mg/140mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£35,787

BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY =quality-adjusted life-year.
*Based on company's reported total costs and QALYs

Table 5.10: Company's deterministic base-case cost effectiveness results (erenumab 140mg)

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Fully incremental ICER (£/QALY)	ICER versus BSC
Company base-case whole migraine population						
BSC	[redacted]	[redacted]				
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£19,827
Company base-case chronic migraine population						
BSC	[redacted]	[redacted]			-	
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,601	£10,601
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,832	£13,340
Company base-case episodic migraine population						
BSC	[redacted]	[redacted]				
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£40,662

BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year.
*Based on company's reported total costs and QALYs

Table 5.11: Company's deterministic base-case cost effectiveness results (erenumab 70mg)

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Fully incremental ICER (£/QALY)	ICER versus BSC
Company base-case whole migraine population						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£26,803
Company base-case chronic migraine population						
BSC	[redacted]	[redacted]			-	
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£8,948	£8,948
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£20,339	£24,668
Company base-case episodic migraine population						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£29,200

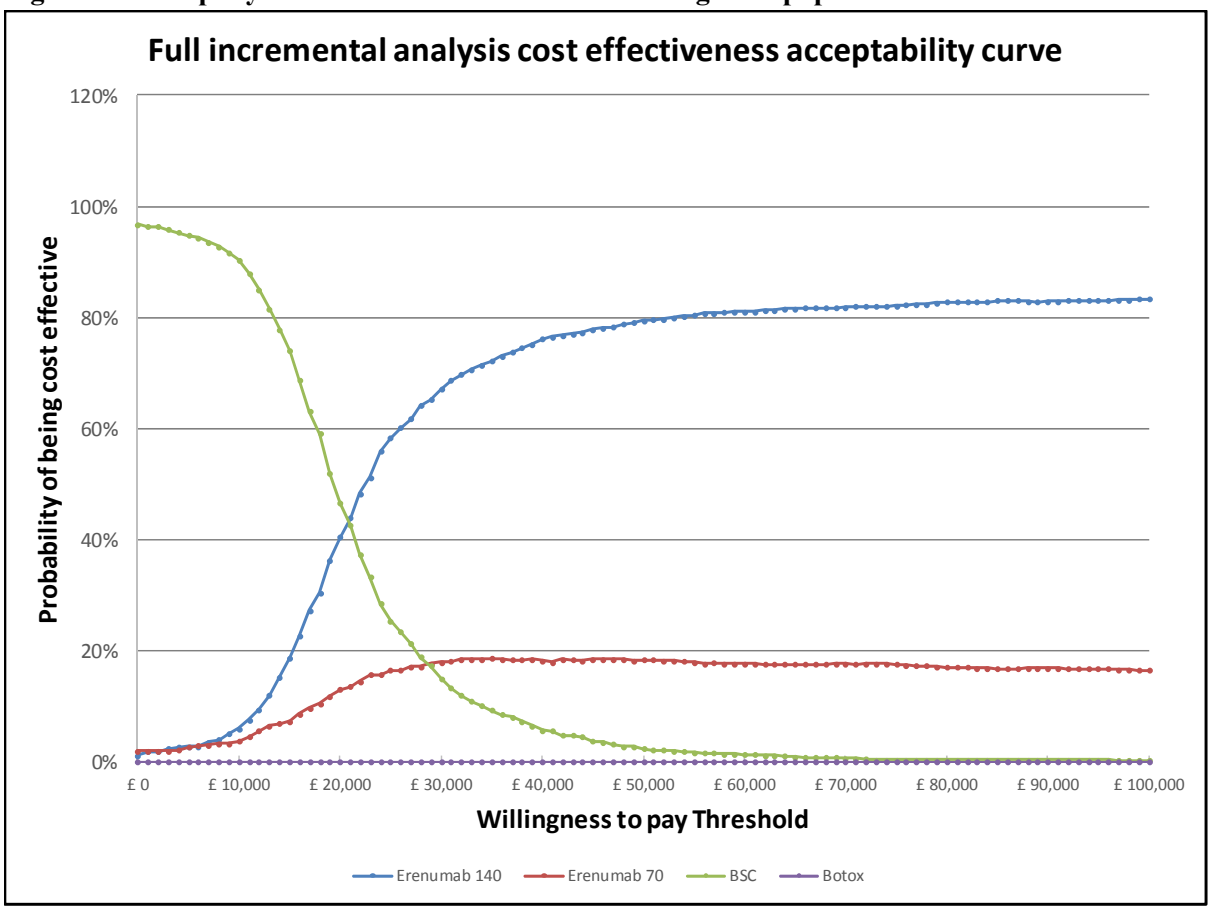
BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY= quality-adjusted life-year.
*Based on company's reported total costs and QALYs

The probabilistic sensitivity analysis (PSA) was run with 1,000 simulations and obtained largely similar results to the deterministic analysis. Results can be found in the CS Tables 72-77[1] and in Figures 30-33.

ERG comment: The main concerns of the ERG relate to: a) lack of presentation of incremental results for the erenumab 140mg and 70mg doses, and b) incomplete PSA.

a) The PSA did not enable simultaneous calculation of outcomes for more than two comparators and representation of multiple comparators in the cost effectiveness acceptability curve (CEAC). The company amended this in their model in response to clarification question B22.
b) The ERG was concerned that not all of the important parameters (treatment discontinuation) were included in the PSA. The company amended this omission in response to clarification question B22. The revised CEAC with all included comparators for the whole migraine population is presented in Figure 5.3.

Figure 5.3 Company's base-case CEAC in the whole migraine population



Source: CS model in response to clarification letter[22]

5.2.11 Sensitivity analyses

The company performed various sensitivity and scenario analyses. Parameter values were varied in one-way sensitivity analyses. For both the whole migraine as well as the episodic migraine population, and for the blended dose compared with BSC, the three most influential parameters included the non-responder MMD frequencies for BSC, erenumab 70mg and 140mg (CS Figures 34 and 40).[1] In the chronic migraine population, for the blended dose compared with botulinum toxin, the three most influential parameters (excluding the discount rate for costs) were the erenumab 140mg and 70mg treatment costs per cycle and the chronic migraine non-responder MMD frequency for erenumab 140mg

(CS Figure 36),[1] but many other parameters had a similar impact (mainly those related to the probabilities of response and the MMD frequencies). Full results were presented in Figures 34-41 of the CS.[1]

Scenario analyses indicated that alternative assumptions could significantly increase or decrease the ICERs in all populations. The most influential alternative scenarios in the comparison with BSC (apart from adopting a societal perspective) for the whole migraine population and blended dose were a) changing the non-responder MMD distribution following the assessment period to that of BSC non-responders (ICER increases), b) applying a 30% stopping rule instead of the 50% stopping rule (ICER increases), and c) changing the non-responder MMD distribution following the assessment period to baseline (ICER increases).

For the chronic population and blended dose compared with botulinum toxin, the most influential alternative scenarios were a) application of a utility decrement related to the method of administration for botulinum toxin (ICER decreases), b) applying periodical re-evaluation where a proportion of patients discontinues (ICER decreases), and c) changing the non-responder MMD distribution following the assessment period to the baseline MMD distribution (ICER decreases).

The impact of alternative scenarios was possibly largest in the episodic migraine population. For the blended dose compared with BSC (apart from adopting a societal perspective) the most influential alternative scenarios were a) applying a 30% stopping rule instead of the 50% stopping rule (ICER increases), b) changing the non-responder MMD distribution following the assessment period to that of BSC non-responders (ICER increases), and c) the use of (EQ-5D-5L) utility values from LIBERTY for episodic migraine patients (ICER increases). Full results were presented in Tables 81-88 of the CS.[1]

In additional to sensitivity and scenario analyses, the company also performed further subgroup analysis, in which the episodic migraine population was restricted to the HFEM population (8-14 MMDs) based on both the whole migraine population and the episodic migraine population base-cases. This resulted in a small decrease in the ICER (by approximately £200 per QALY gained) for the whole migraine population, and an increase in the ICER (by approximately £2,000 per QALY gained) for the episodic migraine population.

ERG comment: The ERG considered the sensitivity analyses to be appropriate. Some further scenario analyses requested by the ERG were provided in response to the clarification letter[22] and are described in the relevant sections of this report.

5.2.12 Model validation and face validity check

Face validity

Discussions with UK clinical experts and a UK health economics expert were held to assess the face validity of the model structure. Further input was sought at advisory boards.[1] It is, however, unclear whether data inputs were agreed on with, or results were presented to, experts.

Internal validity

Two independent health economics experts checked the model for internal validity.

Cross validity

No detailed cross validation was reported in the CS.

External validity

The company provided a comparison between clinical trial data for erenumab 70mg and 140mg versus placebo (Study 295, STRIVE, ARISE and LIBERTY) for mean change from baseline in MMDs, showing overall relatively similar results (see CS Table 93).[1]

Predictive validity

No predictive validation was reported.

ERG comment: The main concerns of the ERG relate to: a) lack of details on internal validation; b) lack of cross validation and; c) inability to reproduce the external validation.

a) The internal validation was not reported in detail. However, the ERG was able to independently rebuild the cohort analysis and recalculated the estimated QALYs for the company base-case, supporting its internal validity.
b) The ERG was concerned about the lack of a detailed cross validity exercise comparing the present model with that developed for botulinum toxin in TA260,[21] which was missing from the CS. The company provided a cross validation in response to clarification question B23 in Table 88,[22] however more detail may have been useful to assess the impact of differences in model structure, assumptions and inputs on results.
c) Although the company did provide external validation, the ERG was unable to reproduce these findings (i.e. the mean change from baseline MMD versus placebo as reported in CS Table 93).[1] As a result the validity of the external validation performed by the company can be questioned.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Table 5.12 summarises the main issues highlighted by the ERG in Section 5.2, and indicates the expected direction of bias introduced by these issues and whether these are examined in any analyses or incorporated in the ERG base-case.

Table 5.12: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Model structure (Section 5.2.2)			
Natural progression of the disease is not fully captured	+/-		Clarification response (partly)
Response was defined as a ≥50% reduction from baseline MMD	+	Scenario	CS scenario 7
Positive discontinuation (according to NICE TA260 treatment should also be stopped in people whose condition has changed from chronic to episodic migraine for 3 consecutive months)	-	Scenario	CS scenario 6
No discontinuation risk the first cycle after response assessment	+	Fixing error	
Botulinum toxin responders have response MMD frequencies (and the associated cost and HRQOL) only 24 weeks after starting treatment	+	Scenario	
Population, interventions and comparators, perspective and time horizon (Sections 5.2.3-5.2.5)			
Lacking evidence for patients with ≥15 MHDs and ≥4 to <8 MMDs	+/-		
Conversion between weekly and annual results	+	Fixing error	
Definition of HFEM subgroup	+	Scenario	Clarification response
Using blended dose for erenumab (instead of 70mg and 140mg separately)	+/-	Fixing violation	Clarification response
Time horizon limited to ten years (i.e. not lifetime time horizon)	+	Fixing violation	
Treatment effectiveness and extrapolation (Section 5.2.6)			
Extrapolation assuming a continued treatment effect (i.e. no waning of treatment effect)	+	Matter of judgement	Clarification response
Definitions of response for erenumab (based on 12 weeks MMD) and botulinum toxin (based on 24 weeks MHD) were (implicitly) assumed to be identical in the indirect treatment comparison	+/-		
Floor and ceiling effects of truncated normal distributions for MMD frequency	+/-		
Inconsistency regarding the use of 24-week MMD distributions for responders.	+	Fixing error	

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Assumption that the nature of treatment discontinuation determines whether patients rebound to the baseline MMD distribution or are assumed to maintain the non-responder MMD	-	Matter of judgement	Clarification response
Adverse events (Section 5.2.7)			
The impact of adverse event on HRQOL and costs is not explicitly modelled	+		Clarification response (partly)
Health-related quality of life (Section 5.2.8)			
HRQOL based on the whole trial population (not restricted to patients for whom ≥3 prior prophylactic treatments have failed)	-	Scenario	
Use of HIT-6 data to map EQ-5D utilities	+		Clarification response
Using mapped utilities instead of Euroqol-5D data from LIBERTY	+	Scenario	CS scenario 13
Resources and costs (Section 5.2.9)			
Resource use and costs are based on the whole trial population (not restricted to patients for whom ≥3 prior prophylactic treatments have failed)	+/-		
Oral triptan medication costs assumed for triptan injections	-	Fixing violations	
Method used for estimating resource use per MMD frequency (i.e. not using a multi-level approach, similar as for HRQOL)	+/-		
Cost effectiveness analyses (Sections 5.2.10 and 5.2.11)			
No incremental analyses (including erenumab 70mg and 140mg separately)	+/-	Fixing violations	Clarification response
Not all relevant parameters are included in the PSA	+/-	Fixing violations	Clarification response

Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.
ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; MJ = matters of judgement

Based on all considerations in Section 5.2 (summarised in Table 5.12), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments, made by the ERG, formed the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[62]):

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing errors

1. No discontinuation risk during the first cycle after response assessment (Section 5.2.2).
   The ERG corrected this error.
2. Conversion between weekly and annual results (Section 5.2.5).
   The ERG corrected this error.
3. Inconsistency between CS and economic model regarding the use of 24-week MMD frequency distributions (Section 5.2.6).
   The ERG corrected this error.

Fixing violations

4. The use of the blended dose for erenumab (Section 5.2.4).
   The ERG considered erenumab 70mg and erenumab 140mg separately.
5. Time horizon limited to 10 years (Section 5.2.5).
   The ERG adopted a lifetime time horizon
6. Oral triptan medication costs were assumed for triptan injections (Section 5.2.9).
   The ERG used triptan injection costs for triptan injections.
7. Not all relevant parameters were included in the PSA (Section 5.2.10).
   The ERG included additional parameters in the PSA.

Matters of judgment

8. Extrapolation assuming a continued treatment effect (Section 5.2.6).
   The ERG adopted a five-year treatment waning effect.
9. Assumptions related to the MMD frequency distributions after treatment discontinuation (Section 5.2.6).
   The ERG assumed the non-responder MMD frequency distribution after treatment discontinuation (independent on the nature of discontinuation)

Tables 6.1 and 6.3 indicate how individual adjustments impact the results plus the combined effect of all of the abovementioned adjustments simultaneously, resulting in the deterministic ERG base-case. The 'fixing error' adjustments were combined and the other ERG analyses were also performed incorporating these 'fixing error' adjustments, given that the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues. The ERG adjustment to the PSA (adjustment 7) was not included separately in the breakdown since this adjustment does not affect the deterministic results. All analyses were presented using incremental analyses. As incremental analyses were not implemented for the blended dose, all analyses were performed considering erenumab 70mg and erenumab 140mg separately (i.e. conditional on adjustment 4).

5.3.1 ERG base-case results

The ERG base-case consisted of an ICER range reflecting the uncertainty surrounding the extrapolation of treatment effectiveness.

The ERG base-case (probabilistic) indicated that erenumab 70mg was dominated in the chronic migraine population. Erenumab 140mg was considered cost effective at willingness to pay thresholds higher than £16,905 and £38,622 per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period, respectively (Table 6.6). For these two assumptions, the probabilities of Erenumab 140mg being cost effective were 75% and 20%, respectively, at a willingness to pay threshold of £20,000 per QALY gained while this increased to 79% and 43%, respectively, at a willingness to pay threshold of £30,000 per QALY gained (Figures 5.4 and 5.5).

For the episodic migraine population, the probabilistic ERG base-case results indicated that erenumab 70mg would be cost effective at willingness to pay thresholds higher than £10,047 and £95,227 per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period respectively (Table 6.7). Erenumab 140mg was either dominated by erenumab 70mg (due to worse non-responder MMD frequencies for erenumab 140mg than for erenumab 70mg) or became cost effective at a willingness to pay threshold of £267,487 per QALY gained. When assuming a constant treatment effect over time, the probability of erenumab 70mg being cost effective was 60% and 64% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively. This decreased to 3% and 8%, respectively, when assuming treatment effect waning over a five-year period (Figures 5.6 and 5.7).

Figure 5.4: ERG base-case CEAC for the chronic migraine population (assuming constant treatment effectiveness)

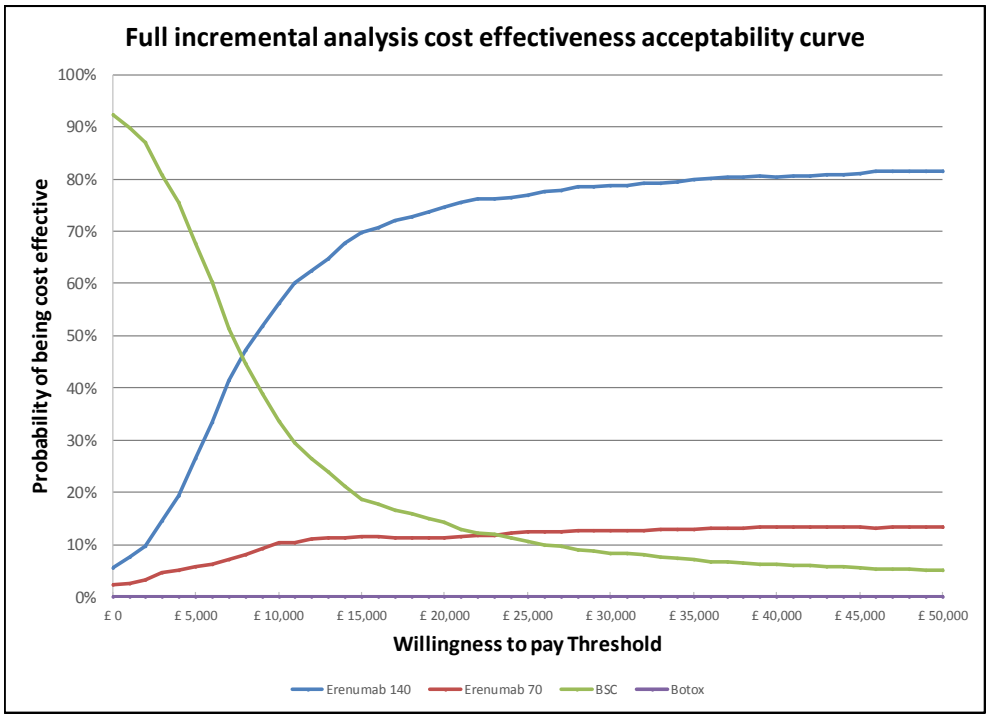


Figure 5.5: ERG base-case CEAC for the chronic migraine population (assuming treatment effect waning over five-year)

