NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Erenumab for preventing migraine [ID1188]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Erenumab for preventing migraine [ID1188]

Contents:

The following documents are made available to consultees and commentators:

1. **Company new evidence submissions**- *from Novartis Pharmaceuticals (UK) Ltd*
    a. Company post appeal submission document
    b. Company post appeal response to the ERG clarification questions

2. **Stakeholder new evidence submissions**
    a. Migraine Trust
    b. Association of British Neurologists headache and pain advisory group
    c. British Association for the Study of Headache (BASH)
    d. Allergan

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

4. **ERG report – factual accuracy check** *prepared by Kleijnen Systematic Reviews Ltd*

5. **Letter from NICE to company regarding differential utilities**

6. **Additional information request** - company evidence submission regarding differential utilities *from Novartis Pharmaceuticals (UK) Ltd*

7. **ERG addendum on differential utilities** *prepared by Kleijnen Systematic Reviews Ltd*

8. **Response to additional information request in ERG addendum 27 October 2020** *from Novartis Pharmaceuticals (UK) Ltd*

9. **ERG additional addendum on differential utilities** prepared by Kleijnen Systematic reviews

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Erenumab for preventing migraine ID1188

Post-appeal company evidence submission

April 2020

File name	Version	Contains confidential information	Date
ID1188 Erenumab migraine post-appeal submission_Redacted	Final	Yes	April 2020

Contents

Tables and figures

Background to the submission

An appeal against the Final Appraisal Document (FAD) for appraisal ID1188 of erenumab for preventing migraine was submitted jointly by the British Association for the Study of Headache (BASH) and the Association of British Neurologists (ABN). This appeal was upheld on the grounds that "The Committee unreasonably failed to consider the cost-effectiveness of erenumab versus best supportive care in those who had failed to benefit from the comparator drug in patients with chronic migraine", where the "comparator drug" in this context refers to botulinum toxin.

Following the outcome of this appeal, NICE has invited Novartis to make a further evidence submission relating to the clinical and cost-effectiveness of erenumab for treating chronic migraine following the failure of treatment with botulinum toxin, or when botulinum toxin is unable to be tolerated or is contraindicated.

In response to this invitation, this post-appeal submission presents evidence in support of the use of erenumab in two subgroups that Novartis considers to be of relevance to the appeal panel's decision:

1. Patients with chronic migraine and four or more prior prophylactic treatment failures, and prior receipt of botulinum toxin (hereafter, 'CM ≥4 TF, inc. botulinum toxin') – *this represents a subgroup of patients for whom at least four prior prophylactic treatments have failed. All patients in this subgroup have a history of treatment with botulinum toxin, which was discontinued due to lack of efficacy, unacceptable tolerability and/or other reasons.*

2. Patients with chronic migraine and three or more prior prophylactic treatment failures, but no prior receipt of botulinum toxin (hereafter, 'CM ≥3 TF, no prior botulinum toxin') – *evidence from this subgroup is provided as a proxy for the clinical and cost-effectiveness of erenumab in a subgroup of patients with chronic migraine who are not eligible to receive botulinum toxin due to contraindication/unsuitability. It should be noted that data are not available specifically for patients treated with erenumab who are known to have a contraindication/unsuitability for botulinum toxin; the presented subgroup data in patients with chronic migraine who have three or more prior treatment failures and no prior receipt of botulinum toxin is considered to act as a proxy for this population.*

The evidence presented in this submission in support of these subgroups consists of:

- Clinical evidence:
    - Study 295 post-hoc subgroup analysis
    - Real-world evidence from the United Kingdom
- Economic evidence: updated cost-effectiveness analysis in the specific subgroups outlined above

Clinical effectiveness – new evidence

- Evidence for the clinical effectiveness of erenumab 140 mg in the 'CM ≥4 TF, inc. botulinum toxin' and 'CM ≥3 TF, no prior botulinum toxin' populations is provided by post-hoc subgroup analyses from Study 295.
- Baseline characteristics in these subgroups are largely consistent with the overall Study 295 population.
- These subgroup analyses demonstrate that erenumab 140 mg is effective in reducing monthly migraine days (MMDs) and increasing the proportion of patients classed as achieving a response versus placebo (a proxy for best supportive care) in these populations:
    - 'CM ≥4 TF, inc. botulinum toxin' subgroup (erenumab 140 mg n=[redacted]; placebo n=[redacted]):
        - Reduction in MMDs at Week 12 compared to placebo of [redacted] days [95% CI: [redacted]; p=[redacted]]
        - Odds ratio of achieving response of ≥30% reduction in MMDs at Week 12 versus placebo of [redacted] (95% CI: [redacted]; p=[redacted])
    - 'CM ≥3 TF, no prior botulinum toxin' subgroup (erenumab 140 mg n=[redacted]; placebo n=[redacted]):
        - Reduction in MMDs versus placebo at Week 12 of [redacted] days [95% CI: [redacted]; p=[redacted]]
        - Odds ratio of achieving response of ≥30% reduction in MMDs at Week 12 versus placebo of [redacted] (95% CI: [redacted]; p=[redacted])
    - Although these results are from post-hoc analyses of small sample size, the clinical effectiveness of erenumab 140 mg demonstrated in these subgroups is consistent with that already demonstrated in the ≥3 prior treatment failures chronic migraine subgroup and the Study 295 whole study chronic migraine population in previous submissions to NICE.
- Furthermore, a targeted literature review conducted for this submission identified a UK open-label, prospective clinical audit that provides real-world support for the effectiveness of erenumab in the 'CM ≥4 TF, inc. botulinum toxin' subgroup, albeit at a 70 mg dose (n=37). The average reduction in MMDs following the three-month trial was –6.1 days, whilst 51.4% of patients achieved a ≥30% reduction in MMDs.

Summary of new evidence sources

Study 295 post-hoc subgroup analysis

Clinical evidence for the 'CM ≥4 TF, inc. botulinum toxin' and 'CM ≥3 TF, no prior botulinum toxin' subgroups is presented from Study 295 of erenumab versus placebo in patients with chronic migraine. The STRIVE, ARISE and LIBERTY studies presented in the original submission are not included in this new evidence submission as they enrolled only episodic migraine patients.

It should be noted that Study 295 was not designed or powered to assess the efficacy of erenumab specifically in the 'CM ≥4 TF, inc. botulinum toxin' or 'CM ≥3 TF, no prior botulinum toxin' subgroups. The data presented for these subgroups are from post-hoc analyses.

The analytic methods used to generate these subgroup analyses are identical to the methods used for the previously submitted subgroup analyses (e.g. the subgroup analysis in patients for whom ≥3 prior prophylactic treatments have failed, reported in Section B.2.6.1 of the original Document B). The only exception to this is that whereas the treatment failure subgroup analyses in the original submission were based on number of prior failed prophylactic *treatment categories*, the subgroup analyses presented in this submission are based on number of prior failed prophylactic *individual treatments*. Throughout the appraisal process, the clinical data used to inform the economic model has been based on number of prior failed *individual treatments* (as described in Section B.3.3.3 of Novartis' original submission [Document B]), and a definition based on prior *individual treatments* is also better aligned with clinical practice. Therefore, presenting subgroup data based on prior *individual treatments* is considered most appropriate and informative for this submission to ensure consistency between clinical and economic analyses and clinical practice.