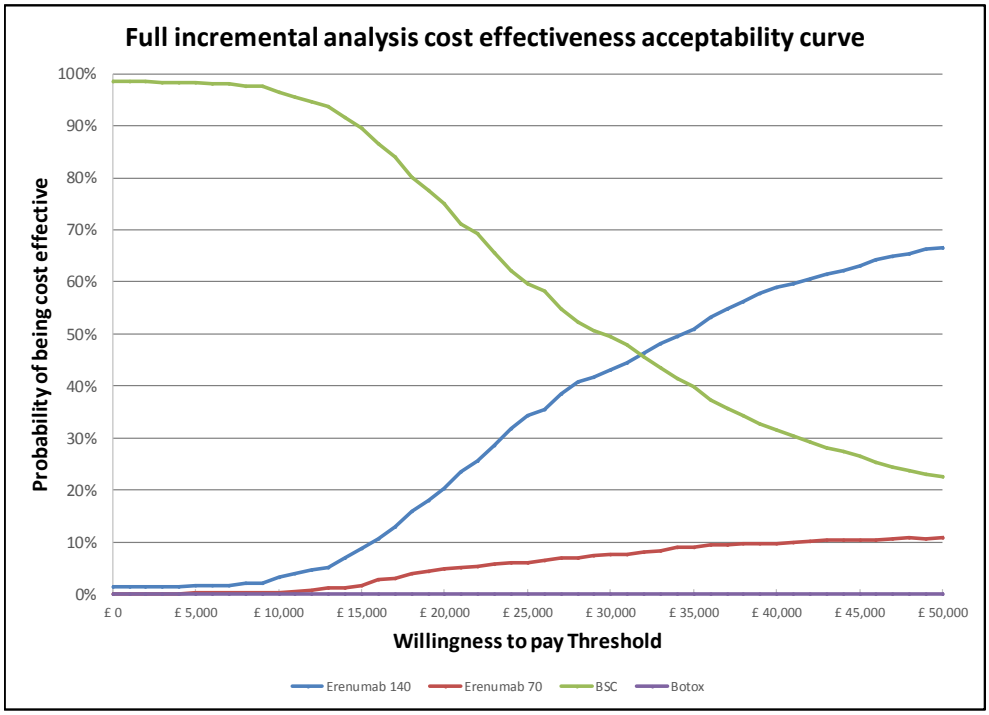


Figure 5.6: ERG base-case CEAC for the episodic migraine population (assuming constant treatment effectiveness)

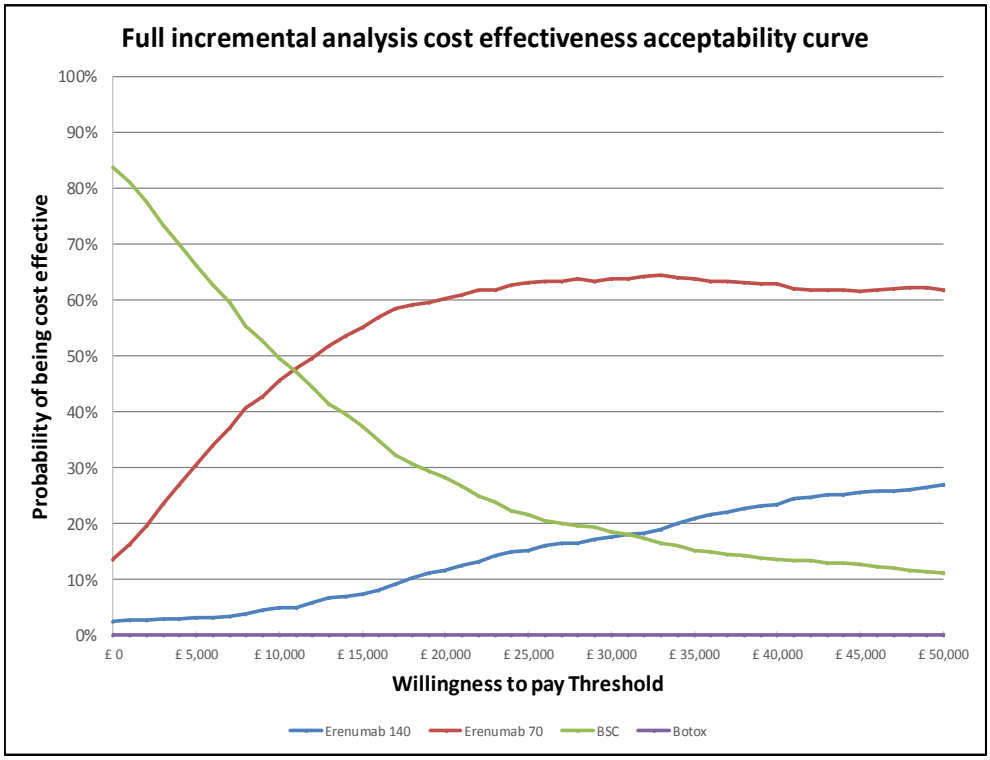
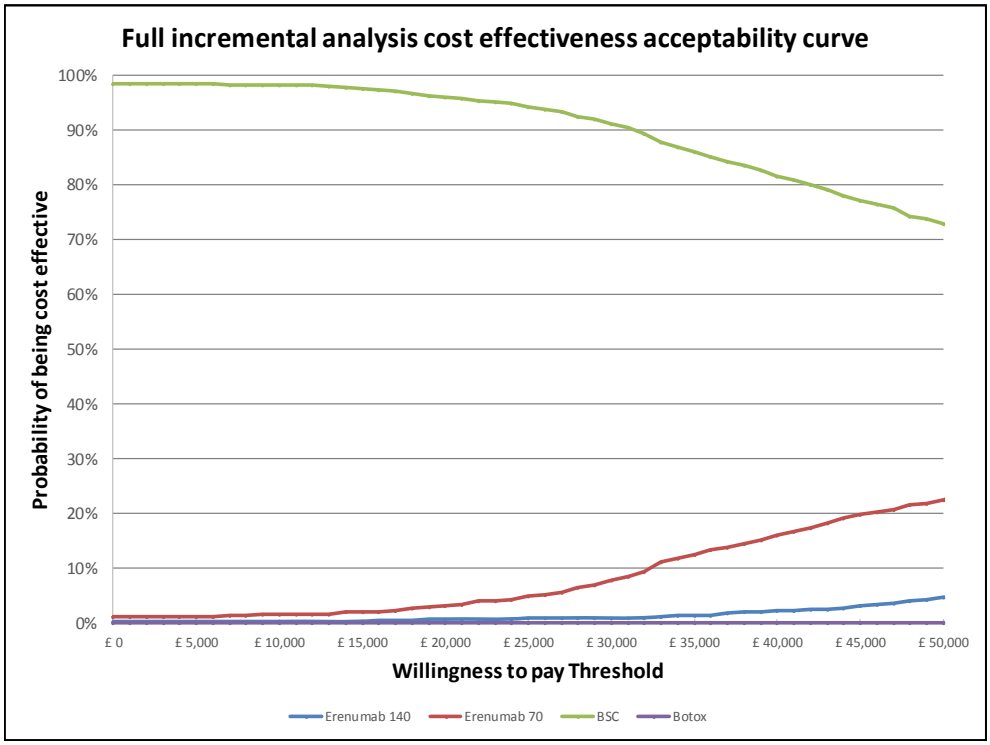


Figure 5.7: ERG base-case CEAC for the episodic migraine population (assuming treatment effect waning over five-year)



5.3.2 Additional exploratory analyses performed based on the ERG base-case

Additional deterministic exploratory scenario analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. The exploratory scenario analyses were performed conditional on the ERG base-case assuming constant treatment effectiveness and are listed below:

1. Assuming a response definition of ≥30% reduction from baseline MMD (Section 5.2.2)
2. Incorporating positive treatment discontinuation (Section 5.2.2)
3. Assuming that patients treated with botulinum toxin would have a response 12 weeks after starting treatment (Section 5.2.2)
4. Assuming a 10-year treatment waning period (Section 5.2.6)
5. Using HRQOL (mapped from MSQ) based on the patients for whom ≥3 prior prophylactic treatments have failed (Section 5.2.8)
6. Using EQ-5D utilities (LIBERTY) instead of mapped utilities (Section 5.2.8)

The results of the deterministic exploratory scenario analyses for the chronic and episodic populations are presented in Tables 6.2 and 6.4 respectively. These analyses indicate that the definition of response (i.e. either 30% or 50% reduction from baseline MMD), incorporating positive treatment discontinuation as well as the source of HRQoL data used might have a substantial impact on the estimated cost effectiveness. It should however be noted that the evidence used to support the positive treatment discontinuation scenario is considered to be weak by the ERG (see Section 5.2.2 for more details).

5.3.3 Subgroup analyses performed based on the ERG base-case

Subgroup analyses, conditional on the ERG base-case, were performed for the HFEM subgroup (8-14 MHD). An exploratory analysis was performed using an alternative (10-14 MHD) definition for HFEM.

Consistent with the ERG base-case results for the chronic and episodic populations, the estimated cost effectiveness for the HFEM subgroup depended on the assumptions related to the extrapolation of treatment effectiveness. The deterministic ERG base-case assuming constant treatment effectiveness over time indicated that erenumab 70mg was cost effective at willingness to pay thresholds higher than £10,781 per QALY gained (erenumab 140mg was dominated). When assuming treatment effect waning over a five-year period, erenumab 70mg only became cost effective at a willingness to pay threshold of £113,172 per QALY gained while this was £126,000 for erenumab 140mg.

5.4 Conclusions of the cost effectiveness section

Cost effectiveness searches in the CS and in the response to clarification were well documented and easily reproducible and were carried out in line with the NICE guide to the methods of technology appraisal. Searches were reported for a wide range of databases and additional searches of conference proceedings, grey literature sources and reference checking were also reported.

The company developed a de novo economic model. The model structure proposed by the company, however, does not fully capture natural progression of migraine. The ERG believes that the justification provided by the company, not to model natural progression of migraine, is reasonable. However, the impact of this simplification is not fully known and hence increases the uncertainty regarding the cost effectiveness results. The definition of response to treatment is another source of uncertainty. The company used a ≥50% reduction in baseline MMDs to define response, however, guidelines state that a ≥30% reduction can be clinically meaningful in patients with chronic migraine. Moreover, for NICE TA260 on botulinum toxin in chronic migraine[21] the committee stated that a 30% (MHD) response rate was the most clinically relevant and reasonable negative (due to no response) stopping rule on which to base its decision. The main uncertainty in this cost effectiveness assessment is the extrapolation of treatment effectiveness. Although the company provided data from open-label extension studies, these studies did not provide comparative effectiveness data and the follow-up of these studies was limited (52 weeks for chronic migraine and 64 weeks for episodic migraine). After this period there was no evidence to inform the extrapolation of treatment effectiveness. There was also a general lack of evidence for patients with ≥15 MHDs and ≥4 to ≤8 MHDs as this population was not considered in the pivotal trials. Additionally, the ERG considers that the economic model and base-case analyses described in the CS only partly meet the NICE reference case. Deviations from the NICE reference case included the restricted time horizon of 10 years and the use of mapped utilities.

In the company base-case (probabilistic, simulation performed by the ERG) erenumab 140mg was cost effective in the chronic population at willingness to pay thresholds higher than £19,113 per QALY gained (erenumab 70mg was dominated). For the episodic population, the company base-case (probabilistic, simulation by the ERG) results indicated that erenumab 70mg was cost effective at willingness to pay thresholds higher than £27,125 per QALY gained. Erenumab 140mg became cost effective at willingness to pay thresholds higher than £83,170 per QALY gained.

The ERG has incorporated various adjustments to the company base-case. The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that erenumab 140mg was cost effective at willingness to pay thresholds higher than £16,905 and £38,622 per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period respectively (erenumab 70mg was dominated). For the episodic population the probabilistic ERG base-case results indicated that erenumab 70mg would be cost effective at willingness to pay thresholds higher than £10,047 per QALY gained, when assuming a constant treatment effect over time (erenumab 140mg is dominated). When assuming treatment effect waning over a five-year period, this would be £95,227 per QALY gained for

erenumab 70mg (erenumab 140mg became cost effective at a willingness to pay threshold of £267,487 per QALY gained).

It should, however, be noted that the increased effectiveness (in terms of QALYs) of erenumab 70mg versus erenumab 140mg (when assuming constant treatment effectiveness), in the episodic migraine population, is inconsistent with the clinical effectiveness evidence presented in chapter 4 (Table 4.9). In Section 4.2.3, the ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed. Indeed, there is a numerically larger difference vs. placebo in change from baseline MMD for 140mg than for 70mg; only the former is statistically significant, and this only in the STRIVE trial. The favourable cost effectiveness of erenumab 70mg for the episodic population seems driven by the MMD frequency distribution for non-responders that is lower than for erenumab 140mg and BSC. It is questionable whether, given the above results for all patients, there would be an advantage for 70mg vs. 140mg for those patients who do not respond. It is also questionable whether extrapolating this benefit for non-responders (or any benefit in MMD frequency distribution for responders) is plausible given the changing response over time. This is to some extent mitigated in the treatment waning scenarios given benefits in terms of MMD frequency distributions are decreased over time.

In conclusion, the cost effectiveness of erenumab in the chronic and episodic migraine populations largely depends on the assumptions related to the extrapolation of treatment effectiveness. Based on willingness to pay thresholds of £20,000 and £30,000 per QALY gained, erenumab 140mg and erenumab 70mg may be cost effective for the chronic and episodic migraine populations respectively if a constant treatment effect over time is assumed. However, as mentioned above, the plausibility of this assumption may be questionable. The estimated ICERs for erenumab increased above these willingness to pay thresholds of £20,000 and £30,000 per QALY gained if a treatment effect waning with a five-year period is assumed. Finally, it is unclear whether these results can be extrapolated to the population with ≥15 MHDs and ≥4 to <8 MMDs as no cost effectiveness evidence is provided for this population.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Tables 6.1 and 6.3 show how individual changes impact the deterministic results plus the combined effect of all changes simultaneously for the chronic and episodic migraine populations, respectively. The deterministic exploratory scenario analyses for these populations are presented in Tables 6.2 and 6.4. These are all conditional on the ERG base-case assuming constant treatment effectiveness. Table 6.5 provides the deterministic results for the HFEM subgroup (described in Section 5.3.3). Finally, probabilistic analyses are provided for the chronic and episodic migraine populations in Tables 6.6 and 6.7, respectively. The submitted model files contain technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

6.1 Deterministic analyses undertaken by the ERG (all with PAS)

Table 6.1: Deterministic ERG base-case for the chronic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,609	£10,609
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£24,668
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,832	£13,340
Fixing errors						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,637	£10,637
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,045
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,001	£13,400
Fixing errors + lifetime time horizon						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£7,093	£7,093
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£36,599
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£27,070	£11,862
Fixing errors + applying triptan injections costs for triptan injections						
BSC	[redacted]	[redacted]				

Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£9,243	£9,243
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,605	£12,005
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£23,650
Fixing errors + assuming non-responder MMD frequency distribution after treatment discontinuation						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£9,546	£9,546
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£23,574
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,198	£12,048
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£3,813	£3,813
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,653	£7,067
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,842
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£26,536	£26,536
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£115,310
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£36,680	£30,896

Table 6.2: Deterministic scenario analyses for the chronic migraine population conditional on ERG base-case (assuming constant treatment effectiveness)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£3,813	£3,813
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,653	£7,067
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,842

ERG base-case + assuming a response definition of ≥30% reduction from baseline MMD						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£17,332	£17,332
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£61,033
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,876	£18,065
ERG base-case + positive discontinuation scenario						
Botulinum toxin	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£1,548	£1,548
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
ERG base-case + assuming response benefits 12 weeks after start treatment for botulinum toxin						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£2,915	£2,915
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,093	£7,067
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,842
ERG base-case + treatment effect waning over ten years						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£15,576	£15,576
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£58,192
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£26,368	£19,798
ERG base-case + MSQ mapped utilities based on patients for whom ≥3 prior prophylactic treatments have failed						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£4,144	£4,144
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,013	£7,681
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£28,087
ERG base-case + EQ-5D-5L utilities (cross-walk) from LIBERTY						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,689	£10,689

Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,880	£19,810
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£72,442

Table 6.3: Deterministic ERG base-case for the episodic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£29,200	£29,200
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£73,282	£40,662
Fixing errors						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£29,690	£29,690
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£74,869	£41,391
Fixing errors + lifetime time horizon						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£13,784	£13,784
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£36,534
Fixing errors + applying triptan injections costs for triptan injections						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£27,634	£27,634
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£72,838	£39,341
Fixing errors + assuming non-responder MMD frequency distribution after treatment discontinuation						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£28,127	£28,127
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£91,053	£41,721
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,207	£10,207
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£35,505

ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£95,010	£95,010
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£311,432	£143,520

Table 6.4: Deterministic scenario analyses for the episodic migraine population conditional on ERG base-case (assuming constant treatment effectiveness)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,207	£10,207
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£35,505
ERG base-case + assuming a response definition of ≥50% reduction from baseline MMD						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£91,042	£91,042
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
ERG base-case + positive discontinuation scenario						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£3,667	£3,667
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,778	£6,754
ERG base-case + treatment effect waning over ten years						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£74,372	£74,372
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£97,660	£84,310
ERG base-case + MSQ mapped utilities based on patients for whom ≥3 prior prophylactic treatments have failed						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£7,528	£7,528
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£26,187
ERG base-case + EQ-5D-5L utilities (cross-walk) from LIBERTY						
BSC	[redacted]	[redacted]				

Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,418	£19,418
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£67,542

Table 6.5: Deterministic ERG base-case and scenario analysis for the HFEM subgroup

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£37,331	£37,331
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£38,194	£37,749
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,781	£10,781
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£29,275
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£113,172	£113,172
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£126,000	£119,426
ERG base-case (assuming constant treatment effectiveness) with alternative HFEM definition (10-14 MHDs)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£13,555	£13,555
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£41,001

6.2 Probabilistic analyses undertaken by the ERG (all with PAS)

Table 6.6: Probabilistic ERG base-case for the chronic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case (PSA run by the ERG)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,075	£10,075
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£23,417
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,113	£14,181
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				

Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£3,695	£3,695
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,905	£6,804
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,912
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£25,402	£25,402
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£115,654
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£38,622	£25,943

Table 6.7: Probabilistic ERG base-case for the episodic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case (PSA run by the ERG)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£27,125	£27,125
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£83,170	£40,204
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,047	£10,047
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£33,943
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£95,227	£95,227
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£267,487	£139,447

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Appendix 1: Details of acute headache medication usage during the erenumab studies

Source: response to clarification question A5 – "Please provide a table with patient numbers showing all concomitant medication received in the 4 main trials (Study 295, STRIVE, ARISE and LIBERTY) in intervention and placebo groups, for the specified optimised population (≥3 failed prophylactic therapies), whole trial populations and exploratory analysis population (≥2 failed prophylactic therapies).

Study 295

The most common acute headache medications used during baseline or during the double-blind treatment phase were in the categories of triptan-based migraine medications ([redacted]%, [redacted]%, and [redacted]% of subjects in the placebo, erenumab 70mg, and erenumab 140mg arms, respectively) and non-opioid acute headache medications ([redacted]%, [redacted]%, and [redacted]%, respectively; see Table A2.1).

Table A1.1: Concomitant medication usage in Study 295

Population	Placebo	Erenumab 70mg	Erenumab 140mg
Full study population	**n=282**	**n=190**	**n=188**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

Patients for whom ≥2 prior treatments have failed	**n=141**	**n=92**	**n=92**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

STRIVE

The most frequent (>10%) acute headache medications used during baseline and during the double-blind treatment phase were in the categories of non-opioid acute headache medications ([redacted]%, [redacted]%, and [redacted]% of subjects in the placebo, erenumab 70mg, and erenumab 140mg arms, respectively) and triptan-based migraine medications ([redacted]%, [redacted]%, and [redacted]%, respectively; see Table A1.2).

Table A1.2: Concomitant medication usage in STRIVE

Population	**Placebo**	**Erenumab 70mg**	**Erenumab 140mg**
Full study population	**n=319**	**n=314**	**n=319**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]

Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥2 prior treatments have failed	**n=54**	**n=49**	**n=58**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

ARISE

The most common acute headache medications used during baseline and during the double-blind treatment phase were in the categories of non-opioid acute headache medications ([redacted]% and [redacted]% of subjects in the placebo and erenumab 70mg arms, respectively) and triptan-based migraine medications ([redacted]% and [redacted]%, respectively; see Table A1.3).

Table A1.3: Concomitant medication usage in ARISE

Population	Placebo	Erenumab 70mg
Full study population	**n=289**	**n=283**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]

Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥2 prior treatments have failed	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]

LIBERTY

Approximately a third of the total safety analysis set ([redacted]%) received concomitant therapy (any ATC class) during the double-blind treatment phase and the proportion was similar between the erenumab 140mg ([redacted]%) and placebo (34.7%) groups. Please see Table 14.3-13 on page 267-276 of the CSR for further details. The majority of patients used acute headache medication during baseline and the double-blind treatment phase. Triptan/ergotamine-based migraine medications and analgesic acute headache medications were the most frequently used headache medications. A similar proportion of patients in the erenumab 140mg and placebo groups had taken triptans/ergotamines ([redacted]% vs [redacted]%, respectively) as well as analgesics ([redacted]% vs. [redacted]%, respectively). In addition, a small percentage of patients in both treatment groups had taken opioid-containing acute headache medications during baseline and the double-blind treatment phase ([redacted]% vs [redacted]%, respectively; see Table A1.4).

Table A1.4: Concomitant medication usage in LIBERTY

Population	Placebo	Erenumab 140mg
Full study population	**n=123**	**n=1118**
Triptan/Ergotamine-based migraine medications	[redacted]	[redacted]
Analgesics acute headache medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	n=[redacted]	n=[redacted]
Triptan/Ergotamine-based migraine medications	[redacted]	[redacted]
Analgesics acute headache medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]

Issue 1 Extrapolation of treatment effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80: "However, it is unclear this is similar for the comparative effectiveness of erenumab versus placebo (i.e. BSC). Particularly, given that based on Figure 7 in the clarification response, the change from baseline MMD seemed to have plateaued at the end of the initial trial period for erenumab (weeks 8-12) while for placebo this was still decreasing."	Please amend as follows: Page 80: "However, it is unclear this is similar for the comparative effectiveness of erenumab versus placebo (i.e. BSC). Particularly, given that based on Figure 7 in the clarification response, the change from baseline MMD seemed to have plateaued at the end of the initial trial period for erenumab (weeks 8-12) while for placebo this was still decreasing. ***However, in the STRIVE study, the reduction from baseline in MMDs for placebo had plateaued by Week 24.***"	Novartis disagrees with the suggestion that the change from baseline in MMDs will continue to decrease in the placebo arm over time. This can be demonstrated in the efficacy results from STRIVE, where the change from baseline in MMDs was measured up to Month 6. Data in the whole trial population from this study clearly indicates a plateau in the reduction of MMDs in the placebo arm, and a slight increase in MMDs was observed between Month 4 and Month 6.[1] These data suggest that the response observed in the placebo arm would not continue to decrease over time. Novartis therefore requests that these data from STRIVE are also referred to here to ensure accurate representation of the entire body of evidence.	Not a factual inaccuracy. This is a factually correct description of the data.
Page 81: "However, the ERG believes that, given the absence of evidence related to the long-term effectiveness, it is uncertain	Please amend as follows: Page 81: "However, the ERG believes that, given the ***limited*** evidence related to the long-term effectiveness, it is uncertain whether there is a treatment waning effect. ***It is noted, however, that the***	Novartis disagrees with the accuracy of the statement that there is an absence of evidence (implying no evidence) related to long-term effectiveness and the uncertainty around whether there	Wording change: "absence of evidence" changed to "very limited evidence". As noted on page 70 of the ERG report, the results of open-label extension

whether there is a treatment waning effect"	***pharmacological principles for erenumab, as well as the lack of neutralizing antibodies observed in the clinical trials, may indicate that the treatment effect does not wane over time***."	is a treatment waning effect. This is based on the following: • As stated by the ERG, long-term data up to 64 weeks are available for erenumab, which provides evidence of long-term effectiveness and no indication of a treatment waning effect over this time period. • Based on pharmacological principles, pre-clinical data, and long-term clinical data, erenumab binds to the CGRP receptor where it modifies CGRP signalling and its role in migraine pathophysiology, but does not otherwise appear to impact CGRP receptor biology (i.e. the biological mechanism of erenumab would be expected to avoid any loss of effect).[2-6] • Data from 884 patients treated with erenumab found that anti-erenumab antibodies have a low occurrence rate and high reversion rate (only three recorded incidences of a neutralising antibody [NAb] in the 70 mg arms, of which two patients were NAb-negative by the end of the study, and no recorded instances in the 140 mg arms).[7] This suggests	studies, described in Appendix L of the CS, are not specific to subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed.

		a lack of immunogenicity to erenumab, which reduces the likelihood of treatment waning. Novartis considers that the statement made by the ERG does not discuss the pharmaceutical principles that contribute to a lack of waning effect and that in omitting this important information from the discussion it presents an inaccurate representation of the evidence regarding treatment waning. Referring to an absence of evidence is also inaccurate in that it does not acknowledge the existence of some clinical data to support the long-term clinical effectiveness of erenumab.	

Issue 2 Dosing of erenumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10: "The company's model assumed that 50% of patients would receive 70mg and 50% of patients 140mg. However, logically, if not all patients would receive the same dose then there must be variation in those patients such that some would benefit more from one dose than another. This would imply two	Please amend as follows: Page 10: "The company's model assumed that 50% of patients would receive 70mg and 50% of patients 140mg. However, logically, if not all patients would receive the same dose then there must be variation in those patients such that some would benefit more from one dose than another. This would imply two different populations~~, but the company did not explicitly differentiate any such populations~~	Throughout the CS it was suggested that the higher dose of erenumab (140 mg) may be more appropriate for patients for whom ≥3 prior prophylactic treatments have failed, as there is a trend towards better efficacy in the higher dose for these patients. The issue of whether certain populations may benefit from one dose or another could	Not a factual inaccuracy.

different populations, but the company did not explicitly differentiate any such populations and neither were such populations described in the scope. Therefore, it follows that both doses are indicated for the same population and therefore should be considered as comparators to each other."	~~and neither were such populations described in the scopeTherefore, it follows that both doses are indicated for the same population and therefore should be considered as comparators to each other~~."	not have been described in the scope as this was developed prior to the EMA approval of two separate doses. Novartis acknowledges the ERG's preference for a fully incremental analysis in which erenumab 70 mg and erenumab 140 mg are comparators to one another. It is correct that both doses are indicated for the same population. However, it does not follow that the two doses should be considered as comparators to one another. We strongly believe that, as per the CS, separate comparison of each dose to a common comparator (BSC for CM and EM, botulinum toxin for CM only) is the most appropriate approach and that a blended dose best reflects the licensed indication in which clinicians have flexibility to treat patients with either dose according to individual patient characteristics.	
Page 16: "In Section 4.2.3, the ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for	Please amend as follows: Page 16: "In Section 4.2.3, the ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior	Novartis believes that information on the efficacy for patients treated with 70 mg erenumab has been omitted in these statements. In the ARISE study, at Week 12, patients treated with erenumab 70 mg	Not a factual inaccuracy. The text on page 16 of the ERG report is factually correct, and the results referenced by the company are included in the report (section 4.2.3, referenced

whom ≥3 prior prophylactic treatments have failed. Indeed, there is a numerically larger difference vs. placebo in change from baseline MMD for 140mg than for 70mg; only the former is statistically significant, and this only in the STRIVE trial." Page 54: "However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed (MMD or MHD, ≥50% responder rates, monthly severity of migraine pain, monthly acute migraine-specific treatment days, monthly cumulative hours of migraine. The ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed."	prophylactic treatments have failed. Indeed, there is a numerically larger difference vs. placebo in change from baseline MMD for 140mg than for 70mg; only the former is statistically significant, and this only in the STRIVE trial. ***Numerical reductions were observed in the erenumab 70 mg arm compared to placebo in the ARISE study.***" Page 54: "However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed (MMD or MHD, ≥50% responder rates, monthly severity of migraine pain, monthly acute migraine-specific treatment days, monthly cumulative hours of migraine)***, although there were numerical reductions compared to placebo***. The ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed."	achieved reductions of [redacted] days, compared to [redacted] days in the placebo arm, which corresponded to a difference of [redacted] (95% CI: [redacted]; [redacted]). This can be considered a numerical reduction, even if not statistically significant. The numerical reduction should be acknowledged by the ERG in these statements to ensure accuracy.	on page 16 of the ERG report).

Issue 3 Positive discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76: "According to NICE TA260 on botulinum toxin in chronic migraine, treatment should also be stopped in people whose condition has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.[21] To reflect the potential impact of this, the ERG adopted the positive discontinuation scenario (CS scenario 6) as a scenario analysis. This scenario assumed that continuously after a maximum of 64.5 weeks all patients on treatment discontinue treatment for a re-evaluation period of 12 weeks. In total, 20% of the re-evaluated patients experience positive treatment discontinuation i.e. they stop treatment and thus do not incur the cost of treatment, but continue to receive the benefit of treatment (i.e. the same MMD frequency distribution as responders that are on treatment). The ERG could not identify any evidence	Please amend as follows: "According to NICE TA260 on botulinum toxin in chronic migraine, treatment should also be stopped in people whose condition has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.[21] ***As erenumab is licensed in all migraine patients with ≥4 migraine days per month, the same stopping rule cannot apply. However,*** the ERG adopted the positive discontinuation scenario (CS scenario 6) as a scenario analysis ***based on feedback from clinicians that they may prefer not to keep patients on erenumab long term***. This scenario assumed that continuously after a maximum of 64.5 weeks all patients on treatment discontinue treatment for a re-evaluation period of 12 weeks. In total, 20% of the re-evaluated patients experience positive treatment discontinuation i.e. they stop treatment and thus do not incur the cost of treatment, but continue to receive the benefit of treatment (i.e. the same MMD frequency distribution as responders that are on treatment). The ERG could not identify any evidence to support these	The rationale for including a positive discontinuation scenario for erenumab in the CS aimed to reflect that in practice clinicians may prefer not to keep patients on treatment with erenumab indefinitely. This is not the same as the positive discontinuation rule adopted in the appraisal of botulinum toxin, as once patients who receive botulinum toxin experience a reduction in monthly headache days below 15 headache days per month, they can no longer receive botulinum toxin as it is not licensed for patients with episodic migraine (<15 headache days per month). As erenumab is licensed for migraine patients with ≥4 monthly migraine days, the same stopping rule cannot apply as erenumab would still be a treatment option for these patients. Therefore, the statement that the positive discontinuation scenario in the company submission reflects the positive discontinuation rule for botulinum toxin is incorrect.	Not a factual inaccuracy. The positive discontinuation scenario was not adopted to reflect a specific positive discontinuation rule (either for specific for botulinum toxin or erenumab), given the evidence to support assumptions for this stopping rule scenario are lacking. It is implemented to reflect the potential impact of a possible positive stopping rule which might be relevant for the population of interest (as illustrated by the statement referring to TA260).

to support these assumptions, hence this scenario should be interpreted with caution."	assumptions, hence this scenario should be interpreted with caution."		

Issue 4 Patient numbers included in clinical trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10: "Of these only 515 are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments" Page 15: "based on post-hoc subgroup analyses of data from four RCTs involving approximately 20% of the total studied population (n=515)" Page 40: "Of these only 515 are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments: Study 295 n=236; STRIVE n=74; ARISE n=56; LIBERTY n=149."	Please amend the numbers to those in bold, as follows: Page 10: "Of these only ***511*** are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments" Page 15: "based on post-hoc subgroup analyses of data from four RCTs involving approximately 20% of the total studied population (n=***511***)" Page 40: "Of these only ***511*** are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments: Study 295 n=***232***; STRIVE n=74; ARISE n=56; LIBERTY n=149."	Correction of patient numbers included in clinical trials.	Corrections made.

Issue 5 Generalisability of patient populations in clinical trials

Description of problem	Description of proposedamendment	Justification for amendment	ERG response
Page 12: "Regarding the extent to which the erenumab studies are representative of the UK population with	Please amend as follows: Page 12: "Regarding the extent to which the erenumab studies are representative	Although the clinical trials for erenumab had more females and Caucasian patients, this is representative of the overall	Not a factual inaccuracy. Even allowing for the over-representation of females and Caucasian patients in

migraine, both males and non-white populations appear to be under represented." Page 15, 42, 66: "Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented in the erenumab studies, both with respect to the whole study population and to the subgroup relevant to this submission." Page 44: "However, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations." Page 47: "In addition, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations."	of the UK population***,*** both males and non-white populations appear to be under represented, ***however this is consistent with profile of the population of patients who experience migraines, in which females and Caucasian patients are over-represented versus the general population***." Page 66: "Regarding the extent to which the erenumab studies are representative of the UK population***,*** both males and non-white populations appear to be under represented in the erenumab studies, both with respect to the whole study population and to the subgroup relevant to this submission. ***However, this is in line with the profile of the population of patients who experience migraines, in which females and Caucasian patients are over-represented versus the general population."*** Page 44: "However, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations, ***although this is in line with previous trials in chronic migraine patients***." Page 47: "In addition, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations. ***However, this is in line with previous trials in chronic migraine patients****."*	population which are affected by migraine; the majority of individuals who suffer from migraine are females and Caucasian.[8, 9] Therefore, the population in the clinical trials for erenumab is representative of the overall migraine patient population.	the population of patients who experience migraine, these groups remain under-represented in the erenumab studies. See section 3.1, page 28 of the ERG report: "Although migraine affects three times as many women as men, and there is also some evidence that migraine prevalence may be lower in non-white populations, both males and non-white populations appear to be under represented in the erenumab trials (See Tables 4.4 and 4.5 in Section 4.2.1 of this report for an overview of all baseline characteristics, for the relevant subgroup, in the four studies).

Page 28: “The CS (Section B.2.12.2) states that: “The study populations were deemed generalisable to the UK migraine population, as validated by expert clinicians at a UK advisory board,” however, the cited report of this advisory board does not include any discussion of the generalisability of trials to the UK population.”	Please amend this statement as follows: “The study populations were deemed generalisable to the UK migraine population, as validated by expert clinicians at a UK advisory board,” ~~however, the cited report of this advisory board does not include any discussion of the generalisability of trials to the UK population.”~~	The minutes from the advisory board cited in the CS state: “[redacted]”, and “[redacted]”. The advisory board report cited in the CS is therefore considered to support the statement on the generalisability of the clinical trials.	Correction made.

Issue 6 Clinical trial description

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16: "There is a lack of long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, for either the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed or the wider population covered by the marketing authorisation." Page 42: "…evidence is lacking about the long-term effectiveness of erenumab treatment."	Please amend to read: Page 16: "There ***are limited*** long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, for either the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed or the wider population covered by the marketing authorisation." Page 42 "…evidence is ***limited for*** the long-term effectiveness of erenumab treatment."	Evidence for the long-term efficacy of erenumab is provided by open-label studies in both chronic and episodic migraine patients. The wording that there is a "lack of" data may be misinterpreted as meaning that there are no data to support the long-term efficacy of erenumab. Instead the data availability should be described as "limited", which leaves less room for misinterpretation.	Wording changes to: "There are limited long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, however, these data are not specific to the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed." "evidence is very limited for the long-term effectiveness of erenumab treatment." As noted on page 70 of the ERG report, the results of open-label extension studies, described in Appendix L of the CS, are not specific to subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed.
Page 44: "However, the ERG note that there remains a lack of evidence about the	Please amend to read: Page 44: "However, the ERG note that there remains ***limited*** evidence about the	Evidence for the efficacy of erenumab in males and non-white populations is available	Not a factual inaccuracy. See response to issue 5.

effectiveness of erenumab in males and in non-white populations." Page 47: "In addition, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations."	effectiveness of erenumab in males and in non-white populations." Page 47: "In addition, the ERG notes that there remains ***limited*** evidence about the effectiveness of erenumab in males and in non-white populations."	from the clinical trial programme of erenumab. The evidence is more limited in these populations given that migraine predominantly affects Caucasian females.	
Page 12, 31: "The ERG also questions the use of the more stringent (≥50% reduction in MMDs vs. ≥30% reduction in MMDs) definition of responder; it seems unlikely that patients in this population would consider a reduction in their MMDs of between 30 and 49% to be not clinically meaningful. Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <30% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 20% reduction in MMDs which	Please amend the statement as follows: Page 12, 31: "The ERG also questions the use of the more stringent (≥50% reduction in MMDs vs. ≥30% reduction in MMDs) definition of responder; it seems unlikely that patients in this population would consider a reduction in their MMDs of between 30 and 49% to be not clinically meaningful. ~~Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <30% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 20% reduction in MMDs which they considered to be beneficial.~~"	It is unclear what is meant by the stopping rule in relation to the clinical effectiveness evidence presented in the company submission. In the economic model the base case stopping rule was <50% reduction in MMDs, and therefore this statement does not represent the stopping rule employed in the economic model. This statement should be removed as it is inaccurate. The statement regarding how a stopping rule would be determined in clinical practice is also inaccurate. This stopping rule is applied for chronic migraine patients who do not respond to treatment with botulinum toxin (NICE TA260).[10] Therefore a stopping rule is already established in clinical practice and practitioners will	The text has been amended to correct the numerical error. However, the remainder of the text is not factually inaccurate; the inclusion of the <30% negative stopping rule in TA260 does not necessarily mean that it is clear that a <50% stopping rule for erenumab would be readily acceptable and easily applied in clinical practice. Indeed, TA260 does not include guidance on how response should be assessed. The company state that: "Therefore a stopping rule is already established in clinical practice and practitioners will discontinue treatment if the patients do not have an adequate response (defined, for botulinum

they considered to be beneficial."		discontinue treatment if the patients do not have an adequate response (defined, for botulinum toxin, as at least a 30% reduction in monthly headache days).	toxin, as at least a 30% reduction in monthly headache days)." However, no evidence is provided in support of this statement and it is unclear whether any data are available on how the negative stopping rule has been applied in clinical practice, since the publication of TA260.