Clinical data are presented for the erenumab 140 mg and placebo groups from Study 295 only; data for patients treated with erenumab 70 mg are not outlined in this document. This reflects the Committee's conclusion from the erenumab FAD (paragraph 3.12) that "it was acceptable to consider only the 140 mg dose in the cost-effectiveness model".[1]

The clinical data presented from Study 295 for these subgroups consists of:

- Baseline characteristics
- Efficacy data, with the key outcomes selected for presentation being those that have been considered most important to assess the effectiveness of erenumab in the chronic migraine population throughout the appraisal process:
    - Mean change from baseline in monthly migraine days (MMDs) at Week 12
    - Proportion of patients with ≥30% reduction in MMDs from baseline at Week 12, considered a clinically meaningful response to treatment in chronic migraine (erenumab FAD, paragraph 3.3)[1]

These data are presented in the 'Study 295 post-hoc subgroup analysis - results' section of this submission.

Targeted literature review of real-world evidence

In addition to the evidence from Study 295, a targeted literature review (TLR) has been performed to identify UK real-world evidence for the clinical effectiveness of erenumab in the 'CM ≥4 TF, inc. botulinum toxin' subgroup. The TLR identified one real-world evidence study providing further evidence in this subgroup. The methods and results of this TLR are presented in the 'Real-world evidence for erenumab' section of the submission.

Study 295 post-hoc subgroup analysis - results

Baseline characteristics

Key baseline characteristics for the patients in the 'CM ≥4 TF, inc. botulinum toxin' and 'CM ≥3 TF, no prior botulinum toxin' post-hoc subgroups of Study 295 are presented in Table 1 and

Table 2, respectively. Overall, considering the small number of patients in these analyses, baseline characteristics remain relatively well balanced across treatment arms in these post-hoc subgroups. Baseline characteristics were also generally aligned to those of the full Study 295 trial population, presented in the original submission to NICE (Document B). As would be expected for subgroups with multiple prior treatment failures, compared to the full Study 295 population patients in these subgroups had, on average, longer disease duration, were more likely to have received prior topiramate, and had slightly higher monthly usage of acute migraine-specific drugs.

Table 1: Baseline characteristics of patients in post-hoc 'CM ≥4 TF, inc. prior botulinum toxin' subgroup

Characteristic	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])	*Overall Study 295 population (n=667)*
Mean age, years (SD)	[redacted]	[redacted]	*42.1 (11.3)*
Range	[redacted]	[redacted]	*18-66*
Sex, n (%)			
Women	[redacted]	[redacted]	*552 (82.8)*
Men	[redacted]	[redacted]	*115 (17.2)*
BMI, kg/m^2 (SD)	[redacted]	[redacted]	*26.15 (5.2)*
Race, n (%)			
White	[redacted]	[redacted]	*628 (94.2)*
Black or African American	[redacted]	[redacted]	*27 (4.0)*
Asian	[redacted]	[redacted]	*8 (1.2)*
Other	[redacted]	[redacted]	*4 (0.6)*
Age at migraine onset, years (SD)	[redacted]	[redacted]	*20.91 (10.3)*
Disease duration, years (SD)	[redacted]	[redacted]	*21.70 (12.5)*
History of migraine with aura, n (%)	[redacted]	[redacted]	*276 (41.4)*
Ever used preventative drug topiramate, n (%)	[redacted]	[redacted]	*336 (50.4)*
Ever used botulinum toxin, n (%)	[redacted]	[redacted]	*158 (23.7)*
Baseline period, mean (SD)			
Monthly migraine days	[redacted]	[redacted]	*17.99 (4.6)*
Monthly headache days	[redacted]	[redacted]	*20.83 (3.9)*
Monthly migraine attacks	[redacted]	[redacted]	*4.33 (1.7)*
Monthly acute migraine-specific drug use days	[redacted]	[redacted]	*9.32 (7.3)*

Footnotes: BMI is calculated based on raw data measurements.
Abbreviations: BMI: body mass index; kg: kilogram; m^2: metres squared; SD: standard deviation.
Source: Novartis data on file.[2]

Table 2: Baseline characteristics of patients in post-hoc 'CM ≥3 TF, no prior botulinum toxin' subgroup

Characteristic	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])	*Overall Study 295 population (n=667)*
Mean age, years (SD)	[redacted]	[redacted]	*42.1 (11.3)*
Range	[redacted]	[redacted]	*18-66*
Sex, n (%)			
Women	[redacted]	[redacted]	*552 (82.8)*
Men	[redacted]	[redacted]	*115 (17.2)*
BMI, kg/m^2 (SD)	[redacted]	[redacted]	*26.15 (5.2)*
Race, n (%)			
White	[redacted]	[redacted]	*628 (94.2)*
Black or African American	[redacted]	[redacted]	*27 (4.0)*
Asian	[redacted]	[redacted]	*8 (1.2)*
Other	[redacted]	[redacted]	*4 (0.6)*
Age at migraine onset, years (SD)	[redacted]	[redacted]	*20.91 (10.3)*
Disease duration, years (SD)	[redacted]	[redacted]	*21.70 (12.5)*
History of migraine with aura, n (%)	[redacted]	[redacted]	*276 (41.4)*
Ever used preventative drug topiramate, n (%)	[redacted]	[redacted]	*336 (50.4)*
Ever used botulinum toxin, n (%)	[redacted]	[redacted]	*158 (23.7)*
Baseline period, mean (SD)			
Monthly migraine days	[redacted]	[redacted]	*17.99 (4.6)*
Monthly headache days	[redacted]	[redacted]	*20.83 (3.9)*
Monthly migraine attacks	[redacted]	[redacted]	*4.33 (1.7)*
Monthly acute migraine-specific drug use days	[redacted]	[redacted]	*9.32 (7.3)*

Footnotes: BMI is calculated based on raw data measurements.
Abbreviations: BMI: body mass index; kg: kilogram; m^2: metres squared; SD: standard deviation.
Source: Novartis data on file.[2]

Efficacy results

Efficacy results at Week 12 for the 'CM ≥4 TF, inc. botulinum toxin' and 'CM ≥3 TF, no prior botulinum toxin' post-hoc subgroups of Study 295 are provided in Table 3 and Table 4, respectively.

In both subgroups, erenumab 140 mg provided numerically greater reductions in MMDs from baseline to Week 12 compared to placebo, corresponding to differences versus placebo of [redacted] days [95% CI: [redacted]; p=[redacted]] in the 'CM ≥4 TF, inc. botulinum toxin' subgroup and a statistically significant [redacted] days [95% CI: [redacted]; p=[redacted]] in the 'CM ≥3 TF, no prior botulinum toxin' subgroup. Additionally, in both subgroups a statistically significantly higher

proportion of patients treated with erenumab 140 mg achieved a ≥30% reduction in MMDs at Week 12 from baseline compared to placebo. This corresponded to an odds ratio of response versus placebo of [redacted] (95% CI: [redacted]; p=[redacted]) and [redacted] (95% CI: [redacted]; p=[redacted]) in the CM ≥4 TF and CM ≥3 TF subgroups, respectively.