Issue 7 Economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74: "From the assessment time point onwards (i.e. either 12 or 24 weeks), the post-assessment costs and utilities (depending on the MMD frequency distribution) were applied."	Please amend as follows: "From the assessment time point onwards ***(i.e. either 12 weeks (for erenumab and BSC)*** or 24 weeks ***(botulinum toxin only))***, the post-assessment costs and utilities (depending on the MMD frequency distribution) were applied."	To accurately describe the economic model structure.	Not a factual inaccuracy.
Page 81: "The MMD frequency distributions were summarised in Table 88 of the CS Appendix S.[38] However, additional MMD distributions to those described in the CS were used for the episodic	Please amend page 81 as follows: "The MMD frequency distributions were summarised in Table ***51 of the CS***." However, additional MMD distributions to those described in the CS were used for the episodic migraine. Specifically, 24-week MMD distributions were added for **episodic migraine** responders. Given that	The MMD frequency distributions are summarised in Table 51 of the CS Document B, not Table 88 of CS Appendix S. STRIVE is the only study in which 24-week randomised data is available. To estimate the 24-week MMD distributions for the	Not a factual inaccuracy. Table 88 of the CS Appendix provides MMD frequency distributions (CS Table 51 only provides an excerpt of the this). The 24-week MMD distributions were not introduced in the CS and

migraine. Specifically, 24-week MMD distributions were added for responders. Given that the rationale for only using 24-week MMD distributions for responders with episodic migraine was lacking, this inconsistency was adjusted in the ERG base-case to be in line with the CS description as well as with the chronic migraine population." And page 96: Inconsistency between CS and economic model regarding the use of 24-week MMD frequency distributions (Section 5.2.6). The ERG corrected this error. And Table 5.12, page 94	the rationale for only using 24-week MMD distributions for responders with episodic migraine was lacking, this inconsistency was adjusted **by** ~~in~~ the ERG ~~base-case~~ to be in line with the CS description as well as with the chronic migraine population." Novartis proposes that this amendment is moved from "Fixing errors" to "Matters of judgement" and the text the "ERG corrected this error" is deleted. The text in Table 5.12 relating to this issue should also be updated from "Fixing errors" to "Matters of judgement". The ERG results tables in the report will require updating with this change.	overall EM dataset, the 24-week data from STRIVE is combined with the 12-week data from LIBERTY and ARISE (i.e. the 12-week LIBERTY and ARISE observations are carried forward to 24 weeks). It was an oversight on the part of the company not to include a description of the 24-week MMD distributions for responders in episodic migraine in the CS. However, further information was not requested at clarification stage. Novartis believes it is more appropriate to use all available data from the randomised controlled trials when looking at this population. The ERG approach omits relevant clinical trial data and therefore Novartis disagrees that the approach used in the CS was "unequivocally wrong" (ERG definition of a fixing error).	hence results in an inconsistency between the model and CS (as well as between the episodic and chronic populations), which is considered unequivocally wrong by the ERG. Given the lack of detail, the ERG was unable to assess the validity of these data and hence had to omit these data.
Page 78: "The ERG also noted that the company converted between weekly and annual results by using the factor 52, because the preferred method is to divide by 52.18 (365.25 divided by 7), the ERG	Please fix the model to use ***52.18*** as an adjuster from weeks to years, for model years, patient age and treatment waning (365.***25***/7). The ERG results tables in the report will required updating with this change.	Novartis agrees with this "fixing error", however we query whether the conversion between weekly and annual results has been implemented correctly. The ERG model uses 52.**22** as	The deterministic ERG base-case has been amended to reflect the corrected adjuster. The probabilistic ERG base-case has not been adjusted given the very small impact of this

amended this in their base-case”		an adjuster, based on the formula 365.**52**/7.	adjustment on the incremental results and any changes in the probabilistic results would most likely mainly be due to simulation error when rerunning the PSA (with 1,000 iterations) than the corrected adjuster.

Issue 8 Reporting inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11: “at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo” Page 54: “at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo” Page 67: “at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo”	Please amend as follows: Page 11: “at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo” Page 54: “at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo” Page 67: “at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo”	Data inaccuracy.	Correction made.
Page 11: “In the LIBERTY trial, [redacted] of patients taking 140mg	Please amend as follows:	Data inaccuracy.	Correction made.

of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks” Page 54: “In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks” Page 54: “In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks”	Page 11: “In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks” Page 54: “In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks” Page 67: “In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks”		
Page 11: “in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks” Page 53: “in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks” Page 67: “in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved	Please amend as follows: Page 11: “in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks” Page 54: “in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks” Page 67: Page 67: “in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo	Data inaccuracy.	Correction made.

a ≥50% reduction in MMDs from baseline to 24 weeks"	achieved a ≥50% reduction in MMDs from baseline to 24 weeks"		
Page 19: "The exception is treatment with botulinum toxin, which is the only NICE-recommended therapy for the prophylaxis of migraine."	Please amend as follows: Page 19: "The exception is treatment with botulinum toxin, which is the only NICE-recommended therapy for the prophylaxis of ***headache in patients with chronic migraine***."	This statement does not accurately report the population of patients for whom botulinum toxin is licensed. Novartis requests that this is updated to represent the licensed indication NICE guidance for botulinum toxin, based on TA260.	Correction made.
Page 54: "The ERG also notes that, for the STRIVE trial, there is an inconsistency between the effect estimate for 140mg erenumab versus placebo in patients with HFEM for whom ≥3 prior prophylactic treatments have failed reported in the summary of key results box on page 80 of the CS (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]]) and that reported in the main text (Section B.2.6.3 of the CS) and in Table 4.11 of this report (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]])."	Apologies for the discrepancy here. The correct value for the effect estimate for 140mg erenumab versus placebo in patients with HFEM for whom ≥3 prior prophylactic treatments have failed is [redacted] days (95% CI: [redacted]).	Correction to error in CS.	A note has been added to the ERG comment confirming the company's correction.
Page 70: "Twenty-two unique utility studies were identified"	Please amend as follows: "***Twenty-one*** unique utility studies were identified"	Data inaccuracy (please see CS Appendix G, Figure 5).	Correction made.

Page 86, Section 5.2.8, comment e) Typographical error The ERG found that utility values per MMD frequency ranged from [redacted] using the HIT-6 instrument, whilst they ranged from [redacted] using the MSQ instrument (whole migraine population). The latter are more aligned with utility ranges considered in the previous TA260,[21] which is likely to be because these were also based on MSQ data. The ERG considers that MSQ is likely to be a better source than HIT-6 for mapped utility data in this population.	Please amend as follows: The ERG found that utility values per MMD frequency ranged from [redacted] using the HIT-6 instrument, whilst they ranged from [redacted] using the MSQ instrument (whole migraine population). The latter are more aligned with utility ranges considered in the previous TA260,[21] which is likely to be because these were also based on MSQ data. The ERG considers that MSQ is likely to be a better source than HIT-6 for mapped utility data in this population.	Data inaccuracy.	Correction made.
Page 84: "It is further noteworthy that the company's results, presented in response to clarification question B17.e, also include a utility decrement for mode of administration associated with botulinum toxin (based on the same vignette-based study)."	Please amend as follows: "It is further noteworthy that the company's results, presented in response to clarification question B17.e ***(a scenario analysis)***, also include a utility decrement for mode of administration associated with botulinum toxin (based on the same vignette-based study)."	For clarity that the mode of administration disutility is not applied in the base case but as a scenario analysis.	Not a factual inaccuracy.

Issue 9 Marking of confidential information

Corrected mark-up has been provided in the in the Erratum for the ERG report, for all instances listed below.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr><td>Page 11: “≥50% responder rate (based on monthly headache days) with an OR = [redacted], this result was similar when using the full trial population (OR 1[redacted]). There were also no significant differences between erenumab 140mg and botulinum toxin in either the optimised population (OR [redacted]) or full trial populations (OR [redacted])”</td><td>Please amend as follows:
“≥50% responder rate (based on monthly headache days) with an OR = [redacted], this result was similar when using the full trial population (OR [redacted]). There were also no significant differences between erenumab 140mg and botulinum toxin in either the optimised population (OR [redacted]) or full trial populations (OR [redacted])”</td><td>The odds ratios and confidence intervals are confidential and should be marked as AIC, as in the CS.</td></tr>
<tr><td>Page 48:
<table><tr><th></th><th colspan="3">Study 295</th></tr><tr><th></th><th>Placebo (n=[redacted])</th><th>Erenumab 70mg (n=[redacted])</th><th>Erenumab 140mg (n=[redacted])</th></tr><tr><td colspan="4">Change from baseline in MMDs</td></tr><tr><td>Baseline, mean (SD)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Mean change at Week 12 (SE)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>LSM difference versus placebo (95% CI)</td><td>NA</td><td>−2.53 (−4.27, −0.78)</td><td>−4.09 (−5.83, −2.33)</td></tr><tr><td>p-value</td><td>NA</td><td>0.005</td><td><0.001</td></tr></table></td><td>Please amend confidentiality highlighting in Table 47 as follows:
<table><tr><th></th><th colspan="3">Study 295</th></tr><tr><th></th><th>Placebo (n=[redacted])</th><th>Erenumab 70mg (n=[redacted])</th><th>Erenumab 140mg (n=[redacted])</th></tr><tr><td colspan="4">Change from baseline in MMDs</td></tr><tr><td>Baseline, mean (SD)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Mean change at Week 12 (SE)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>LSM difference versus placebo (95% CI)</td><td>NA</td><td>−2.53 (−4.27, −0.78)</td><td>−4.09 (−5.83, −2.33)</td></tr><tr><td>p-value</td><td>NA</td><td>0.005</td><td><0.001</td></tr></table></td><td>The number of patients in each arm is confidential and should be marked as AIC. Please note, these values should also be marked as AIC on page 24 of the CS.</td></tr>
<tr><td>Page 56:</td><td>Please amend confidentiality highlighting in Table 4.12 as follows:</td><td>The patient numbers in Study 295 erenumab 70</td></tr>
</table>

Total no. of patients (%)	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])

Total no. of patients (%)	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 140mg (n=[redacted])

mg arm, ARISE and LIBERTY 140 mg arm are confidential and should be marked as AIC, as in the CS.

Page 61:

Study 295 (NCT02066415)	Treatment	Population	CfB mean monthly migraine days, mean (SE)	CfB mean monthly headache days, mean (SE)	Patients with a 50% reduction in mean monthly headache days, n/N (%)
Study 295 (NCT02066415)	Erenumab 70mg	Full trial population, 12 weeks	[redacted]	[redacted]	[redacted]
	Erenumab 70mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Erenumab 140mg	Full trial population, 12 weeks	[redacted]	[redacted]	[redacted]
	Erenumab 140mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Placebo	Full trial population, 12 weeks	[redacted]	[redacted]	[redacted]
	Placebo	≥3 previous prophylaxis	[redacted]	[redacted]	[redacted]

Please amend confidential highlighting in Table 4.16 as follows:

CfB mean monthly migraine days, mean (SE)	CfB mean monthly headache days, mean (SE)	Patients with a 50% reduction in mean monthly headache days, n/N (%)
–6.63 (0.45)	–6.43 (0.45)	[redacted]
[redacted]	[redacted]	[redacted]
–6.53 (0.50)	–6.96 (0.52)	[redacted]
[redacted]	[redacted]	[redacted]
–4.24 (0.38)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

These data are publicly available, and do not require confidential highlighting, as per the CS.

		treatments, 12 weeks					

Page 87 to 88:

Health state	Erenumab 70mg	Botulinum toxin[d]	Erenumab 140mg	Botulinum toxin[e]	BSC
Total population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Episodic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please underline and highlight blue the information in Table 5.8 as follows:

Health state	Erenumab 70mg	Botulinum toxin[d]	Erenumab 140mg	Botulinum toxin[e]	BSC
Total population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Episodic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The data in Table 5.8 should be marked as CIC as they could be used to calculate commercially sensitive information, as per the CS appendices.

Page 115: **Patients for whom ≥3 prior treatments have failed**	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**

Please amend confidentiality highlighting in Table A1.2 as follows: **Patients for whom ≥3 prior treatments have failed**	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**

The patient numbers in this table are confidential and should be marked as AIC. These should also be marked as confidential in the response to clarification questions (A5), where the highlighting was erroneously omitted.

References

1. Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med 2017a;377:2123-2132.
2. Sun Hea. Effect of anti-CGRP receptor antibody AA58 on CGRP receptor internalization and trafficking. Presented at: IHC 2017; Vancouver, Canada [PO-01-087].
3. Pavlos NJ, Friedman PA. GPCR Signaling and Trafficking: The Long and Short of It. Trends Endocrinol Metab 2017;28:213-226.
4. Amgen. Data on File: Raffi, et al. 20180220 manuscript draft.
5. Lane JR, Abdul-Ridha A, Canals M. Regulation of G protein-coupled receptors by allosteric ligands. ACS Chem Neurosci 2013;4:527-34.
6. Littleton J. Receptor regulation as a unitary mechanism for drug tolerance and physical dependence--not quite as simple as it seemed! Addiction 2001;96:87-101.
7. Vargas B, Starling A, Silberstein S, et al. Erenumab Immunogenicity: a Pooled Analysis of Phase 2 and Phase 3 Migraine Prevention Clinical Trials. Presented at the 70th AAN Annual Meeting, 2018.
8. Steiner TJ, Scher AI, Stewart WF, et al. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia 2003;23:519-27.
9. World Health Organisation. Atlas of headache disorders and resources in the world 2011. Available at: http://www.who.int/mental_health/management/atlas_headache_disorders/en/. Accessed: 14.11.18.
10. National Institute for Health and Care Excellence. TA260: Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. Available at: https://www.nice.org.uk/guidance/ta260. Last accessed: 06/04/18.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Erenumab for preventing migraine

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check. The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
10	Typographical error: "Of these only 515 are directly relevant to the decision" replaced with "Of these only 511 are directly relevant to the decision"
11	Typographical errors: "at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo" changed to "at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo"; "In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks" changed to "In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks"; "in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks" changed to "in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks" Addition of AiC mark-up: "≥50% responder rate (based on monthly headache days) with an OR = 1.10 (95% CI 0.42 to 2.83), this result was similar when using the full trial population (OR 1.02, 95% CI 0.63 to 1.65). There were also no significant differences between erenumab 140mg and botulinum toxin in either the optimised population (OR 1.80, 95% CI 0,.72 to 4.49) or full trial populations (OR 1.19, 95% CI 0.74 to 1.92)" changed to: "≥50% responder rate (based on monthly headache days) with an OR = [redacted], this result was similar when using the full trial population (OR [redacted]). There were also no significant differences between erenumab 140mg and botulinum toxin in either the optimised population (OR [redacted]) or full trial populations (OR [redacted])"
12	Numerical error: "Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <30% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 20% reduction in MMDs which they considered to be beneficial." Changed to: "Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <50% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 40% reduction in MMDs which they considered to be beneficial."
15	Typographical error: "based on post-hoc subgroup analyses of data from four RCTs involving approximately 20% of the total studied population (n=515)" changed to "based on post-hoc subgroup analyses of data from four RCTs involving approximately 20% of the total studied population (n=511)"
16	Wording change: "There is a lack of long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, for either the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed or the wider population covered by the marketing authorisation." Changed to: "There are limited long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, however, these data are not specific to the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed."

19	Text amended: "The exception is treatment with botulinum toxin, which is the only NICE-recommended therapy for the prophylaxis of migraine." Changed to: "The exception is treatment with botulinum toxin, which is the only NICE-recommended therapy for the prophylaxis of headache in patients with chronic migraine."
28	Text deleted: "~~however, the cited report of this advisory board does not include any discussion of the generalisability of trials to the UK population.~~"
31	Numerical error: "Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <30% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 20% reduction in MMDs which they considered to be beneficial." Changed to: "Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <50% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 40% reduction in MMDs which they considered to be beneficial."
40	Typographical error: "Of these only 515 are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments: Study 295 n=232; STRIVE n=74; ARISE n=56; LIBERTY n=149" changed to "Of these only 511 are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments: Study 295 n=232; STRIVE n=74; ARISE n=56; LIBERTY n=149"
42	Wording change: "evidence is lacking about the long-term effectiveness of erenumab treatment." Changed to: "evidence is very limited for the long-term effectiveness of erenumab treatment."
48	Addition of AiC mark-up to patient numbers in the header of Table 4.7.
54	Typographical errors: "at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo" changed to "at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo"; "In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks" changed to "In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks"; "in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks" changed to "in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks" Text added: "The ERG also notes that, for the STRIVE trial, there is an inconsistency between the effect estimate for 140mg erenumab versus placebo in patients with HFEM for whom ≥3 prior prophylactic treatments have failed reported in the summary of key results box on page 80 of the CS (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]]) and that reported in the main text (Section B.2.6.3 of the CS) and in Table 4.11 of this report (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]])." Changed to: "The ERG also notes that, for the STRIVE trial, there is an inconsistency between the effect estimate for 140mg erenumab versus placebo in patients with HFEM for whom ≥3 prior prophylactic treatments have failed reported in the summary of key results box on page 80 of the CS (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]]) and that reported in the main text (Section B.2.6.3 of the CS) and in Table 4.11 of this report (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]]). The company acknowledged this error in the factual accuracy check and confirmed that [redacted] days (95% CI: [redacted] is the correct figure."

56	Addition of AiC mark-up to patient numbers in the header of Table 4.12.
61	Unnecessary AiC mark-up remived from Table 4.16, as indicated by the company.
67	Typographical errors: “at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo” changed to “at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo”; “In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks” changed to “In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks”; “in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks” changed to “in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks”
70	Typographical error: “Twenty-two unique utility studies were identified” changed to “Twenty-one unique utility studies were identified”
81	Wording change: “However, the ERG believes that, given the absence of evidence related to the long-term effectiveness, it is uncertain whether there is a treatment waning effect” changed to: “However, the ERG believes that, given the very limited evidence related to the long-term effectiveness, it is uncertain whether there is a treatment waning effect”
86	Typographical error: “The ERG found that utility values per MMD frequency ranged from [redacted] using the HIT-6 instrument, whilst they ranged from [redacted] using the MSQ instrument (whole migraine population).” Changed to: “The ERG found that utility values per MMD frequency ranged from [redacted] using the HIT-6 instrument, whilst they ranged from [redacted] using the MSQ instrument (whole migraine population).”
87 to 88	Addition of CiC mark-up to Table 5.8.
100	Deterministic results presented in section 5.3.3 have been corrected.
102 to 107	Deterministic results presented in section 6.1 have been corrected
115	Addition of AiC mark-up to patient numbers, patients for whom ≥3 prior treatments have failed, in Table A1.2.

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the NICE scope is people with migraine. Erenumab has received marketing authorisation from the European Medicines Agency (EMA) for the prophylaxis of migraine in adults who have at least four migraine days per month. However, the population in the company's submission represents a subset both of the population in the NICE scope and in the marketing authorisation. The targeted population is adult patients with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed. The population addressed is likely to reflect the expected use of erenumab in the NHS as it targets those with the highest unmet need. Furthermore, erenumab would not be expected to be used in treatment-naïve patients due to the low cost of oral prophylactics. The submission relies, primarily, on four randomised, placebo-controlled trials of erenumab, of which three were conducted in patients with episodic migraine and one in patients with chronic migraine. For all four trials, the data used in the submission were derived from *post-hoc* subgroup analyses of patients for whom ≥3 prior prophylactic treatment categories had failed.

The intervention (erenumab) is in line with the scope. The recommended dosage is 70mg every four weeks administered as a subcutaneous injection using a pre-filled pen for self-injection, although some patients may benefit from a dosage of 140mg every for weeks (Q4W), which is administered as two consecutive injections of 70mg each. The company's model assumed that 50% of patients would receive 70mg and 50% of patients 140mg. However, logically, if not all patients would receive the same dose then there must be variation in those patients such that some would benefit more from one dose than another. This would imply two different populations, but the company did not explicitly differentiate any such populations and neither were such populations described in the scope. Therefore, it follows that both doses are indicated for the same population and therefore should be considered as comparators to each other. The implications of this are discussed in the economic modelling sections of this report.
The description of comparators in the NICE scope is: "Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies". For the main comparator, best supportive care (BSC), the company considered the placebo arms of the main erenumab trials to be representative of BSC and provided full details of concomitant treatments. No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus BSC. Although these comparators are appropriate for the patients addressed in the company's submission (for whom ≥3 prior prophylactic treatment categories had failed), any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s).
Relevant outcomes were described in the submission, although it is noted that the double-blind phases of the included trials are only up to 24 weeks. Data from open label phases of the trials are available up to 52 weeks but the effectiveness of erenumab as a long-term prophylaxis of migraine requires extrapolation from the data available.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company's submission (CS) included four key erenumab studies. Study 295 was the only erenumab study conducted in patients with chronic migraine. Three studies (STRIVE, ARISE and LIBERTY) were conducted in patients with episodic migraine. Across the four trials, a total of 2,445 patients were included (full intention-to-treat [ITT] population). Of these only 511 are directly relevant to the decision

problem as they had failed ≥3 prior prophylactic treatments. All erenumab trials were randomised, double-blind, placebo-controlled, parallel-group studies and all trials had open-label or active treatment extensions. Double-blind phases were either 12 or 24 weeks in duration. Eligible patients were adults, defined as 18 to 65 in all trials. The trials were international and, with the exception of the ARISE trial, all had a small number of UK sites. Overall, 60 patients from the UK were included across the four trials. Although all trials compared erenumab to placebo, dosages varied (70mg and/or 140mg). All outcomes related to change in the number of migraine days as a primary outcome but this was measured differently and at different time points across the trials.

In Study 295 (chronic migraine) the optimised population (≥3 prior prophylactic treatments have failed) had statistically significantly better outcomes in the erenumab 70mg and 140mg groups than in the placebo group. More specifically, at week 12 patients experienced approximately two and a half fewer migraine days whilst taking erenumab 70mg and four fewer whilst taking erenumab 140mg than on placebo. In total, 34.8% of patients taking 70mg of erenumab and 38.5% of patients taking 140mg erenumab achieved a ≥50% reduction in monthly migraine days (MMDs) from baseline, compared to 15.3% of patients on placebo. In studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks, and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. With the exception of change in MMDs in the LIBERTY trial, these effects were statistically significant. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed.

Across all four trials, the vast majority of adverse events experienced by patients in the erenumab treatment arms were of mild or moderate severity and very low numbers of patients experienced any serious adverse events.

In the absence of direct evidence comparing erenumab to botulinum toxin, the company conducted three indirect treatments comparisons (ITCs) using erenumab data from Study 295 and botulinum toxin data from PREEMPT. In the optimised population (≥3 prior prophylactic treatments have failed) there was no significant difference between erenumab 70mg and botulinum toxin for ≥50% responder rate (based on monthly headache days) with an OR = [redacted], this result was similar when using the full trial population (OR = [redacted]. There were also no significant differences between erenumab 140mg and botulinum toxin in either the optimised population (OR = [redacted] or full trial populations (OR = [redacted]. The indirect comparison results also showed no significant differences between treatments when the outcome of ≥50% responder rate was calculated from monthly migraine days and monthly headache days (MHDs).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company conducted a systematic review to identify studies reporting the efficacy and safety of erenumab and botulinum toxin (as the only active comparator) for the prophylaxis of migraine in adults. The CS and response to clarification provided sufficient details for the ERG to appraise the literature

searches. A wide range of databases were searched, and additional searches of conference proceedings, HTA websites and a trials register were conducted. Relevant systematic literature reviews (SLRs) and

network meta-analyses (NMAs) identified through database and grey literature searches were also reference checked. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.

The ERG notes that the evidence for erenumab is based on four international RCTs investigating patient-relevant outcomes. However, only one trial was conducted in patients with chronic migraine and the number of trial participants for whom ≥3 prior prophylactic treatments had failed is relatively low (approximately 20% of the total studied population). Furthermore, three of the four studies had a double-blind phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was mean monthly migraine days. It is certainly inadequate to show the effect on a condition that would be expected to last far beyond this period, thus the long-term effectiveness of erenumab treatment remains unknown.

The ERG also questions the use of the more stringent (≥50% reduction in MMDs vs. ≥30% reduction in MMDs) definition of responder; it seems unlikely that patients in this population would consider a reduction in their MMDs of between 30 and 49% to be not clinically meaningful. Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <50% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 40% reduction in MMDs which they considered to be beneficial.

Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented. This observation applies to both the whole study populations and to the subgroups which are relevant to this submission. There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

With respect to the definitions of chronic and episodic migraine used in the included studies, there is a potential population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population.

With respect to the ITC of erenumab versus botulinum toxin in the chronic migraine population, the ERG notes that there is a lack of evidence to support the company's assertion that the difference in the time point at which the primary outcome was measured, between the erenumab and botulinum toxin studies used in the ITC, would be likely to favour botulinum toxin. The effect of this difference is unclear. The ERG does not have any concerns about the methods or results of the ITC analyses.

1.4 Summary of cost effectiveness evidence submitted by the company

The company developed a decision-tree plus state transition model. The decision tree represented the assessment period. At the end of the assessment period, the probability of treatment response was estimated. Thereafter, responders and non-responders were modelled as separate health states in the post-assessment period using a state transition model. The costs and quality-adjusted life years (QALYs) associated with these health states were calculated conditional on the MMD frequency distributions.
Erenumab, as per marketing authorisation, is indicated for the treatment of all migraine patients who experience ≥4 MMDs. However, the company assessed the cost effectiveness of erenumab in adults with migraine with ≥4 MMDs for whom ≥3 prior prophylactic treatments have failed. This subgroup was further separated into three populations:

migraine and 64 weeks for episodic migraine). After this period there was no evidence to inform the extrapolation of treatment effectiveness.

Regarding adverse events, the main concerns of the ERG relate to not explicitly modelling the impact of adverse event on costs and HRQoL.

Whilst treatment effectiveness was based on the population with ≥3 prior prophylactic treatments failed, utility values in the model were informed by the full trial population. According to the company, using the population with ≥3 prior prophylactic treatments failed, the number of patients available in the analysis would be significantly reduced, particularly for STRIVE and ARISE. In response to clarification question B14.b, the company implemented a scenario using utility values estimated from the population with ≥3 prior prophylactic treatments, but only for the whole migraine population (not separately for chronic and episodic migraine) due to small sample sizes. Since the company only provided this analysis in the whole migraine population, the ERG maintained the company's base-case analysis using the full trial population in the ERG base-case. This ensures consistency in the derivation of utilities and resource use, but results in inconsistencies between utility and effectiveness estimates.

Similarly, all estimates of resource use and costs were obtained from patient populations not specified to have ≥3 prior failures of prophylactic treatment. The company provided no evidence that prior treatment failure does not impact the costs of migraine treatment. Hence, the ERG cannot rule out that the estimates presented are subject to bias. Additionally, the company assumed sumatriptan injections to have the same price as oral sumatriptan, without appropriate justification.

The main concerns related to the results presented by the company were the lack of full incremental analyses separately including both the erenumab 140mg and 70mg doses, and the failure to include all important parameters in the probabilistic sensitivity analyses.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The searches in the CS were well presented and easily reproducible. A good range of databases and grey literature sources were searched and reference checking was also undertaken. Recognised study design filters were applied to all clinical effectiveness searches and searches for costs, resource use and HRQoL. Furthermore, relevant terms were added to the study design filters to increase sensitivity. Reference checking was also undertaken by the company in order to identify additional studies not retrieved by the main searches. The clinical evidence is based on four multinational RCTs in a relevant patient group. Relevant outcomes are assessed.

The model developed by the company provides granularity with respect to MMD frequency. By reproducing the patient distributions across MMDs for each treatment for multiple time-points, the economic model retains a strong faithfulness to the trial data and captures information that would otherwise be lost through grouping patients.

1.6.2 Weaknesses and areas of uncertainty

The evidence for erenumab in the submission population (adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed) is based on *post-hoc* subgroup analyses of data from four RCTs involving approximately 20% of the total studied population (n=511). Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented in the erenumab studies, both with respect to the whole study population and to the subgroup relevant to this submission. There is also a lack of

evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age. Given the definitions of chronic (≥15 headache days per month, of which ≥8 were migraine days) and episodic (≥4 and <15 migraine days per month with <15 headache days per month) migraine used in the included studies, there is a population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population.

There are limited long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, however, these data are not specific to the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed.

The ERG is concerned that a separate search for adverse events (AEs) was not undertaken. In response to clarification the company reported that AEs were identified by screening the results of database searches. However, clinical effectiveness searches applied a study design filter to identify randomised clinical trials (RCTs) and guidance by the Centre for Reviews and Dissemination (CRD) recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure AEs that are long-term, rare or unanticipated are not missed. It is possible that some relevant evidence may not have been identified as a consequence of this.

There is no direct evidence to compare the effectiveness of erenumab to botulinum toxin.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has incorporated various adjustments to the company base-case. The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that erenumab 140mg was cost effective at willingness to pay thresholds higher than £16,905 and £38,622 per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period respectively (erenumab 70mg was dominated). For the episodic population the probabilistic ERG base-case results indicated that erenumab 70mg would be cost effective at willingness to pay thresholds higher than £10,047 per QALY gained, when assuming a constant treatment effect over time (erenumab 140mg is dominated). When assuming treatment effect waning over a five-year period, this would be £95,227 per QALY gained for erenumab 70mg (erenumab 140mg became cost effective at a willingness to pay threshold of £267,487 per QALY gained).

It should, however, be noted that the increased effectiveness (in terms of QALYs) of erenumab 70mg versus erenumab 140mg (when assuming constant treatment effectiveness), in the episodic migraine population, is inconsistent with the clinical effectiveness evidence presented in chapter 4 (Table 4.9). In Section 4.2.3, the ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed. Indeed, there is a numerically larger difference vs. placebo in change from baseline MMD for 140mg than for 70mg; only the former is statistically significant, and this only in the STRIVE trial. The favourable cost effectiveness of erenumab 70mg for the episodic population seems driven by the MMD frequency distribution for non-responders that is lower than for erenumab 140mg and BSC. It is questionable whether, given the above results for all patients, there would be an advantage for 70mg vs. 140mg for those patients who do not respond. It is also questionable whether extrapolating this benefit for non-responders (or any benefit in MMD frequency distribution for responders) is plausible given the changing response over time. This is to some extent mitigated in

ERG comment:
The ERG checked the references cited by the company to support the statements made above and considered the company to have provided an appropriate description of the underlying health problem. However, the estimate of 100,000 migraine patients in England and Wales expected to be eligible for erenumab treatment (based on failure of ≥3 prior prophylactic treatments) was not adequately supported; this estimate was based on unpublished company data, which were not included in the CS. It should also be noted that the article cited in support of the statement that "around 30% of patients fail to respond to any particular prophylactic medication" concerns triptans only. The statement that "up to 20% of migraine patients do not respond to more than three different prophylactic treatment options" is solely supported in un-published Novartis survey of 40 neurologists; summary data provided suggest that the 20% estimate applies specifically to chronic migraine patients.[16]

2.2 Critique of company's overview of current service provision

The company states that the optimised positioning of erenumab within the care pathway is for the prophylaxis of migraine in patients for whom ≥3 prior prophylactic therapies have failed. This optimised positioning reflects the expected use of erenumab in the National Health Service (NHS), given the high burden of disease, the context of the availability of low-cost oral prophylactics as initial treatment options and the high unmet need for these patients; the only currently recommended treatment option at this point in the pathway is botulinum toxin, which is recommended only for chronic migraine patients who have not responded to ≥3 prior prophylactic treatments.

Current NICE clinical guidelines (CG150) recommend oral prophylactic treatments (typically topiramate, propranolol or amitriptyline) in the first instance for migraine patients.[11] However, these treatments are poorly tolerated, with patients frequently switching, discontinuing or delaying therapies due to a lack of efficacy or adverse events (AEs); reported adherence rates range from 17–20% after one year.[18-20] The CS (Appendix C: Health condition and position of the technology in the treatment pathway) states that, once patients reach a point where ≥3 prophylactic therapies have failed for them, there are no further treatment options for the majority of patients and these patients therefore receive best supportive care (BSC). For some patients, contraindications, special warnings and precautions mean that this point is reached after fewer than three prophylactic therapies have failed. The exception is treatment with botulinum toxin, which is the only NICE-recommended therapy for the prophylaxis of headache in patients with chronic migraine. However, botulinum toxin is only available for patients who have not responded to ≥3 prior prophylactic treatments and who meet the definition of chronic migraine specified in the NICE guidance (TA 260).[21]

ERG comment:
NICE clinical guidelines on diagnosis and management of headaches in over 12s (CG150)[11] include a statement about the possible use of acupuncture in relation to tension-type headache: "Consider a course of up to ten sessions of acupuncture over 5–8 weeks for the prophylactic treatment of chronic tension-type headache." No recommendations about acupuncture are included in the section of the guideline dealing with prophylactic treatment of migraine. Recommendations of the prophylactic treatment of migraine include the following statement on vitamin B2 supplementation: "Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people." The following special consideration is also noted, with respect to women and girls experiencing menstrual-related migraine: "For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) on the days migraine is expected."

3.1 Population

The population defined in the scope is people with migraine and the population in the submission is a subset of this population.

The submission focuses on adult patients with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed (CS, Section B.1.1).[1] The specification of patients with ≥4 migraine days per month is in line with the marketing authorisation from the European Medicines Agency (EMA), issued on 26 July 2018, for the "prophylaxis of migraine in adults who have at least 4 migraine days per month when initiating treatment with erenumab."[1] The CS (Section B.1.1) states that "The optimisation to patients for whom ≥3 prior prophylactic treatments have failed is relevant and appropriate in the context of clinical practice within the National Health Service (NHS); erenumab would not be expected to be used in treatment-naïve patients due to the low cost of oral prophylactics. As such, at this position in the pathway, erenumab targets patients facing the highest unmet need and a lack of treatment options."[1] The population in the submission is likely to reflect the expected use of erenumab in the NHS. However, it does not fully reflect the final scope, and does not represent the whole population for which erenumab has received marketing authorisation from the EMA.

The submission relies, primarily, on four randomised, placebo-controlled trials of erenumab, of which three were conducted in patients with episodic migraine (STRIVE,[28] ARISE,[29] and LIBERTY[30]) and one, Study 295,[31] was conducted in patients with chronic migraine. For all four trials, the data used in the submission were derived from *post-hoc* subgroup analyses of patients for whom ≥3 prior prophylactic treatment categories had failed. With regard to the episodic migraine studies, the submission focuses on LIBERTY. The CS (Section B.2.6) states that: "the number of patients who had received ≥3 prior prophylactic treatments in STRIVE and ARISE was small (n=[redacted] and n=[redacted], [redacted]% and [redacted]% of the study populations, respectively). Analyses across all outcome measures in these subgroups are not therefore considered to be meaningful, and are presented in this section for completeness. LIBERTY provides more relevant clinical evidence in this subgroup as this was a study specifically designed to assess the efficacy and tolerability of erenumab in patients who have failed 2–4 previous migraine prophylactic treatments."[1]

The CS (Section B.2.12.2) reports that the trial populations included patients from [redacted] UK sites ([redacted] patients) in Study 295, [redacted] ([redacted] patients) in STRIVE and [redacted] ([redacted] patients) in LIBERTY,[1] however, it is unclear how many (if any) UK patients were included of patients for whom ≥3 prior prophylactic treatment categories had failed; the ARISE study had no UK sites. The CS (Section B.2.12.2) states that: "The study populations were deemed generalisable to the UK migraine population, as validated by expert clinicians at a UK advisory board,"[23]

Although migraine affects three times as many women as men,[32] and there is also some evidence that migraine prevalence may be lower in non-white populations,[33] both males and non-white populations appear to be under represented in the erenumab trials (See Tables 4.4 and 4.5 in Section 4.2.1 of this report for an overview of all baseline characteristics, for the relevant subgroup, in the four studies). There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

ERG comment:

The company were asked to provide clarification on whether erenumab is expected to be used in patients under 18 or over 65 years of age. The following response was provided:

conducted in patients with episodic migraine (STRIVE, ARISE and LIBERTY); HRQoL outcomes were only reported for the whole study populations. There were no safety, tolerability or quality of life outcomes reported in the subgroup who did not respond to ≥3 previous prophylactic treatments for either botulinum toxin (PREEMPT study) or for erenumab in the chronic migraine population (Study 295).

The CS includes response rate, defined as the proportion of patients with ≥50% reduction in mean MMDs from baseline as a primary outcome measure (used in economic modelling).[1] The company were asked to provide justification and supporting references for this definition, and provided the following response:

"The definition of a responder as achieving a ≥50% reduction in MMDs from baseline in the company submission was informed by the definition of responder used in the clinical trials for erenumab. The responder rate defined as a ≥50% reduction in MMDs from baseline was the primary endpoint in LIBERTY, and a key secondary endpoint in Study 295, STRIVE and ARISE. This definition of a responder aligns with the International Classification of Headache Disorders (ICHD) guidelines for controlled trials of drugs in migraine, which state that the proportion of patients with a 50% reduction in number of migraine days (i.e. responder rate), as compared to baseline values, is an important efficacy outcome.[37] Whilst it is acknowledged that the choice of a ≥50% reduction is arbitrary, it is considered to be clinically relevant, as most patients with migraine value a ≥50% improvement in headache frequency as the most important attribute of an effective migraine preventive drug.[37] Similarly, International Headache Society (IHS) guidelines for conducting clinical trials in migraine state that responder rates in migraine have traditionally been defined as a ≥50% reduction in MMDs.[37] Whilst these guidelines state that a ≥30% reduction can be clinically meaningful in patients with chronic migraine, the more stringent ≥50% definition was considered to be more appropriate for this submission, where patients across the entire spectrum of migraine patients with ≥4 MMDs are considered, as per the licence for erenumab.[34] Finally, EMA guidelines suggest that the responder rate, where a 'responder' is defined as "*a patient with a 50% or greater reduction in attack frequency during treatment compared to baseline*", is collected as an endpoint in trials of migraine prophylactic therapies.[22]

This is supported further by feedback from six expert UK neurologists, who recommended that clinical trials should capture the percentage responder rates rather than MMD frequencies. The advisors considered it more helpful to tell patients the chance of a therapy working, or how many migraine patients usually respond to a therapy, rather than how many fewer MMDs they could expect to experience.[23]"

ERG comment:

The ERG questions the use of the more stringent (≥50% reduction in MMDs vs. ≥30% reduction in MMDs) definition of responder; it seems unlikely that patients in this population would consider a reduction in their MMDs of between 30 and 49% to be not clinically meaningful. Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <50% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 40% reduction in MMDs which they considered to be beneficial.