Table 3: Overview of key efficacy results from Study 295 post-hoc 'CM ≥4 TF, inc. prior botulinum toxin' subgroup

Outcome	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Change from baseline in MMDs at Week 12[a]		
LSM (SE)	[redacted]	[redacted]
Difference (95% CI)	-	[redacted]
p-value	-	[redacted]
Proportion of patients with ≥30% reduction in MMDs from baseline at Week 12[b]		
Responders, n (%)	[redacted]	[redacted]
Difference versus placebo, %	-	[redacted]
Odds ratio (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 medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. [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.
Abbreviations: CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; SE: standard error.
Source: Novartis data on file.[2]

Table 4: Overview of key efficacy results from Study 295 post-hoc 'CM ≥3 TF, no prior botulinum toxin' subgroup

Outcome	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Change from baseline in MMDs at Week 12[a]		
LSM (SE)	[redacted]	[redacted]
Difference (95% CI)	-	[redacted]
p-value	-	[redacted]
Proportion of patients with ≥30% reduction in MMDs from baseline at Week 12[b]		
Responders, n (%)	[redacted]	[redacted]
Difference versus placebo, %	-	[redacted]
Odds ratio (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 medication overuse, and baseline value as covariates and assumed a first-order autoregressive covariance structure. [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.
Abbreviations: CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; SE: standard error.
Source: Novartis data on file.[2]

Real-world evidence for erenumab

A TLR has been performed to identify real-world evidence from the UK for the clinical effectiveness of erenumab in the 'CM ≥4 TF, inc. botulinum toxin' subgroup. Full details of the methodology of this TLR, including search terms and details of databases and congresses searched, are presented in Appendix A. The eligibility criteria for the TLR are presented in Table 5.

Table 5: Eligibility criteria for the TLR

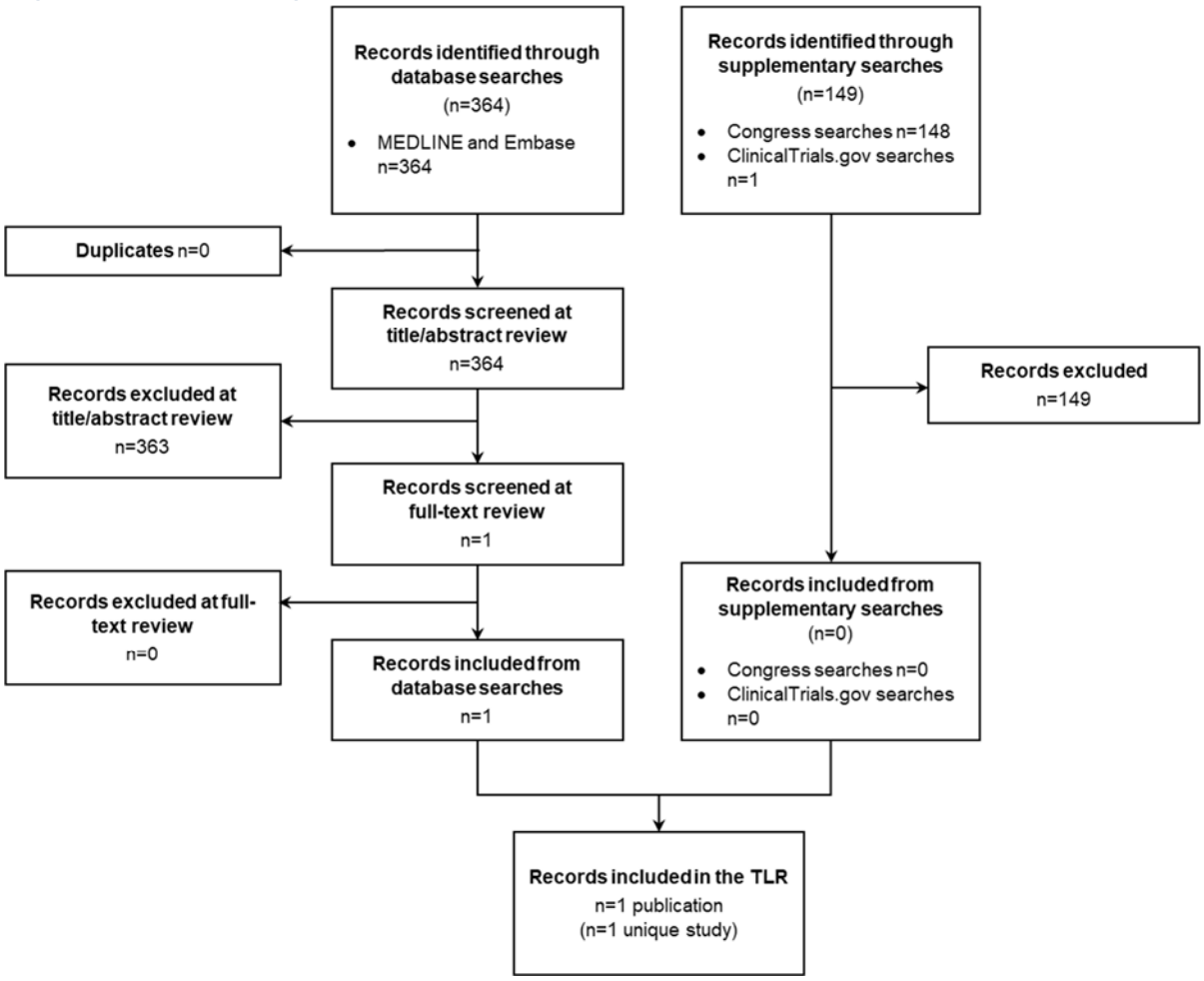
Category	Inclusion Criteria
Population	• Adult patients who have chronic migraine with 4 or more prior preventive/prophylactic treatment failures, one of which is botulinum toxin
Intervention	• Erenumab
Comparators	• Any or none
Outcomes	• Any effectiveness outcomes
Study design	• Real-world evidence such as prospective or retrospective observational studies, database/registry studies or cross-sectional studies
Other considerations	• Records with abstract or full text in English • Journal articles from any date, conference abstracts published since 2018, and ClinicalTrials.gov records from any date • Studies conducted in the United Kingdom

As presented in Figure 1, a total of 364 records were retrieved by the electronic database searches. After de-duplication of results, 364 unique records were suitable for review (i.e. no duplicates identified). After title and abstract review, one record was selected to be reviewed at the full-text stage and this record was found to fulfil the eligibility criteria for inclusion in the TLR.

Supplementary searches of conferences and clinical trial registries yielded 149 records. Of these, one record was identified as relevant, but was subsequently excluded as a duplicate of the record that was included from the database searches. Overall, no unique records fulfilled the eligibility criteria for inclusion in the TLR.

Therefore, in total the TLR identified one real-world evidence study (Lambru *et al.* 2019) providing further evidence in the 'CM ≥4 TF, inc. botulinum toxin' subgroup.[3] The evidence from this study is summarised below.

Figure 1: PRISMA diagram of included and excluded studies for the TLR



Lambru *et al.* 2019[3]

The real-world study identified by the TLR was a report of a UK open-label, prospective clinical audit of erenumab for the treatment of refractory chronic migraine, reported at the International Headache Society 2019 congress (abstract IHC-PO-390). This study evaluated 75 chronic migraine patients for whom at least three prior preventative treatments and botulinum toxin A had failed, and who received at least one erenumab 70 mg treatment. Efficacy was assessed via a number of outcomes, including change in migraine days and proportion of patients obtaining at least a 30% reduction in migraine days. This study therefore provides UK real-world evidence of the effectiveness of erenumab (albeit at a 70 mg dose) in the 'CM ≥4 TF, inc. botulinum toxin' subgroup, to support the clinical trial data for this subgroup from Study 295 reported above.

Thirty-seven patients completed the three-month trial period. At baseline, the patients captured in this study had an average of 20.3 migraine days per month, which is similar to the baseline migraine day frequency of the 'CM ≥4 TF, inc. botulinum toxin' subgroup in Study 295. The average reduction in monthly migraine days following the three-month trial was –6.1 days, whilst 51.4% of patients achieved a ≥30% reduction in migraine days, supporting the real-world effectiveness of erenumab on key outcomes for this population (as stated in Table 3, the equivalent results for erenumab 140 mg from the 'CM ≥4 TF, inc. botulinum toxin' subgroup in Study 295 were [redacted] days and [redacted] respectively).

Cost-effectiveness – new evidence

- Cost-effectiveness analysis was performed for the 'CM ≥4 TF, inc. botulinum toxin' and 'CM ≥3 TF, no prior botulinum toxin' subgroups, adopting all of the Committee's preferred assumptions up to the publication of the FAD.
- These analyses demonstrate that erenumab is a cost-effective use of resources in both subgroups:
    - Incremental cost-effectiveness ratio (ICER) of [redacted] per QALY gained versus best supportive care (BSC) in the 'CM ≥4 TF, inc. botulinum toxin' subgroup
    - ICER of [redacted] per QALY gained versus BSC in the 'CM ≥3 TF, no prior botulinum toxin' subgroup
- A scenario analysis adopting the preferred assumption of the Committee in the fremanezumab appraisal regarding distribution of MMDs upon treatment discontinuation also found erenumab 140 mg to be a cost-effective treatment option versus BSC with ICERs in the above populations of [redacted] and [redacted] per QALY gained, respectively.

Summary of methods

The economic model used to conduct cost-effectiveness analyses for this post-appeal submission is identical to the latest model submitted to NICE prior to the third Appraisal Committee meeting in August 2019. This model reflects all of the Committee's preferred assumptions up to the publication of the FAD; the only update being the incorporation of clinical effectiveness subgroup data from Study 295 for chronic migraine patients by prior or no prior use of botulinum toxin and for chronic migraine patients with ≥4 prior prophylactic treatment failures.

A summary of the model settings is provided in Table 6 below.

[redacted]

6 [redacted]

Table 6: Model settings for analyses provided in this submission

Model feature	Approach for analyses presented in this post-appeal submission	Comparison to most recent analyses submitted prior to third Appraisal Committee meeting
Population	Adult patients with chronic migraine and: A. Four or more prior prophylactic treatment failures, including prior receipt of botulinum toxin B. Three or more prior prophylactic treatment	Previously the population considered was adult patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed. This submission therefore presents a potential revised positioning of erenumab in the treatment pathway, in line with the appeal panel's decision.

	failures, but no prior receipt of botulinum toxin	
Comparator	Best supportive care (BSC)	Previously analyses were provided versus botulinum toxin and BSC, but botulinum toxin is no longer a relevant comparator in the population of interest following the appeal panel's decision (as erenumab is now being positioned for use after botulinum toxin). As there is only a single relevant comparator, the results presented are pairwise analyses of erenumab 140 mg vs BSC.
Erenumab dose	140 mg	Consistent with most recent analyses
Patient access scheme	Simple discount giving a PAS price for erenumab 140 mg of [redacted]	The simple discount is consistent with most recent analyses. [redacted]
Time horizon	Lifetime	Consistent with most recent analyses
Response assessment definition	30% reduction in MMDs	Consistent with most recent analyses
Treatment effect waning assumption	No waning; 2.38% all-cause discontinuation per 12 week cycle	Various analyses incorporating no waning or a range of waning assumptions have been considered previously by the Committee.

		However, modelling of no treatment effect waning and negative discontinuation as a 2.38% all-cause discontinuation rate per 12 week cycle is consistent with the Novartis base case in the most recent submission, and with the conclusion of the NICE Committee in the erenumab FAD (paragraph 3.14) that it was "reasonable to assume that the treatment effect does not wane over time".[1]
Positive discontinuation	Not included	Scenario analyses incorporating positive discontinuation were provided as part of the most recent submission. However, exclusion of positive discontinuation is consistent with the base case of the most recent submission and with the Committee's stated preference in the erenumab FAD (paragraph 3.17).[1]
Assumption regarding MMDs after stopping treatment	**Base case:** Patients who discontinue treatment for any reason maintain the non-responder MMD improvement achieved at week 12. **Scenario analysis:** Patients who discontinue treatment for any reason rebound to baseline MMDs.	**Base case:** Consistent with most recent submission and ERG and NICE Committee preference in this appraisal to date. **Scenario analysis:** The original submission contained the assumption that patients rebound to baseline MMDs after discontinuation due to adverse events or long-term discontinuation. Based on feedback from the ERG, this was subsequently changed to the base case as described above. However, Novartis noted that rebound to baseline MMDs was the preferred assumption of the ERG and Committee in the recent appraisal of fremanezumab for preventing migraine (ID1368), for all causes of discontinuation.[a,4] A scenario analysis employing this assumption for post-discontinuation MMDs is therefore provided as part of this post-appeal submission.

[a]It was noted that in the NICE appraisal of fremanezumab, the ERG preferred scenario also included the assumption that the treatment effect for people whose migraine responded to best supportive care diminished to baseline over 1 year.[4] However, it is not clear from the fremanezumab FAD whether the Committee also adopted this additional assumption (which is distinct from the assumption that patients would rebound to baseline MMDs following discontinuation). As such, a diminishing of response to best supportive care over 1 year has not been incorporated in the base case or scenario analysis presented in this submission.

Cost-effectiveness results

Base-case incremental cost-effectiveness analysis results

Cost-effectiveness analysis was performed for each of the two subgroups of relevance to this submission.

For the 'CM ≥4 TF, inc. botulinum toxin' subgroup, the base case deterministic ICER was [redacted] per QALY gained (Table 7).

Table 7: Base case deterministic results for the 'CM ≥4 TF, inc. botulinum toxin' subgroup

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For the 'CM ≥3 TF, no prior botulinum toxin' subgroup, the base case deterministic ICER was [redacted] per QALY gained (Table 8).

Table 8: Base case deterministic results for the 'CM ≥3 TF, no prior botulinum toxin' subgroup

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario analysis

As noted in Table 6, a scenario analysis was conducted to explore the impact of aligning the assumption regarding MMDs on stopping treatment with that preferred by the ERG and NICE Committee in the recent appraisal of fremanezumab for preventing migraine (ID1368).[4]

In this scenario analysis, patients who discontinue treatment are assumed to rebound to baseline MMDs, rather than maintain the non-responder MMD improvement achieved at week 12 as in the base case analysis.

The results of this scenario analysis for the 'CM ≥4 TF, inc. botulinum toxin' and 'CM ≥3 TF, no prior botulinum toxin' subgroups are presented in Table 9 and Table 10, respectively.