3.5 Other relevant factors

The company argues that erenumab is innovative because: "it is the only licensed treatment to have been developed specifically for the prophylaxis of migraine, based on an understanding of the

Across the four trials, a total of 2,445 patients were included (full ITT population): Study 295 n=667; STRIVE n=955; ARISE n=577; LIBERTY n=246. Of these only 511 are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments: Study 295 n=232; STRIVE n=74; ARISE n=56; LIBERTY n=149.

All erenumab trials were randomised, double-blind, placebo-controlled, parallel-group studies and all trials had open-label or active treatment extensions. Double-blind phases were either 12 or 24 weeks in duration. This report will present data from the blinded phases of the trials only. Eligible patients were adults, defined as 18 to 65 in all trials. The trials were international and, with the exception of the ARISE trial, all had a small number of UK sites. Overall [redacted] patients from the UK were included across the four trials. Although all trials compared erenumab to placebo, dosages varied. Study 295 in patients with chronic migraine and STRIVE in patients with episodic migraine allowed patients to receive 70 or 140mg doses. However, in ARISE patients could only receive the 70mg dose and in LIBERTY only the 140mg dose was given. All outcomes related to change in the number of migraine days as a primary outcome but this was measured differently and at different time points across the trials.

As the population of interest in this submission is patients for whom ≥3 prior prophylactic treatments have failed, we will not describe or comment in detail on the baseline characteristics of the whole study populations in the four included studies, but will focus on the information provided for the relevant subgroups. Baseline characteristics for the population for whom ≥2 prior prophylactic treatments have failed, used in exploratory economic analyses, were provided in Appendix E of the CS and are not reproduced in this report.[38]

ERG comment:

The ERG notes that the evidence for erenumab is based on international RCTs investigating patient-relevant outcomes, however, only one trial was conducted in patients with chronic migraine and the number of trial participants for whom ≥3 prior prophylactic treatments had failed is relatively low (approximately 20% of the total studied population). Furthermore, three of the four studies had a double-blind phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was mean monthly migraine days; evidence is very limited for the long-term effectiveness of erenumab treatment.

Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented (see Tables 4.4 and 4.5); this observation applies to both the whole study populations and to the subgroups which are relevant to this submission. There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

With respect to the definitions of chronic and episodic migraine used in the included studies (see Table 4.3), there is a potential population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population. This was confirmed in the company's response to clarification questions: "Given the definitions of chronic and episodic migraine used in the clinical trial programme, which were based on clinical guidelines, patients falling outside of these definitions were not included in the clinical trials. However, the license for erenumab covers all patients that have ≥4 MMDs, therefore under the terms of this license, erenumab could be used in patients with ≥15 MHDs, and ≥4 to <8 MMDs."[22]

Studies evaluated different doses of erenumab; Study 295 and STRIVE evaluated 70mg and 140mg Q4W, ARISE evaluated 70mg Q4W, and LIBERTY evaluated 140mg Q4W. The company were asked to provide clarification on which patients are expected to benefit from the 140mg Q4W dose and how these patients can be identified before initiating treatment with erenumab. The following response was provided: "The licence for erenumab does not indicate the specific patient population expected to benefit from the 140mg dose of erenumab. However, numerically superior clinical outcomes were observed for patients treated with erenumab 140mg compared to erenumab 70mg in the subgroup of patients for whom ≥3 prior treatments have failed. Additionally, there is no difference in the safety profiles of the 70mg and 140mg doses. The 140mg dose may therefore be most appropriate for the patient population for whom ≥3 prior treatments have failed: the optimised population considered in this submission."

No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus Botulinum toxin, in patients with chronic migraine (see Section 4.4). For the main comparator, BSC, the company considered the placebo arms of the erenumab trials to be representative of BSC and provided full details of concomitant treatments, by study arm, for the optimised population (patients for

Trial number (acronym)	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT NCT02483585)	LIBERTY (NCT03096834)
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	No
Source: CS Table 14				

ERG comment:
The ERG agrees with the risk of bias assessment provided in the CS.

4.2.3 Clinical effectiveness results for included erenumab studies

This section focuses on the key clinical effectiveness outcomes, reported in the CS and used to inform economic modelling, change in MMD/MHD from baseline to week 12 and responder rate (proportion of patients achieving ≥50% reduction in MMD/MHD from baseline week 12). As the population of interest in this submission is patients for whom ≥3 prior prophylactic treatments have failed, results are reported for this population rather than for the whole study ITT population; results are also provided for the two populations used in exploratory economic analyses (patients for whom ≥2 prior prophylactic treatments have failed, and patients with HFEM (defined as MMD eight to 14 in all three studies of erenumab for the prophylactic treatment of episodic migraine) for whom ≥3 prior prophylactic treatments have failed).

Table 4.7: Key clinical effectiveness results for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in Study 295

	Study 295		
	Placebo (n=[redacted])	**Erenumab 70mg (n=[redacted])**	**Erenumab 140mg (n=[redacted])**
Change from baseline in MMDs			
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change at Week 12 (SE)	[redacted]	[redacted]	[redacted]
LSM difference versus placebo (95% CI)	NA	−2.53 (−4.27, −0.78)	−4.09 (−5.83, −2.33)
p-value	NA	0.005	<0.001
≥50% responder rate (MMDs)			
n (%)	15 (15.3)	23 (34.8)	25 (38.5)
Odds ratio (95% CI)	NA	3.0 (1.4, 6.3)	3.5 (1.6, 7.4)
p-value	NA	0.004	0.001
Change from baseline in MHDs			
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]

ERG comment:

The ERG notes that in studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks, and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed (MMD or MHD, ≥50% responder rates, monthly severity of migraine pain, monthly acute migraine-specific treatment days, monthly cumulative hours of migraine. The ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed.

Results were similar for the expanded subgroup of patients for whom ≥2 prior prophylactic treatments had failed. The ERG notes that numbers of study participants were very small for the subgroup of patients with HFEM, for whom ≥3 prior prophylactic treatments have failed. The ERG also notes that, for the STRIVE trial, there is an inconsistency between the effect estimate for 140mg erenumab versus placebo in patients with HFEM for whom ≥3 prior prophylactic treatments have failed reported in the summary of key results box on page 80 of the CS (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]) and that reported in the main text (Section B.2.6.3 of the CS) and in Table 4.11 of this report (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]). The company acknowledged this error in the factual accuracy check and confirmed that [redacted] days (95% CI: [redacted] is the correct figure.

The CS does not include any long-term (beyond 24 weeks) data on the effectiveness of erenumab compared to placebo in people with episodic migraine. The open-label extension of a phase II study (NCT01952574),[43] described in Appendix L of the CS,[38] provides some information about the longer term maintenance of the effects, relative to baseline, of erenumab (70mg, Q4W): At Week 64, patients achieved a mean reduction of 5.0 (SD: 4.2) MMDs from a baseline of 8.8 MMDs (SD: 2.6), with 65% of patients achieving a reduction of ≥50% in MMDs from baseline.[43] The double-blind phase of this study was not included in the clinical effectiveness section of the CS.

4.4.4 Health-related quality of life data for included erenumab studies

The erenumab studies included in the CS used a variety of instruments to assess the impact of erenumab treatment on health-related quality of life: Study 295, HIT-6, MSQ 2.1, MIDAS and PROMIS; STRIVE, HIT-6, MSQ 2.1, MIDAS and MPFID; ARISE, HIT-6, MSQ 2.1 and MPFID; LIBERTY, HIT-6, EQ-5D-5L and WPAI. All health-related quality of life results were for the full study populations; no health-related quality of life data were provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Economic modelling used utility values which were derived by mapping patient-level MSQ 2.1 data from Study 295, STRIVE and ARISE onto EQ-5D-3L (CS, Section B.3.4.1).[1] This approach is discussed in detail in Section 5.2.8 of this report.

Table 4.12: Treatment-emergent AEs in patients for whom ≥3 prior prophylactic treatments have failed in Study 295, STRIVE, ARISE and LIBERTY (safety analysis set)

Total no. of patients (%)	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 140mg (n=[redacted])
With AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With AEs leading to discontinuation of investigational product	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 6, Response to clarification[22]
AE: adverse event; SAE: serious adverse event

Table 1.16: Summary of study results used in the ITC

Study	Treatment	Population	CfB mean monthly migraine days, mean (SE)	CfB mean monthly headache days, mean (SE)	Patients with a 50% reduction in mean monthly headache days, n/N (%)
PREEMPT	Botulinum toxin 155U –195U	Full trial population, 24 weeks	–8.2 (–8.69, –7.70)[a]	–8.4 (–8.90, –7.92)[a]	NR (47.1)
	Botulinum toxin 155U –195U	Full trial population, 12 weeks	–7.09 (0.13)	–7.15 (0.26)	339/688 (49.3)
	Botulinum toxin 155U –195U	≥3 previous prophylaxis treatments, 24 weeks	–7.1[b] (NR)	–7.4[b] (NR)	76/189 (40)
	Placebo	Full trial population, 24 weeks	–6.2 (–6.69, –5.68)[a]	–6.6 (–7.07, –6.08)[a]	NR (35.1)
	Placebo	Full trial population, 12 weeks	–5.59 (0.23)	–5.97 (0.23)	NR
	Placebo	≥3 previous prophylaxis treatments, 24 weeks	–4.3[b] (NR)	–4.7[b] (NR)	51/207 (25)
Study 295 (NCT02066415)	Erenumab 70mg	Full trial population, 12 weeks	–6.63 (0.45)	–6.43 (0.45)	[redacted]
	Erenumab 70mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Erenumab 140mg	Full trial population, 12 weeks	–6.53 (0.50)	–6.96 (0.52)	[redacted]
	Erenumab 140mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Placebo	Full trial population, 12 weeks	–4.24 (0.38)	[redacted]	[redacted]
	Placebo	≥3 previous prophylaxis treatments, 12 weeks	[redacted]	[redacted]	[redacted]

Source: Table 17, Appendix D of the CS and Response to clarification, question A17

[a]95% confidence intervals are reported instead of standard error; [b]Means reported for these outcomes are least-squares means, not absolute means. [c]Note that the ITC utilised data from patients who had failed on ≥3 prior prophylactic treatments irrespective of category, in order to most accurately reflect the decision problem

CfB: change from baseline; NR: not reported; SE: standard error

in the erenumab 70mg and 140mg groups than in the placebo group. More specifically, at week 12 patients experienced approximately two and a half fewer migraine days whilst taking erenumab 70mg and four fewer whilst taking erenumab 140mg than on placebo. In total, 34.8% of patients taking 70mg of erenumab and 38.5% of patients taking 140mg erenumab achieved a ≥50% reduction in MMDs from baseline, compared to 15.3% of patients on placebo. In studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks, and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed.

The erenumab studies included in the CS used a variety of instruments to assess the impact of erenumab treatment on health-related quality of life: Study 295, HIT-6, MSQ 2.1, MIDAS and PROMIS; STRIVE, HIT-6, MSQ 2.1, MIDAS and MPFID; ARISE, HIT-6, MSQ 2.1 and MPFID; LIBERTY, HIT-6, EQ-5D-5L and WPAI. All health-related quality of life results were for the full study populations; no health-related quality of life data were provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Economic modelling used utility values which were derived by mapping patient-level MSQ 2.1 data from Study 295, STRIVE and ARISE onto EQ-5D-3L.

The rates of SAEs in the erenumab treatment arms were generally low, across all four studies. No adverse events data were provided for the active comparator, botulinum toxin, but data from the PREEMPT trials indicated that botulinum toxin may be associated with a higher rate of SAEs than erenumab.

No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus botulinum toxin, in patients with chronic migraine. The ERG does not have any concerns about the methods or results of the ITC analyses.

Overall, although the evidence for erenumab is based on international RCTs investigating patient-relevant outcomes, there is uncertainty about the effectiveness of the lower (70mg Q4W) dose for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, particularly for those patients with episodic migraine. There is also a lack of data for male patients, those over 65 years of age and for non-white populations. The long-term effectiveness of erenumab (beyond 24 weeks) is unknown.

PICOS	Inclusion criteria	Exclusion criteria
	• Cost benefit • Cost minimisation • Cost consequence • SLRs of economic reviews (for reference list search)	• Non-systematic/narrative reviews • Articles not in the English language • Studies not in human subjects • Studies not conducted from a UK or Irish perspective (applicable to cost effectiveness studies and cost and resources use studies)
Study design 2 (Utility studies)	• Primary research publications on any study design • HTAs, or SLRs of relevant primary publications (for reference list search)	
Study design 3 (Cost/resource use studies)	• Primary research publications on any study design • HTAs, or SLRs of relevant primary publications (for reference list search)	
Source: CS Appendix Tables 35-37[38] Abbreviations: EQ-5D: EuroQol 5-Dimensions; HTA: Health Technology Assessment; HUI3: Health Utilities Index; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHS: National Health Service; PSS: Personal and Social Services; QALYs: quality-adjusted life years; SF-6D: Short-Form Six-Dimension; SLR: systematic literature review; UK: United Kingdom		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. However, the ERG is concerned about the potential language bias arising from restricting searches to English language only; this is not in line with current best practice.

5.1.3 Included/excluded studies in the cost effectiveness review

The initial SLR related to cost effectiveness evidence identified 30 publications which met the inclusion criteria, 3,410 titles/abstracts and 205 full texts were reviewed. Six additional publications were found through handsearching of conference proceedings and websites. The 2018 update of the SLR resulted in additional six publications, the updated hand search resulted in one additional article. Hence, a total of six unique economic evaluations, and 19 unique cost/resource use studies were identified. Twenty-one unique utility studies were identified of which 13 reported EQ-5D utility values (see Appendix G of the CS Figure 5 for the PRISMA diagram).[38] The included cost effectiveness studies were summarised and critically appraised using the checklist of Drummond et al. (1996),[51] in Tables 40 and 41 of the CS Appendix.[38] Summaries of utility studies, and cost and resource use studies included were presented in Tables 42 and in Appendices G, H and I of the CS.[38]

ERG comment: The rationale for excluding cost effectiveness studies after full paper reviewing is considered appropriate given the defined inclusion and exclusion criteria. Nine publications identified in the SLR were not fully extracted because they did not report EQ-5D data and were thus not in line with the NICE reference case (Table 43 of the CS Appendix H[38]). Considering the potential limitations of the EQ-5D in migraine patients and the scarcity of utility data in migraine patients with ≥3 prior prophylactic treatment failures, as outlined in Section 5.2.8, the ERG is concerned that relevant HRQoL

a) baseline MMD seemed to have plateaued at the end of the initial trial period for erenumab (weeks 8-12) while for placebo this was still decreasing.
b) Considering the extrapolation beyond the open-label extension studies (after 52 weeks for chronic migraine and after 64 weeks for episodic migraine) up to 10 years (model time horizon), the company argued, in response to clarification question B9b, that "Whilst no data are available from longer-term follow-up of patients treated with erenumab, the results of these [open-label extension] studies provide no indication of a waning in the treatment effect: in both studies, patients experienced numerical reductions in MMDs from the end of the double-blind treatment phase to Week 52 or Week 64". However, the ERG believes that, given the very limited evidence related to the long-term effectiveness, it is uncertain whether there is a treatment waning effect. In response to clarification question B9d, the company explored an alternative scenario for the long-term effectiveness by reducing the health state costs and health state utilities for erenumab and botulinum toxin linearly over time, to eventually reflect the health state costs and health state utilities associated with BSC non-responders. This scenario indicated that a treatment waning effect could substantially increase the estimated ICERs. The scenario presented by the company assumed a treatment waning period of 10 years: decreasing this period would be likely to further increase the estimated ICERs. This scenario, as well as a similar scenario with a five-year waning period is adopted by the ERG.
c) For the implementation of the MMD frequency distributions in the model, the company assumed normal distributions with a range truncated between 0-28 migraine days per month. This restricted range resulted in floor and ceiling effects (see for instance CS Figure 24), which the company acknowledged may introduce bias (response to clarification question B12c). Although the company argues that this bias is conservative, this is not completely convincing to the ERG given that no evidence was provided to support this.
d) The MMD frequency distributions were summarised in Table 88 of the CS Appendix S.[38] However, additional MMD distributions to those described in the CS were used for the episodic migraine. Specifically, 24-week MMD distributions were added for responders. Given that the rationale for only using 24-week MMD distributions for responders with episodic migraine was lacking, this inconsistency was adjusted in the ERG base-case to be in line with the CS description as well as with the chronic migraine population.
e) For the indirect comparison the different timings of response for erenumab (based on 12 weeks MMD) and botulinum toxin (based on 24 weeks MHD) were (implicitly) assumed to have no effect on the size of the response. This may have biased the estimated cost and effects of botulinum toxin. However, the direction and magnitude of this bias is unclear to the ERG (see Sections 4.3 and 4.4 for more details).
f) The company assumed that the nature of treatment discontinuation determines whether patients either return to the baseline MMD distribution (discontinuation due to adverse events or long-term discontinuation) or maintain the non-responder MMD as measured at week 12 (discontinuation due to non-response at week 12). In response to clarification question B10 the company argued that response status reveals heterogeneity within the patient population of interest and thus it was assumed that a different propensity to respond to treatment also means a different disease status when coming off treatment. The company argued that those who respond to treatment would hence have experienced a 'better' natural improvement in MMDs compared to non-responders. The ERG believes that this argumentation is inconsistent with the modelling approach adopted by the company, given that in chronic migraine non-responders actually have a [redacted] MMD frequency than the baseline MMD frequency and in episodic migraine [redacted]. (see Table 5.6). Therefore, the ERG assumed that all treatment discontinuers would have the week 12 non-responder MMD frequency.

a) migraine patients, which is not in accordance with the NICE reference case.[50] It is further noteworthy that the company's results, presented in response to clarification question B17.e, also include a utility decrement for mode of administration associated with botulinum toxin (based on the same vignette-based study).
b) The company's argument that EQ-5D values did not capture the impact of migraine on HRQoL because they were elicited mostly during migraine-free days (and hence preferred mapped utilities from MSQ data over EQ-5D utilities), is plausible. However, using EQ-5D utilities from LIBERTY had a large impact on the ICER (increased from £35,787 in the CS base-case to £68,080 per QALY gained in the company's scenario, see CS Table 87). Since using EQ-5D utilities is in line with the NICE reference case, the ERG considers the use of LIBERTY EQ-5D data as a scenario analysis.
c) The company used mapped utilities from MSQ data, whilst mapped utilities from HIT-6 data could also have been used. In response to clarification questions B16, the company provided scenarios using the mapping algorithm by Gillard et al (2012)[56] to map HIT-6 data to EQ-5D utilities. In these scenarios, ICERs in all populations and comparisons increased by at least £10,000 per QALY gained (Tables 72-79 of response to the clarification letter).[22] However, the company pointed out that the HIT-6 instrument measures the impact of headaches, rather than that of migraines, on HRQoL. The ERG found that utility values per MMD frequency ranged from [redacted] using the HIT-6 instrument, whilst they ranged from [redacted] using the MSQ instrument (whole migraine population). The latter are more aligned with utility ranges considered in the previous TA260,[21] which is likely to be because these were also based on MSQ data. The ERG considers that MSQ is likely to be a better source than HIT-6 for mapped utility data in this population.