Table 9: Scenario analysis results for the 'CM ≥4 TF, inc. botulinum toxin' subgroup

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			

Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10: Scenario analysis results for the 'CM ≥3 TF, no prior botulinum toxin' subgroup

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Interpretation and discussion

This post-appeal submission presents clinical and cost-effectiveness evidence for erenumab 140 mg in two populations: 1. patients with chronic migraine and four or more prior prophylactic treatment failures, and prior receipt of botulinum toxin; and 2. patients with chronic migraine and three or more prior prophylactic treatment failures, but no prior receipt of botulinum toxin (a proxy for patients with three or more prior prophylactic treatment failures who are contraindicated/ unsuitable for botulinum toxin treatment). These two subgroups for whom botulinum toxin treatment has failed or is not an option face a particularly high unmet need in UK clinical practice.

Novartis acknowledges the limitations arising from the post-hoc nature and small sample sizes of the subgroup analyses from Study 295 provided in this submission. However, further reassurance regarding the clinical effectiveness of erenumab in the 'CM ≥4 TF, inc. botulinum toxin' subgroup is provided by the UK real-world clinical evidence presented in this submission, as well as the wider context that erenumab has demonstrated consistent efficacy in chronic migraine patient populations throughout the appraisal process, including the Study 295 chronic migraine population as a whole as well as other treatment failure-related subgroups previously presented to NICE.

In the base case cost-effectiveness analyses provided for the subgroups of interest, Novartis has adopted all of the preferred assumptions adopted by the Committee during the appraisal process. The analyses show erenumab 140 mg to be a cost-effective use of NHS resources, with an ICER well below a threshold of £20,000 per QALY gained for the 'CM ≥4 TF, inc. botulinum toxin' subgroup, and within the £20,000−£30,000 per QALY gained range considered by NICE for the 'CM ≥3 TF, no prior botulinum toxin' subgroup.

In addition, it was noted in the recent fremanezumab appraisal that the ERG and NICE Committee adopted an assumption regarding the MMDs of patients who discontinue treatment (MMDs rebound to baseline) that differs from the base case approach adopted for this appraisal (discontinuers maintain non-responder MMD improvement). In order to explore the potential impact of this alternative assumption, a scenario analysis was conducted to align the approach to that preferred by the Committee for the fremanezumab appraisal. This scenario analysis found erenumab to be a cost-effective treatment in both subgroups, with ICERs below £20,000 per QALY gained in both populations.

Although the conclusion of cost-effectiveness for erenumab is consistent across analyses, the ICERs vary between the base case and scenario analyses. In the base case, the MMD distributions of patients discontinuing treatment differ between the erenumab and BSC arms of the model, as per the clinical trial data. In contrast, in the scenario analysis the MMD distribution of discontinuing patients is the same (i.e. the baseline level) across erenumab and BSC arms of the model. Therefore, the more substantially the non-responder MMD distributions for erenumab and BSC differ, the more the results of the base case analysis and the scenario analysis will differ. The analyses presented in this post-appeal submission are based on subgroup data of relatively small sample size, and it is differences in non-responder MMDs between erenumab and BSC in these small sample size subgroups that explain the differences in the ICERs between the base case and scenario analyses.

However, ultimately erenumab 140 mg is found to be a cost-effective treatment option whether the base case or scenario analysis assumption regarding MMD distribution upon treatment discontinuation is adopted.

Conclusion

The clinical and cost-effectiveness evidence presented in this submission supports a decision to make erenumab available to a restricted patient subgroup who currently face a considerable unmet need for a condition that is debilitating at both an individual and societal level.

References

1. National Institute for Health and Care Excellence. Erenumab for preventing migraine [ID1188] - Final Appraisal Document. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10302/documents [Last accessed 27/03/2020].
2. Novartis Data on File.
3. Lambru G, Hill B, Murphy M, et al. IHC 2019 Abstracts. IHC-PO-390. Erenumab for the treatment of refractory chronic migraine: a UK prospective real world experience. Cephalalgia 2019;39:1-337.
4. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [ID1368] - Final Appraisal Document. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10339/documents [Last accessed 27/03/2020].

Appendix A

A TLR was conducted to identify published real-world evidence from the UK on the effectiveness of erenumab in patients with chronic migraine and four or more prior treatment failures, one of which was botulinum toxin. The search included peer-reviewed journal articles and data from ClinicalTrials.gov and relevant conference proceedings as summarised in Table 11.

The database searches were undertaken on 25th March 2020 and databases were searched from inception. The conference proceedings of major migraine and neurology congresses from the last two years (i.e. January 2018 onwards) and ClinicalTrials.gov were manually hand-searched on 27th March 2020. The exclusion of abstracts from conferences prior to 2018 was justified, as the marketing authorisation for erenumab in the European Union was only granted in July 2018 and under the additional assumption that high-quality research would since have been published in a peer-reviewed journal.

Table 11: Information sources searched in the TLR

Electronic databases/Resources	Interface/URL
MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE EPub Ahead of Print (1946 to 2020 March 24)	Ovid SP
Embase (1974 to 2020 March 24)	
ClinicalTrials.gov	https://clinicaltrials.gov/
European Headache Federation (EHF)	https://ehf-org.org/
International Headache Society (IHS)	http://www.ihs-headache.org/congress-and-calendar/2019
Association of British Neurologists (ABN)	https://jnnp.bmj.com/content/89/10#Electronicpages
European Academy of Neurology (EAN)	https://www.ean.org/
European Association of Neurosurgical Societies (EANS)	https://www.eans.org/
World Congress of Neurology (WCN)	http://2019.wcn-neurology.com/
American Academy of Neurology (AAN)	https://www.aan.com/conferences-community/annual-meeting/
American Headache Society (AHS)	https://americanheadachesociety.org/events/61st-annual-scientific-meeting/
Migraine Trust International Symposium (MTIS)	https://www.migrainetrust.org/

Details of the search terms used in the MEDLINE and Embase databases are provided in Table 12. Table 13 presents the search strategy for the manual conference searches and Table 14 provides search terms used in ClinicalTrials.gov.

Table 12: Search terms for MEDLINE and Embase (searched via the Ovid SP platform)

Interface: Ovid SP Date searched: 25th March 2020 Records retrieved: 364		
#	**Search terms**	**Results**
1	(erenumab$ or aimovig$ or amg-334 or amg334).ti,ab,kw,kf.	501
2	remove duplicates from 1	364

Table 13: Search strategy for the conference proceedings

Conference	Year	Source	Search strategy	Results
European Headache Federation (EHF)	2019	Abstract book	Searched the abstract book using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	3 identified; 0 included
International Headache Society (IHS)	2019	Abstract book	Searched the abstract book using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	41 identified; 1 relevant but excluded as duplicate
Association of British Neurologists (ABN)	2018[a]	https://jnnp.bmj.com/content/90/3#Electronicpages	Searched the title list using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	0 identified; 0 included
	2018	https://jnnp.bmj.com/content/89/10#Electronicpages		0 identified; 0 included
	2019	Abstracts unavailable		Abstracts unavailable
European Academy of Neurology (EAN)	2018	Abstract book	Searched the abstract book using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	7 identified; 0 included
	2019	Abstract book		7 identified; 0 included
European Association of Neurosurgical Societies (EANS)	2018	Abstract book (titles only)	Searched the abstract book using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	0 identified; 0 included
	2019	Abstract book (titles only)		0 identified; 0 included
World Congress of Neurology (WCN)	2019	Abstract book	Searched the abstract book using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	4 identified; 0 included
American Academy of Neurology (AAN)	2018	Abstract book (titles only)	Searched the abstract book using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	10 identified; 0 included
	2019	Abstract book (titles only)		8 identified; 0 included
	2020[b]	https://index.mirasmart.com/AAN2020/index.php	Using the 'advanced search' function, searched each term individually in the titles or abstracts of records: erenumab, aimovig, amg-334, amg 334, amg334	21 identified; 0 included

Conference	Year	Source	Search strategy	Results
American Headache Society (AHS)	2018	Abstract book	Searched the abstract book using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	8 identified; 0 included
	2019	Abstract book		30 identified; 0 included
Migraine Trust International Symposium (MTIS)	2018	Abstract book	Searched the abstract book using Ctrl+f for the following terms: erenumab, aimovig, amg-334, amg 334, amg334	9 identified; 0 included

[a]Joint meeting with the Society of British Neurological Surgeons (SBNS).
[b]The most recent conference proceedings were also identified online and included in the search.

Table 14: Search strategy for ClinicalTrials.gov

Condition	Other terms	Study type	Study results	Recruitment status	Results
Any	erenumab	“Observational studies”	"All Studies"	All	1 identified; 0 included
Any	aimovig	“Observational studies”	"All Studies"	All	1 identified (duplicated with above); 0 included
Any	amg-334	“Observational studies”	"All Studies"	All	0 identified; 0 included
Any	amg 334	“Observational studies”	"All Studies"	All	0 identified; 0 included
Any	amg334	“Observational studies”	"All Studies"	All	0 identified; 0 included

Records were reviewed in three stages (titles, abstracts, full-text articles) by a single reviewer, with a second senior reviewer checking all included records and 10% of excluded records at each stage. Studies were selected for inclusion if they met all pre-specified eligibility criteria presented in Table 5. Data extraction and quality assessments of included studies were not performed.

Novartis Pharmaceuticals UK Limited
2nd Floor, The WestWorks Building
White City Place, 195 Wood Lane
London W12 7FQ
United Kingdom

11 May 2020

Single technology appraisal

Erenumab for preventing migraine [ID1188]

Dear Jasdeep,

Thank you for the opportunity to respond to the clarification letter from the Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE, regarding the Novartis post-appeal evidence submission for erenumab for preventing migraine [ID1188].

Responses to the clarification questions are provided below. As requested, two versions of the company response have been uploaded to NICE Docs, one with academic-in-confidence information underlined and clearly marked in yellow and one with this information redacted.

A new confidentiality checklist, covering the additional post-hoc analyses presented in this response, has also been uploaded to NICE Docs, along with the additional references.

Please let us know should you have any questions regarding our response.

Kind regards,
Katharina Pannagl

Novartis Pharmaceuticals UK Limited
Health Economics and Outcomes Research Manager

Section A: Clarification on effectiveness data

Definition of prior prophylactic treatment failure in the subgroup of interest

A1. The clinical effectiveness section of the original company submission (CS) defined the subgroup of interest as *'the subgroup of patients for whom ≥3 prior prophylactic treatment categories had failed'*.

The post appeal submission states that: *'the treatment failure subgroup analyses in the original submission were based on number of prior failed prophylactic treatment categories, the subgroup analyses presented in this submission are based on number of prior failed prophylactic individual treatments'.*

a. Please confirm that the definition of the treatment failure subgroup, used in the clinical effectiveness section of the submission, has changed and provide the reason for this change.

The manner of counting treatment failures employed throughout the post-appeal evidence submission (individual treatment failures) differs from the manner of counting treatment failures employed in the subgroup analyses presented in the clinical effectiveness section of the original submission (treatment category failures). However, it is consistent with the manner of counting treatment failures employed in the cost-effectiveness section of the original submission, as shown in Table 1.

Table 1: Treatment failure definitions in the original and post-appeal submissions

	Clinical effectiveness section	Cost-effectiveness section
Original submission	Failure of prior prophylactic treatment *categories*	Failure of prior prophylactic *individual* treatments
Post-appeal submission	Failure of prior prophylactic *individual* treatments	Failure of prior prophylactic *individual* treatments

The difference in definitions used in the clinical and cost-effectiveness sections of the original submission was highlighted in Section B.3.3.3 and in Appendix T of the original submission and further explained in the response to the ERG addendum clarification questions in December 2018. At the time of the original submission, efficacy data using the individual treatment failure definition were not available for all scope outcomes. Therefore, analyses using the treatment category failure definition, which were available for all efficacy outcomes at time of submission, were presented instead in the clinical section.

Our original submission acknowledged that in UK clinical practice and the NICE guidance for botulinum toxin, the number of treatment failures refers to individual treatments. The individual treatment failure definition also most accurately reflects the decision problem. However, as outlined previously, patient numbers differed only slightly between definitions. This supports the notion that if a treatment of one pharmacological class fails, patients tend to switch to a treatment of a different pharmacological class.

For the post-appeal evidence submission, analyses employing the individual treatment failure definition were available for the relevant subgroups for all outcomes of interest. This definition was therefore used throughout the post-appeal submission, as it is better aligned with how treatment failures are counted in clinical practice and in order to achieve consistency between the clinical and cost effectiveness parts of the submission.

All supplementary post-hoc analyses presented in this response document are also based on the individual treatment failure definition.

b. For clarity, please provide details of the specific prior prophylactic treatments failed, for each patient included in the subgroup analyses presented in the post appeal submission.

Prior prophylactic treatments failed for patients included in the 'CM ≥4 TF, inc. prior botulinum toxin' and 'CM ≥3 TF, no prior botulinum toxin' subgroups from study 295, as presented in the post-appeal evidence submission, are shown in Table 2 and Table 3, respectively. The most commonly failed treatments (in addition to botulinum toxin in the 'CM ≥4 TF, inc. prior botulinum toxin' subgroup) were topiramate, beta blockers, and tricyclic antidepressants.

Table 2: Prior prophylactic treatments failed for patients in post-hoc 'CM ≥4 TF, inc. prior botulinum toxin' subgroup

	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Patients who failed prior prophylactic treatment - n (%)		
Beta blockers	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]
Divalproex sodium, sodium valproate	[redacted]	[redacted]
Flunarizine or verapamil	[redacted]	[redacted]
Lisinopril or candesartan	[redacted]	[redacted]
Serotonin-norepinephrine reuptake inhibitors	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]
Tricyclic antidepressants	[redacted]	[redacted]
Other	[redacted]	[redacted]

Footnotes: Categories are not mutually exclusive and subjects may contribute to more than one category.
Abbreviations: CM: chronic migraine; TF: treatment failure.
Source: Novartis data on file.[1]

Table 3: Prior prophylactic treatments failed for patients in post-hoc 'CM ≥3 TF, no prior botulinum toxin' subgroup

	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Patients who failed prior prophylactic treatment - n (%)		
Beta blockers	[redacted]	[redacted]
Divalproex sodium, sodium valproate	[redacted]	[redacted]
Flunarizine or verapamil	[redacted]	[redacted]
Lisinopril or candesartan	[redacted]	[redacted]
Serotonin-norepinephrine reuptake inhibitors	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]
Tricyclic antidepressants	[redacted]	[redacted]
Other	[redacted]	[redacted]

Footnotes: Categories are not mutually exclusive and subjects may contribute to more than one category.
Abbreviations: CM: chronic migraine; TF: treatment failure.
Source: Novartis data on file.[1]

Definition of botulinum toxin treatment failure in the subgroup of interest

A2. The post appeal submission states that: '*All patients in this subgroup have a history of treatment with botulinum toxin, which was discontinued due to lack of efficacy, unacceptable tolerability and/or other reasons.'*

Please provide detail of the reasons for discontinuation included in the category 'other'. Please also provide the number of patients, included in the subgroup analysis, who had discontinued botulinum toxin for each of the reasons, lack of efficacy, unacceptable tolerability and 'other reasons'.