5.2.9 Resources and costs

The cost categories included in the model were treatment costs and costs of disease management. Treatment costs included drug costs, administration costs and initiation costs. Costs for disease management included visits to the emergency department, general practitioner, nurse practitioner and neurologist, hospitalisations, migraine-specific medication (assumed to be represented by triptan use) and other medication (assumed to be represented by analgesics).

Unit prices stemmed from the manufacturer, the British National Formulary (BNF) 2017,[59] the National Health Service (NHS) Tariff 2017[60] and the Personal Social Services Research Unit (PSSRU) 2017.[61]

Resource use and costs data identified in the review

According to the CS, the SLR identified 22 publications reporting UK relevant resource use and costs, corresponding to 19 unique studies.[1] The company did not use these studies to inform resource use as none of them reported costs or resource use by MMD frequency. Instead resource use data from their National Health and Wellness survey (NHWS) of 2017 and 2018 were used.[52, 53]

Treatment costs (with PAS)

An overview of treatment costs is provided in CS Table 48.[1] Erenumab is either delivered per 70mg (1 × 70mg pre-filled pen) or per 140mg (currently two packs of 1 × 70mg pre-filled pen). The prices of the 70mg dose and 140mg dose are £[redacted] and £[redacted] respectively. Erenumab was administered three times per model cycle (of 12 weeks), the treatment cost per cycle were thus £[redacted] and £[redacted] for 70mg and 140mg respectively. Administration costs do not apply but a one-off initiation cost of £40.04 was incorporated to reflect training of the patient on how to use the injection (assumed to be the cost of one working hour of a Band 5 hospital nurse, applied in the first cycle only).[61]

No treatment costs for BSC were incorporated (besides the health state costs described below) given that both erenumab and botulinum toxin are used in conjunction with BSC. Botulinum toxin for chronic migraine was used at a list price of £276.40 per 200 IU vial, corresponding to the Summary of Product Characteristics (SmPC) recommended dose of 155 to 195 units, applied once per cycle. Administration costs of £116.00 were applied (assumed to be the tariff "WF01A Follow Up Attendance - Single Professional (code 400)" in the non-mandatory prices worksheet).[60] This resulted in treatment cost per model cycle (of 12 weeks) of £392.40.

Health state costs

Acute and background disease management costs were applied to all patients. This was solely dependent on the number of MMDs, i.e. independent of treatment status (see CS Table 51[1] for resource use frequency and cost per cycle by MMD frequency). Each model health state was associated with a different MMD frequency distribution (see Section 5.2.6 for more details). By combining these MMD frequency distributions with the costs per MMD frequency, average costs were calculated per health state.

The following components were included in the health state costs: emergency department (A&E) visits, hospitalisations, general practitioner visits, nurse practitioner visits, neurologist visits. Resource use by MMD frequency was informed by the NHWS 2017[52] and unit prices were taken from the NHS Tariff 2017[60] and the PSSRU 2017,[61] see CS Table 57.[1]

Migraine-specific medication use and other medication use per MMD frequency were also included. The company assumed migraine-specific medication could be represented by triptan use and other medication use could be represented by use of analgesics. The proportions of medications used were informed by the NHWS 2018,[53] unit prices and doses per migraine drug day/other medication day were taken from the BNF 2017.[59] A regression model based on pooled clinical data from Study 295, ARISE, LIBERTY and STRIVE informed the number of migraine drug days/other medication days per cycle by MMD frequency. Health state costs based on MMD distribution and MMD frequency-dependent healthcare utilisation are shown in Table 5.8.

Table 1.1: Health state costs per cycle (of 12 weeks)

Health state	Erenumab 70mg	Botulinum toxin[d]	Erenumab 140mg	Botulinum toxin[e]	BSC
Total population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Episodic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	Erenumab 70mg	Botulinum toxin[d]	Erenumab 140mg	Botulinum toxin[e]	BSC
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Model sheet 'Costs'[1]
Abbreviations: BSC: Best supportive care
[a] Patients with adverse event-related or long-term discontinuation in the post-assessment period are assumed to have baseline health state costs
[b] Referring to non-responders in the assessment period and patients off treatment in the post-assessment period due to initial non-response
[c] See critique in 5.2.6 (ERG comments point d) regarding the addition of this time point for responders with episodic migraine only.
[d] When compared to erenumab 70mg
[e] When compared to erenumab 140mg

Adverse event related costs
As described in Section 5.2.7., costs and resource use related to adverse events were not explicitly included in the cost effectiveness analysis.

ERG comment: The main concerns of the ERG relate to: a) the use of evidence from populations without ≥3 prior failures of prophylactic treatment, b) the merging of datasets related to migraine and other medication days, c) the inconsistency and representativeness of medication brands selected, d) assumptions related sumatriptan injections costs, e) patient grouping by MHDs for medication use per MMD and, f) the exclusion of the cost impact of AEs.

a) Due to the scarcity of data on patients with ≥3 prior failures of prophylactic treatment, all estimates of resource use and costs were obtained from patient populations not specified to have ≥3 prior failures of prophylactic treatment. The company provided no evidence that prior treatment failure does not impact the costs of migraine treatment.[22] Given that no evidence was provided, the ERG cannot rule out that the estimates presented are subject to bias.
b) The company pooled data on acute medication days and other headache medication days from Study 295, STRIVE and ARISE by merging datasets. This approach differs from the method used to pool QoL data (using a multi-level regression model) and assumes that there is no trial-level effect and that the trials sample from the same patient population with the same MMD frequency. It is unclear to the ERG to what extent these assumptions are reasonable or may induce bias.
c) To inform the prices of acute medication and other headache medication days, per medication item, a brand was selected to inform the price per medication dose. No specified criteria were used in the selection of the brand, causing inconsistency. It is unclear to what extent the brands chosen correspond with the brands predominantly used in UK clinical practice. The identified prices may therefore not be fully representative of the mix of brands used in UK clinical practice.
d) The company assumed sumatriptan injections (used in 18.4% of patients as headache medication,[22]) to have the same price as oral sumatriptan.[38] The justification for this assumption is unclear to the ERG. The ERG therefore amended the cost per triptan medication to reflect the costs of sumatriptan injections (instead of the costs of oral sumatriptan) in the ERG base-case analysis.
e) In their clarification response, the company amended a typographical error in Table 58 of the CS and clarified that patients were grouped by number of MHDs to estimate medication use by MMD.[22] The ERG considers the assumption of MHDs approximating MMDs to be questionable, given that

The deterministic ERG base-case assuming constant treatment effectiveness over time indicated that erenumab 70mg was cost effective at willingness to pay thresholds higher than £10,782 per QALY gained (erenumab 140mg was dominated). When assuming treatment effect waning over a five-year period, erenumab 70mg only became cost effective at a willingness to pay threshold of £113,147 per QALY gained while this was £126,000 for erenumab 140mg.

6.1 Deterministic analyses undertaken by the ERG (all with PAS)

Table 6.2: Deterministic ERG base-case for the chronic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,609	£10,609
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£24,668
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,832	£13,340
Fixing errors						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,629	£10,629
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,026
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,987	£13,390
Fixing errors + lifetime time horizon						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£7,090	£7,090
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£36,554
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£27,038	£11,855
Fixing errors + applying triptan injections costs for triptan injections						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£9,236	£9,236

Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,593	£11,996
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£23,633
Fixing errors + assuming non-responder MMD frequency distribution after treatment discontinuation						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£9,539	£9,539
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£23,556
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,186	£12,039
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£3,813	£3,813
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,641	£7,064
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,818
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£26,526	£26,526
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£115,183
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£36,659	£30,881

Table 6.3: Deterministic scenario analyses for the chronic migraine population conditional on ERG base-case (assuming constant treatment effectiveness)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) vs BSC

					full incremental	
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£3,813	£3,813
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,641	£7,064
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,818
ERG base-case + assuming a response definition of ≥30% reduction from baseline MMD						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£17,320	£17,320
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£60,941
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,862	£18,052
ERG base-case + positive discontinuation scenario						
Botulinum toxin	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£1,549	£1,549
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
ERG base-case + assuming response benefits 12 weeks after start treatment for botulinum toxin						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£2,915	£2,915
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,083	£7,064

Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,818
ERG base-case + treatment effect waning over ten years						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£15,568	£15,568
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£58,135
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£26,351	£19,787
ERG base-case + MSQ mapped utilities based on patients for whom ≥3 prior prophylactic treatments have failed						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£4,144	£4,144
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,000	£7,678
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£28,061
ERG base-case + EQ-5D-5L utilities (cross-walk) from LIBERTY						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,688	£10,688
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,847	£19,803
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£72,375

Table 6.4: Deterministic ERG base-case for the episodic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				

Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£29,200	£29,200
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£73,282	£40,662
Fixing errors						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£29,668	£29,668
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£74,813	£41,360
Fixing errors + lifetime time horizon						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£13,782	£13,782
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£36,510
Fixing errors + applying triptan injections costs for triptan injections						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£27,613	£27,613
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£72,785	£39,312
Fixing errors + assuming non-responder MMD frequency distribution after treatment discontinuation						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£28,106	£28,106
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£90,985	£41,690
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,207	£10,207

Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£35,482
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£94,984	£94,984
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£310,725	£143,414

Table 6.5: Deterministic scenario analyses for the episodic migraine population conditional on ERG base-case (assuming constant treatment effectiveness)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,207	£10,207
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£35,482
ERG base-case + assuming a response definition of ≥30% reduction from baseline MMD						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£90,984	£90,984
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
ERG base-case + positive discontinuation scenario						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£3,670	£3,670
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,773	£6,755
ERG base-case + treatment effect waning over ten years						
BSC	[redacted]	[redacted]				

Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£74,349	£74,349
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£97,527	£84,245
ERG base-case + MSQ mapped utilities based on patients for whom ≥3 prior prophylactic treatments have failed						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£7,528	£7,528
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£26,170
ERG base-case + EQ-5D-5L utilities (cross-walk) from LIBERTY						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,418	£19,418
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£67,498

Table 6.6: Deterministic ERG base-case and scenario analysis for the HFEM subgroup

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£37,331	£37,331
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£38,194	£37,749
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,782	£10,782
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£29,259
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				

Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£113,147	£113,147
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£125,865	£119,351
ERG base-case (assuming constant treatment effectiveness) with alternative HFEM definition (10-14 MHDs)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£13,556	£13,556
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£40,972

Patients for whom ≥2 prior treatments have failed	**n=141**	**n=92**	**n=92**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

STRIVE

The most frequent (>10%) acute headache medications used during baseline and during the double-blind treatment phase were in the categories of non-opioid acute headache medications ([redacted]%, [redacted]%, and [redacted]% of subjects in the placebo, erenumab 70mg, and erenumab 140mg arms, respectively) and triptan-based migraine medications ([redacted]%, [redacted]%, and [redacted]%, respectively; see Table A1.2).

Table A1.2: Concomitant medication usage in STRIVE

Population	**Placebo**	**Erenumab 70mg**	**Erenumab 140mg**
Full study population	**n=319**	**n=314**	**n=319**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Erenumab for preventing migraine (addendum)

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Re. Exclusion criteria for Study 295, STRIVE, ARISE and LIBERTY and how these may influence the applicability of the trial to the subgroup of the UK migraine population specified in the submission.

Table 1 in the company submission (CS) defines the population considered as: "Adults with migraine with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed." – **This definition does not specify individual treatments or treatment classes failed.**

However, the treatment pathway proposed by the company (see Figure 2.1, ERG report) indicates that would be third- or fourth-line treatment **after failure of at least two of three specified drugs (propranolol, amitriptyline and topiramate).**

As noted by the committee chair (Professor Gary McVeigh) during the pre-meeting briefing teleconference on 27th November, the exclusion criteria for Study 295, STRIVE, ARISE and LIBERTY appear to conflict with the population defined above. Appendix M of the CS includes Tables showing all inclusion and exclusion criteria for each study used in the CS; these are reproduced in Tables 1 to 4 below, with the relevant information highlighted.

The exclusion criteria specified for LIBERTY (failure of >4 migraine prophylaxes from a specified list) appear to allow inclusion of patients in the relevant subgroup, using ether of the two definitions above; i.e. a patient can have failed **propranolol, amitriptyline and topiramate** or **≥3 prior prophylactic treatments** without having failed >4 migraine prophylaxes, however, excluding patients who have failed >4 prophylaxes may mean that more severely affected patients within the subgroup of interest may have been excluded.

For study 295, STRIVE and ARISE the specified exclusion criteria (no therapeutic response to >3, >2 and >2, respectively, classes of migraine prophylaxis) appear to indicate that patients who had failed at least two of **propranolol, amitriptyline and topiramate** (the subgroup of interest, as indicated in the proposed treatment pathway) would have been excluded from these studies, unless the definition of failure did not include lack of response (e.g. definition of failure based on tolerability rather than efficacy). Patients who had failed **≥3 prior prophylactic treatments** could have been included in these studies provided that they had failed multiple treatments in the same category (e.g. 2 beta-blockers an d1 tricyclic antidepressant), however, this would not be consistent with the drugs specified in the proposed treatment pathway.

The first draft of our clarification letter included the following question, in relation to this issue:

"Priority: Page 40 of the CS and Appendix M detail the exclusion criteria for the main trials. It is noted that patients were excluded from Study 295 if they gained no therapeutic response to > 3 treatment categories (> 2 categories in STRIVE and ARISE, and > 4 in LIBERTY). What are the implications of this when assessing response in patients who have failed on ≥ 3 treatments which is the main focus of the submission?"

However, in our final version, we replaced this question with:

"Please provide details of the previous failed prophylactic treatments (with numbers of patients), by treatment group, for the optimised population (≥3 previous failed prophylactic treatments) in each of the 4 main trials."

The company did provide this information (see Tables 5 and 6, below). However, the information provided does not clarify the issue described above as it describes only how many patients had failed each drug or class. It does not provide a definition of failure, nor does it provide information on the combinations of multiple drugs or treatment classes failed.

In summary, the issue(s) to be explored with the company are

- **What is the definition of treatment failure, as applied to the subgroup of interest (people who have failed ≥3 previous prophylactic treatments)?**
- **Does failure of ≥3 previous prophylactic treatments mean failure of ≥3 individual treatments (possibly including multiple treatments within the same class), failure of ≥3 treatment classes, or failure of the three treatments specified in the proposed care pathway (propranolol, amitriptyline and topiramate)?**
- **Based on the study exclusion criteria (described in appendix M of the CS and reproduced in Tables 1 to 4 below) how many people, who would have been in the subgroup of interest, were excluded from each study?**

Table 1: Eligibility criteria for Study 295

Inclusion criteria	Exclusion criteria
Screening phase (prior to enrolment into the baseline phase)	
Adults, aged 18–65 years, provided informed consent prior to initiation of any study-specific activities/procedures History of at least five attacks of migraine with/without aura per the IHS Classification ICHD-III based on medical records and/or patient self-report: ICHD-III Diagnostic criteria for migraine without aura (the following criteria must be fulfilled and symptoms not attributed to another disorder): Headache attacks lasting four to 72 hours (untreated or unsuccessfully treated) Headache with at least two of the following characteristics: Unilateral location Pulsating quality Moderate or severe pain intensity Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) During headache, at least one of the following: Nausea and/or vomiting Photophobia and phonophobia	Older than 50 years of age at migraine onset History of cluster headache or hemiplegic migraine headache Chronic migraine with continuous pain, in which the patient does not experience any pain free periods (of any duration) during the one month prior to screening Unable to differentiate migraine from other headaches Taken an opioid and/or opioid-containing analgesic for any indication on >12 days during the three months prior to screening Taken a butalbital-containing analgesic for any indication on >6 days during the three months prior to screening No therapeutic response[a] in prophylaxis of migraine after an adequate therapeutic trial to >3 of the following medication categories, including: Category 1: Divalproex sodium, sodium valproate Category 2: Topiramate Category 3: Beta blockers Category 4: Tricyclic antidepressants Category 5: Flunarizine or verapamil Category 6: Venlafaxine or desvenlafaxine, duloxetine or milnacipran

ICHD-III Diagnostic criteria for migraine with aura (the following criteria must be fulfilled and symptoms not attributed to another disorder; i.e. transient ischaemic attack has been excluded): One or more of the following fully reversible aura symptoms: Visual Sensory Speech and/or language Retinal Brainstem At least two of the following four characteristics: At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession Each individual aura symptom lasts 5–60 minutes At least one aura symptom is unilateral The aura is accompanied, or followed within 60 minutes, by headache History of ≥15 headache days per month of which ≥8 headache days were assessed by the subject as migraine days in each of the three months prior to screening	Category 7: Botulinum toxin Category 8: Lisinopril or candesartan Changing the dose of a concomitant medication that is not prescribed for migraine prophylaxis but that may have migraine prophylaxis effects within one month prior to screening Using a prohibited migraine prophylactic medication, device or procedure within two months prior to the start of the baseline phase Received botulinum toxin in the head and/or neck region within four months prior to screening Anticipated to require any excluded medication/device (e.g. nerve stimulators, transcranial magnetic stimulation) or procedure during the study History or evidence of unstable or clinically significant medical condition that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion Excluded medical conditions include: Currently diagnosed with fibromyalgia, and/or chronic pelvic pain History of major psychiatric disorder or current evidence of depression based on a BDI-II total score >24 at screening[b]. History of seizure disorder or other significant neurological conditions other than migraine (childhood febrile seizures are not exclusionary) Use of any anticoagulant within six months prior to screening (antiplatelet agents are allowed)