In study 295, a patient was considered to have experienced a treatment failure if the study site checked "lack of efficacy" or "adverse reaction" as the reason for ending prior prophylactic medication.

In the 'CM ≥4 TF, inc. prior botulinum toxin' subgroup, the large majority of patients had discontinued prior treatment with botulinum toxin due to treatment failure ([redacted] out of [redacted] patients ([redacted]%) in the erenumab 140 mg group; [redacted] out of [redacted] patients ([redacted]%) in the placebo group), mostly due to lack of efficacy ([redacted]% of patients in the erenumab 140 mg group; [redacted]% of patients in the placebo group). Few patients had a treatment failure due to an adverse reaction to botulinum toxin. Further details are presented in

Table 4. Of note, patients could state more than one reason for discontinuation of each prior prophylactic treatment.

The most common reason for discontinuation due to reasons other than treatment failure was that prophylactic medication was no longer clinically necessary. Within the “Other” category, the most frequently mentioned reasons related to affordability issues.[1]

Table 4: Prior botulinum toxin discontinuation reasons in post-hoc 'CM ≥4 TF, inc. prior botulinum toxin' subgroup

	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Botulinum toxin discontinuation reason - n (%)		
Treatment failure	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Adverse reaction	[redacted]	[redacted]
Discontinue due to reason other than treatment failure	[redacted]	[redacted]
Prophylactic medication no longer clinically necessary	[redacted]	[redacted]
Other	[redacted]	[redacted]

Footnotes: Categories are not mutually exclusive and subjects may contribute to more than one category.
Abbreviations: CM: chronic migraine; TF: treatment failure.
Source: Novartis data on file.[1]

Number of patients included in the subgroup of interest

A3. Table 32 (Section B.2.6.1 of the original CS), gives the number of patients, in study 295 (patients with chronic migraine), for whom ≥3 prior prophylactic treatment categories had failed as n=[redacted] in the placebo group and n=[redacted] in the erenumab 140mg group, with n=[redacted] the placebo group and n=[redacted] in the erenumab 140mg group having previously received treatment with botulinum toxin.

The number of patients in the post appeal subgroup analysis of study 295 (patients with chronic migraine and four or more prior prophylactic treatment failures, including prior receipt of botulinum toxin) is lower, n=[redacted] in the placebo group and n=[redacted] in the erenumab 140mg group.

This might appear counterintuitive, as patients who have failed ≥3 prior prophylactic treatment categories must, by definition, also have failed ≥3 prior individual prophylactic treatments.

Please provide an explanation for this apparent discrepancy, e.g. were there some patients, included in study 295, who had received treatment with botulinum toxin before than the 4th line? If so, please provide the number of patients for whom botulinum toxin had failed by line of therapy.

Study 295 also included patients who had received botulinum toxin in an earlier than the 4th treatment line, as shown below in

Table 5. Among the patients who had used botulinum toxin prior to the study, [redacted] had a total of ≥4 prophylactic treatment failures before inclusion in the trial.

Table 5: Number of prophylactic treatment failures among patients with botulinum toxin use prior to study inclusion

	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Patients with number of prior prophylactic treatment failures - n (%)		
0 treatment failures	[redacted]	[redacted]
1 treatment failure	[redacted]	[redacted]
2 treatment failures	[redacted]	[redacted]
3 treatment failures	[redacted]	[redacted]
≥4 treatment failures	[redacted]	[redacted]

Footnotes: The sum of the bottom two rows reflects patients with ≥3 prior prophylactic treatment failures and prior botulinum toxin use included in the original submission (placebo n=[redacted]; erenumab 140 mg n=[redacted]). In this subgroup, the individual treatment failure definition results in the same patient numbers in the placebo and erenumab 140 mg arms as the treatment category failure definition.
Source: Novartis data on file.[1]

As a multinational trial, study 295 was conducted at 69 centres in Canada, Czech Republic, Denmark, Germany, Finland, Norway, Poland, Sweden, United Kingdom, and the United States of America. The fact that some patients included in the trial had received botulinum toxin before having failed at least 3 oral prophylactic treatments may be a reflection of differing clinical practice and local reimbursement criteria in the participating countries.

A separate analysis explored the treatment line in which patients in the 'CM ≥4 TF, inc. prior botulinum toxin' subgroup had received botulinum toxin. However, data collected upon trial inclusion was not detailed enough to determine the order of prior treatments for [redacted]% of patients in the erenumab 140 mg arm and [redacted]% of patients in the placebo arm; for example, because a patient had discontinued botulinum toxin and another treatment within the same calendar year and the month or date of discontinuation were not recorded.

Among the patients with sufficient data available to conduct this analysis, [redacted]% of patients in the erenumab 140 mg arm and [redacted]% of patients in the placebo arm had received botulinum toxin as a 4th or later line prophylactic treatment.

Table 6: Position of botulinum toxin among prior prophylactic treatments in patients in post-hoc 'CM ≥4 TF, inc. prior botulinum toxin' subgroup

	Placebo (n=[redacted])*	Erenumab 140 mg (n=[redacted])*
Position of botulinum toxin among prior prophylactic treatments - n (%)		
1st line	[redacted]	[redacted]
2nd line	[redacted]	[redacted]
3rd line	[redacted]	[redacted]
4th or later line	[redacted]	[redacted]

*Patients with sufficient data to determine order of prior prophylactic treatments.
Footnotes: Order of prior prophylactic treatments could not be determined in [redacted] patients in the placebo group and [redacted] patients in the erenumab 140 mg group. Total number of patients in 'CM ≥4 TF, inc. prior botulinum toxin' subgroup: placebo n=[redacted]; erenumab 140 mg n=[redacted].
Abbreviations: CM: chronic migraine; TF: treatment failure.
Source: Novartis data on file.[1]

Section B: Clarification on cost effectiveness data

Consistency between the clinical effectiveness and cost effectiveness sections of the submission

B1. The original CS contained an inconsistency between the subgroup analysis presented in the clinical effectiveness section and that used in the economic model:

'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.'

Please confirm that in the current, post appeal submission, the subgroup analyses presented in the clinical effectiveness section are consistent with those used to inform the economic model.

Please refer to the response to question A1.a in this document. The subgroup analyses informing the economic model used the same treatment failure definition as the clinical effectiveness section of the post-appeal submission.