	Malignancy, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last five years Known HIV infection Known hepatic disease or evidence of acute or chronic hepatitis B or hepatitis C, evaluated by testing for hepatitis B surface antigen (HepBsAg), total hepatitis B core antibody (HepBcAb) and hepatitis C antibody at screening Diagnosis of Gilbert's Syndrome Total bilirubin ≥1.5 x ULN or ALT or AST ≥2.0 x ULN Poorly controlled hypertension in the judgment of the investigator, or systolic BP ≥60 mm Hg or diastolic BP ≥100 mm Hg MI, stroke, TIA, unstable angina, coronary artery bypass surgery or other revascularisation procedure within 12 months prior to screening Significantly impaired renal function as determined by an estimated GFR of ≤30 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease equation assessed by the central laboratory at screening Body Mass Index >40 kg/m^2 as assessed at screening At risk of self-harm or risk of harm to others as evidenced by endorsing items four or five on the C-SSRS assessed at screening, or reporting suicidal ideation or suicidal behaviour within the 12 months prior to screening Evidence of drug or alcohol abuse or dependence or recreational use of illicit drugs within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (excluding prescribed medications)

	Pregnant or breastfeeding, is a female expecting to conceive during the study or who is unwilling to use an acceptable method of contraception up to 16 weeks after the last dose of investigational product Known sensitivity to any component of the investigational product Previously received IP administration with either erenumab or placebo in another Amgen clinical study Investigational site staff or relatives of the investigator Likely to not be able or available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (e.g. independent completion of eDiary items) to the best of the subject's and investigator's knowledge
Baseline phase (prior to randomisation into the double-blind treatment phase)	
≥15 headache days of which ≥8 headache days meet criteria as migraine days during the baseline phase based on the eDiary calculation ≥4 distinct headache episodes, each lasting ≥4 hours or if shorter, associated with use of a triptan or ergot-derivative on the same calendar day during the baseline phase, based on the eDiary calculations Demonstrated at least 80% compliance with the eDiary (e.g. must complete eDiary items on at least 23 out of 28 days during the baseline phase)	Develop cluster headache or hemiplegic migraine headache during baseline phase Taken an opioid and/or butalbital-containing analgesic for any indication on >4 days during baseline phase Development of unstable or clinically significant medical condition that, in the opinion of the investigator, poses a risk to the patient's safety or interfere with the study evaluation, procedures or completion Excluded medical conditions include: Diagnosis of fibromyalgia, and/or chronic pelvic pain As stated in the screening phase, diagnosis of major psychiatric disorder (such as schizophrenia or other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), or current

	evidence of depression based on a BDI-II total score >24 during baseline. Subjects may not have experienced an anti-anxiety or anti-depressant medication adjustment since screening and must demonstrate clinical stability. Seizure disorder or other significant neurological conditions other than migraine Use of any anticoagulant during baseline (antiplatelet agents are allowed) Poorly controlled hypertension in the judgment of the investigator, or systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg as measured at Day 1 pre-randomisation MI, stroke, TIA, unstable angina, coronary artery bypass surgery or other revascularisation procedure during baseline phase At risk of self-harm or harm to others as evidenced by endorsing items four or five on the C-SSRS assessed at baseline Evidence[c] of drug or alcohol abuse or dependence or "recreational use" of illicit drugs (excluding prescribed medications such as opioids or barbiturates) Pregnant or breastfeeding, or is a female expecting to conceive during the study, including through 16 weeks after the last dose of investigational product Likely to not be able or available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (e.g. independent completion of eDiary items) to the best of the subject's and investigator's knowledge Evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the

	investigator or physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion Changing the dose of a concomitant medication that may have migraine prophylaxis effects during the baseline phase Use of any of the excluded concomitant medications outlined

[a]No therapeutic response was defined as no reduction in headache frequency, duration or severity after administration of the medication for at least six weeks at the generally accepted therapeutic dose(s) and was based on the investigator's assessment. Patients did not meet this exclusion criteria if the patient discontinued the medication prior to achieving a therapeutic response due to adverse events related to the medication or if, based on investigator opinion, the patient did not receive an adequate dose of the medication for at least 6 weeks. [b]Patients with generalised anxiety disorder and/or major depressive disorder were permitted in the study if they were on no more than one medication for each disorder. Patients may not have experienced an anti-anxiety or anti-depressant medication adjustment in the three months prior to screening. Patients who required the daily use of anti-psychotic medications (drugs whose primary indication is for use in the treatment of schizophrenia) or as needed (PRN) use of anti-psychotic medications for any major psychiatric disorder were excluded. Use of low doses of anti-psychotic medications as symptomatic treatment for nausea or insomnia (for example, 50 mg or less of quetiapine for insomnia) was acceptable. [c] Urine drug screen test was performed at weeks 4, 8 and 12. Patients who tested positive in the absence of prescribed medications with use documented on the eDiary were to be urine drug screen retested and the patient's continued eligibility discussed with the medical monitor. Urine drug screen test was permitted during baseline based on investigator's clinical suspicion.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BDI-II: Beck Depression Inventory; BP: blood pressure; C-SSRS: Columbia-Suicide Severity Rating Scale; GFR: glomerular filtration rate; HIV: human immunodeficiency virus; ICHD-III: International Classification of Headache Disorders, 3rd edition; IHS: International Headache Society; IP: intraperitoneal; IV: intravenous; MI: myocardial infarction; TIA: transient ischemic attack; ULN: upper limit of normal.

Source: Study 295 Protocol

Table 2: Eligibility criteria for STRIVE

Inclusion criteria	Exclusion criteria
During the screening epoch	**During the screening epoch and/or baseline epoch**
Adults aged 18–65 years, who provided informed consent History of migraine (with or without aura) for ≥12 months prior to screening according to the ICHD-III based on medical records and/or patient self-report Migraine frequency of ≥4 and <15 days per month on average across the three months prior to screening Headache (migraine and non-migraine headache) <15 days per month of headache symptoms (i.e. migraine and non-migraine)	Older than 50 years of age at migraine onset Unable to differentiate migraine from other headaches History of cluster headache or hemiplegic migraine headache No therapeutic response[a] with >2 of the following seven medication categories for prophylactic treatment of migraine after an adequate therapeutic trial: Category 1: Divalproex sodium, sodium valproate Category 2: Topiramate Category 3: Beta blockers (e.g. atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol) Category 4: Tricyclic antidepressants (e.g. amitriptyline, nortriptyline, protriptyline) Category 5: Serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine, desvenlafaxine, duloxetine, milnacipran) Category 6: Flunarizine, verapamil Category 7: Lisinopril, candesartan Use of a prohibited medication, device or procedure within two months prior to the start of the baseline phase or during the baseline phase
During the baseline epoch	
Migraine frequency of ≥4 and <15 migraine days during the baseline phase based on the eDiary calculations Headache frequency of <15 headache days during the baseline phase based on the eDiary calculations Demonstrated at least 80% compliance with the eDiary (e.g. completing eDiary items for at least 23 out of 28 days during the baseline phase)	

	Prior botulinum toxin treatment in the head/neck region within four months prior to the start of the baseline phase or during the baseline phase Use of the following for any indication in any month during the two months prior to the start of the baseline phase: Ergotamines or triptans ≥10 days/month Simple analgesics (NSAIDs, acetaminophen) ≥15 days/month Opioid- or butalbital-containing analgesics ≥4 days/month Anticipated to require any excluded medication, device or procedure during the study Active chronic pain syndromes (e.g. fibromyalgia or chronic pelvic pain) History of major psychiatric disorder (such as schizophrenia and bipolar disorder), or current evidence of depression based on a BDI-II total score >19 at screening[b] History of seizure disorder or other significant neurological conditions other than migraine. Single childhood febrile seizure is not exclusionary Malignancy within the five years prior to screening, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ HIV infection by history Hepatic disease by history or total bilirubin ≥2.0 x ULN or ALT or AST ≥3.0 x ULN, as assessed by the central laboratory at initial screening MI, stroke, TIA, unstable angina, or coronary artery bypass surgery or other revascularisation procedure within 12 months prior to screening

	History or evidence of any other unstable or clinically significant medical condition, that in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion Patient has any clinically significant vital sign, laboratory, or ECG abnormality during screening that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation The patient is at risk of self-harm or harm to others as evidenced by past suicidal behaviour or endorsing items four or five on the C-SSRS assessed at screening Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates) Pregnant or breastfeeding, or is a female expecting to conceive during the study, including through 16 weeks after the last dose of investigational product Female of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with investigational product through 16 weeks after the last dose of investigational product Currently receiving treatment in another investigational device or drug study, or less than 90 days prior to screening since ending treatment on another investigational device or drug study/ies Known sensitivity to any component of the investigational product Previously randomised into an erenumab study Member of investigational site staff or relative of the investigator

	Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (e.g. independent completion of electronic diary items) to the best of the patient's and investigator's knowledge

[a]No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally-accepted therapeutic dose(s) based on the investigator's assessment. Either a lack of sustained response to a medication or failure to tolerate a therapeutic dose do not constitute lack of therapeutic response. [b]Patients with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than one medication for each disorder. Patients must have been on a stable dose within the 3 months prior to the start of the baseline phase.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BDI-II: Beck Depression Inventory; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; HIV: human immunodeficiency virus; ICHD-III: The International Classification of Headache Disorders, 3rd edition; MI: myocardial infarction; NSAIDS: nonsteroidal anti-inflammatory drug; TIA: transient ischemic attack; ULN: upper limit of normal.

Source: STRIVE Protocol

Table 3: Eligibility criteria for ARISE

Inclusion criteria	Exclusion criteria
During the screening epoch	**During the screening epoch and/or baseline epoch**
Adults ≥ 18 to ≤ 65 years of age who provided informed consent History of migraine (with or without aura) for ≥ 12 months prior to screening according to the IHS Classification ICHD-3, based on medical records and/or patient self-report Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening Headache (ie, migraine and non-migraine headache) frequency: < 15 headache days per month on average across the 3 months prior to screening	Older than 50 years of age at migraine onset Unable to differentiate migraine from other headaches History of cluster headache or hemiplegic migraine headache No therapeutic response[a] with >2 of the following seven medication categories for prophylactic treatment of migraine after an adequate therapeutic trial: Category 1: Divalproex sodium, sodium valproate Category 2: Topiramate
During the baseline epoch	

Migraine frequency of ≥4 and <15 migraine days during the baseline phase based on the eDiary calculations Headache frequency of <15 headache days during the baseline phase based on the eDiary calculations Demonstrated at least 80% compliance with the eDiary (e.g. completing eDiary items for at least 23 out of 28 days during the baseline phase)	Category 3: Beta blockers (e.g. atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol) Category 4: Tricyclic antidepressants (e.g. amitriptyline, nortriptyline, protriptyline) Category 5: Serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine, desvenlafaxine, duloxetine, milnacipran) Category 6: Flunarizine, verapamil Category 7: Lisinopril, candesartan Use of a prohibited medication, device or procedure within two months prior to the start of the baseline phase or during the baseline phase Prior botulinum toxin treatment in the head/neck region within four months prior to the start of the baseline phase or during the baseline phase Use of the following for any indication in any month during the two months prior to the start of the baseline phase: Ergotamines or triptans ≥10 days/month Simple analgesics (NSAIDs, acetaminophen) ≥15 days/month Opioid- or butalbital-containing analgesics ≥4 days/month Anticipated to require any excluded medication, device or procedure during the study Active chronic pain syndromes (e.g. fibromyalgia or chronic pelvic pain) History of major psychiatric disorder (such as schizophrenia and bipolar disorder), or current evidence of depression based on a BDI-II total score >19 at screening[b]

	History of seizure disorder or other significant neurological conditions other than migraine. Single childhood febrile seizure is not exclusionary Malignancy within the five years prior to screening, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ HIV infection by history Hepatic disease by history or total bilirubin ≥2.0 x ULN or ALT or AST ≥3.0 x ULN, as assessed by the central laboratory at initial screening MI, stroke, TIA, unstable angina, or coronary artery bypass surgery or other revascularisation procedure within 12 months prior to screening History or evidence of any other unstable or clinically significant medical condition, that in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion Patient has any clinically significant vital sign, laboratory, or ECG abnormality during screening that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation The patient is at risk of self-harm or harm to others as evidenced by past suicidal behaviour or endorsing items four or five on the C-SSRS assessed at screening Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates) Pregnant or breastfeeding, or is a female expecting to conceive during the study, including through 16 weeks after the last dose of investigational product

	Female of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with investigational product through 16 weeks after the last dose of investigational product Currently receiving treatment in another investigational device or drug study, or less than 90 days prior to screening since ending treatment on another investigational device or drug study/ies Known sensitivity to any component of the investigational product Previously randomised into an erenumab study Member of investigational site staff or relative of the investigator Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (e.g. independent completion of electronic diary items) to the best of the patient's and investigator's knowledge

[a]No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally-accepted therapeutic dose(s) based on the investigator's assessment. Either a lack of sustained response to a medication or failure to tolerate a therapeutic dose do not constitute lack of therapeutic response. [b]Patients with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than one medication for each disorder. Patients must have been on a stable dose within the 3 months prior to the start of the baseline phase.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BDI-II: Beck Depression Inventory; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; HIV: human immunodeficiency virus; ICHD-III: The International Classification of Headache Disorders, 3rd edition; MI: myocardial infarction; NSAIDS: nonsteroidal anti-inflammatory drug; TIA: transient ischemic attack; ULN: upper limit of normal.

Source: ARISE Protocol

Table 4: Eligibility criteria for LIBERTY

Inclusion criteria	Exclusion criteria
During the screening epoch	**During the screening epoch and/or baseline epoch**

Adults aged 18–65 years, with written informed consent Documented history of migraine (with or without aura) for ≥12 months prior to screening according to ICHD-III 4–14 days per month (in at least two separate attacks) of migraine symptoms (based on ICHD-III criteria) on average across the three months prior to screening based on retrospective reporting <15 days per month of headache symptoms (i.e., migraine and non-migraine) Patients must have: Failed 2–4 prior migraine prophylaxis treatments out of the following[a]: ▪ Propranolol/metoprolol ▪ Topiramate ▪ Flunarizine ▪ Valproate/divalproex ▪ Amitriptyline ▪ Venlafaxine ▪ Lisinopril ▪ Candesartan ▪ Locally approved products (e.g. oxeterone or pizotifen) Failed one, and failed, or not be suitable for a second of the following[a]:	Older than 50 years of age at migraine onset Unable to differentiate migraine from other headaches History of cluster headache or hemiplegic migraine headache Failed more than four prior migraine prophylaxis treatments out of the following: Propranolol/metoprolol Topiramate Flunarizine Valproate/divalproex Amitriptyline Venlafaxine Lisinopril Candesartan Locally approved products (e.g., oxeterone or pizotifen) Use of a prophylactic migraine medication within five half-lives, or a device or procedure within one month prior to the start of the baseline phase or during the baseline phase Prior botulinum toxin treatment in the head/neck region (including cosmetic use or other licensed indications for Botox®) within four months prior to randomisation

▪ Propranolol or metoprolol ▪ Topiramate ▪ Flunarizine Failed or not be suitable for valproate or divalproex[a]	Use of the following for any indication in the one month prior to the start of the baseline phase or during the baseline phase: Ergotamines or triptanes ≥0 days/month Simple analgesics (NSAIDs, acetaminophen, paracetamol) ≥15 days/month Opioid- or butalbital-containing analgesics ≥4 days/month Anticipated to require any excluded medication, device or procedure (e.g. occipital nerve stimulators, transcranial magnetic stimulation, acupuncture) during the study Active chronic pain syndromes (e.g., fibromyalgia or chronic pelvic pain) History or current evidence of major psychiatric disorder (e.g. schizophrenia, bipolar disorder or type B personality disorder that might interfere with the ability to properly report clinical outcomes) Evidence of drug or alcohol abuse or dependence within 12 months prior to screening based on medical records or patient self-report Current evidence of depression based on a BDI-II total score of >19 at screening[b] History of seizure disorder or other significant neurological conditions other than migraine Score 'yes' on item four or item five of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past six months, or 'yes' on any item of the Suicidal Behaviour section, except for the 'Non-Suicidal Self-Injurious Behaviour', if this behaviour occurred in the past two years MI, stroke, TIA, unstable angina, or coronary artery bypass surgery or other revascularization procedures within 12 months prior to screening
During the baseline epoch	
Migraine frequency of 4–14 migraine days during the baseline epoch, confirmed by the eDiary ≥80% eDiary compliance during the baseline epoch	

	History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study History of malignancy of any organ system (other than localised basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past five years, regardless of whether there is evidence of local recurrence or metastases Hepatic disease by history or total bilirubin ≥2 x ULN or ALT or AST ≥3 x ULN as assessed by central laboratory at initial screening Pregnant or nursing (lactating) women Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 110 days after stopping of study medication. Use of other investigational drugs within five half-lives of enrolment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer History of hypersensitivity to the study drug or its excipients Any prior exposure to investigational products targeting the CGRP pathway, including previous erenumab studies Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (e.g. independent completion of electronic diary items) to the best of the patient's and investigator's knowledge

[a]Failure was divided into three key categories; 'efficacy failure', 'tolerability failure' and 'not suitable for the purpose of this study'. 'Efficacy failure' was defined as no meaningful reduction in headache frequency after administration of the respective medication for an adequate period of time (European Headache Federation treatment guidelines recommend at least 2–3 months) at generally accepted therapeutic doses based on the investigator's assessment

within the five years prior to screening. 'Tolerability failure' was defined as documented discontinuation due to adverse events of the respective medication at any previous time. Finally, 'not suitable for the purpose of this study' was defined as patient is not considered to be suitable for the treatment for medical reasons such as contraindications or precautions included in local labels, national guidelines or other locally binding documents, or other medically relevant reasons as confirmed by the treating physician. [b]Patients with anxiety disorder and/or major depressive disorder were permitted in the study if they were considered by the investigator to be stable and taking no more than one medication per disorder. Patients must have been on a stable dose within the 3 months prior to the start of the baseline phase.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BDI-II: Beck Depression Inventory; CGRP: calcitonin gene-related peptide; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; ICHD-III: The International Classification of Headache Disorders, 3rd edition; MI: myocardial infarction; NSAIDS: nonsteroidal anti-inflammatory drug; TIA: transient ischemic attack; ULN: upper limit of normal.

Source: LIBERTY Protocol

Table 5: Prior prophylactic treatment failures, by study arm, in patients for whom ≥3 prior treatments have failed in Study 295, STRIVE and ARISE

Treatment	Study 295			STRIVE			ARISE	
	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])	Erenumab 140 mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])	Erenumab 140 mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70 mg (n=[redacted])
Divalproex sodium, sodium valproate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blockers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tricyclic antidepressants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flunarizine or verapamil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SNRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril or candesartan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Prior prophylactic treatment failures, by study arm, in patients for whom ≥3 prior treatments have failed in LIBERTY

Treatment	**LIBERTY**	
	Placebo (n=[redacted])	**Erenumab 140 mg (n=[redacted])**
Amitriptyline	[redacted]	[redacted]
Candesartan	[redacted]	[redacted]
Flunarizine	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]
Metoprolol	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]
Valproate	[redacted]	[redacted]
Venlafaxine	[redacted]	[redacted]
Other	[redacted]	[redacted]