References

1. Novartis Data on File.

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. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The Migraine Trust
3. Job title or position	Policy and Research Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Migraine Trust is the largest research and support charity for people affected by migraine in the UK. Our role is to fund and promote new research into migraine, provide day-to-day support for people affected by migraine, and campaign for change. Since we were founded in 1965, we have funded over 130 medical research projects that have improved our understanding of migraine and encouraged new researchers into the field. We hold an international symposium every two years, bringing together the world's leading experts on migraine and headache to share latest research findings and discuss current trends in treatment and prevention. The next Migraine Trust International Symposium (MTIS) will be in London on 10-13 September 2020. We also provide evidence-based information and support on all aspects of migraine and help for people with migraine experiencing difficulties at work, in education, or in accessing healthcare services via our website and our information and advocacy helplines. Every year over two million people visit our website and over 2,300 people receive support through our helplines. We campaign for national policy change to improve the lives of people affected by migraine. We are currently developing a 'State of the Migraine Nation' report that aims to explore the challenges and opportunities facing the migraine community today and identify priorities for future change across the UK. We are funded through legacies, individual donations, community and event fundraising, corporate partnerships, trusts and foundations, and industry. We are not a membership organisation, but we do have over 25,000 people signed up to receive our monthly e-bulletin.
4b. Has the organisation received any funding from the	Yes

manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**Eli Lilly** – We received £24,200 from Eli Lilly towards the production of our 'State of the Migraine Nation' policy report **Allergan** – We received £15,000 for our Information & Support Services team nurse specialist role **Amgen/Novartis** – We received £10,507 for our Information & Support Services team nurse specialist role
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We ran three surveys of people affected by migraine and migraine health professionals to help inform this submission. They are: **1. Migraine community survey** – This was the largest survey of the UK's migraine population that we've ever done in our nearly 55-year history. It was completed by over 1,800 people affected by migraine, including patients, their carers, and friends and family. It asked respondees about all aspects of their migraine, including: their experience of care and treatment, their main symptoms, and the impact that their migraine has had on their quality of life, family, education and/or career, and mental health and wellbeing. It ran from 7 October 2019 to 19 November 2019.

	2. CGRP Patient Experience Survey – We surveyed 203 patients between 14 October 2019 and 19 November 2019 who are currently taking (or had recently taken) a CGRP drug for the prevention of their migraine. The survey asked a variety of questions about the patient experience of using CGRP inhibitors, including about effectiveness, tolerability, and comparisons with Botox. **3. Snap poll of neurologists and headache nurses** – There are currently 60 headache nurses and 38 neurologists with a special interest in headache, according to the Association of British Neurologists (ABN). We surveyed 5 headache nurses and 11 neurologists between 22 November and 5 December 2019 about the experiences of their chronic migraine patients with Botox and CGRP drugs. In total, the snap poll results speak to the experience of 9,490 chronic migraine patients across the UK. We would be happy to share the full results of all three surveys with the committee if that would be helpful.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**What is migraine?** Migraine is a complex brain disease that greatly impacts individuals, their families, and society as a whole. It is the third most common disease in the world, affecting around 1 in 7 of the global population. According to NHS England, in the UK there are around 10 million people living with migraine. It is three times more common in women compared to men and around 9% of school children will experience a migraine every year. If you have migraine, you are likely to experience regular migraine 'attacks' that can last for up to four days. More than 75% of people living with migraine experience at least one attack every month, but the number of attacks varies considerably. People with migraine can experience an incredible range of debilitating symptoms. According to our recent survey of people affected by migraine, the ten most common symptoms are fatigue, severe head pain, light sensitivity, difficulty concentrating, nausea, stiff neck or back, feeling down, sound sensitivity, 'background' headache, and visual aura. But people affected by migraine cited more than 30 different symptoms in total.

	People with ‘chronic migraine’ have at least eight migraine attacks per month. It is estimated that between 660,000 and 1.3 million people in the UK are living with chronic migraine right now. The World Health Organization (WHO) categorises chronic migraine as causing the same level of disability as dementia and quadriplegia. At the moment, there is no cure. **What is it like to live with the condition?** Migraine exacts a large personal toll on people’s lives. People with migraine most commonly report that migraine has significantly impacted the following aspects of their life: work and career, family relationships, social life, and mental health and wellbeing. **a. Work and career** – Migraine is the leading cause of disability for people aged 15-49 and the second most disabling medical condition in the world. Our Migraine Community Survey found that nearly half (47%) of respondees consider themselves to have a disability as defined by the Equality Act 2020 because of their migraine. Our CGRP Patient Experience Survey found that for chronic migraine patients who have failed three other preventives, the percentage of respondees who identify as having a disability as defined by the Equality Act 2010 rises to 84%. This can create challenges in the workplace as people with migraine try to access the support they need to stay in work, develop, and progress. Our Migraine Community Survey found that 41% of eligible respondees ‘definitely agree’ that migraine has significantly impacted their career. People with migraine told us: “I lost my job because of migraine.” “My migraine has been the reason for taking early retirement.”

	"The lack of understanding of what migraine is…means that I was recently threatened with a level 3 disciplinary. I may lose my job despite 35 years of experience. It made me feel undervalued and discriminated against." **b. Family relationships** Over half (54%) of respondees to our CGRP Patient Experience Survey strongly agree that migraine has had a significant impact on their relationship with their partner or spouse and one-third (35%) strongly agree that migraine has significantly impacted their relationship with their children. People with migraine told us: "My family have suffered in helplessness for decades, unable to ease my pain…While they have lived their lives together I have been alone in a dark room isolated by my disease." "Migraine has stolen years of my life. I have missed so many events and missed out on so much of my son's life because of it." "I am not able to look after my child." **c. Social life** Migraine can be a very isolating condition, with 83% of respondees to our CGRP Patient Experience Survey strongly agreeing that migraine has significantly impacted their social life. The unpredictable nature of migraine, both episodic and chronic, can prevent people from being able to make plans or commit fully to family or leisure activities. People with migraine told us: "My friends have disappeared. This condition has ruined my existence." "My whole life revolves around migraine. I never see my friends or make any plans because migraine rules everything."

	d. Mental health and wellbeing People with migraine are three times more likely than people without migraine to have depression. 70% of respondees to our CGRP Patient Experience Survey strongly agree that migraine has significantly impacted their mental health and wellbeing.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**What options are currently available to patients and which are patients using?** While migraine cannot be cured, there are numerous acute and preventive treatments currently available to patients on the NHS in England and Wales to help them work with their clinician to manage this condition. Our Migraine Community Survey found that patients are most likely to be using the following types of treatments to help them manage their migraine: triptans (58%), lifestyle modifications (56%), over the counter painkillers (51%), and preventives (39%). However, it is important to emphasise that patients often have to try numerous different medicines before they find something that may work for them. Our Migraine Community Survey found that only around one-third of patients are satisfied with the care they receive for their migraine and only 31% believe they are effective at self-managing their migraine. **What do patients think of current acute options?** Acute treatments include pain-relief medicine, such as codeine, triptans, and paracetamol. People with migraine can experience adverse side effects from acute treatments, including fatigue, nausea, medication overuse headache, confusion and anxiety. For many, this limits the number of treatment options available to them. **What do patients think of current preventive options?**

	For the prevention of migraine, NICE clinical guideline 150 recommends a suite of different drugs that can be considered by patients and their clinician, including anticonvulsants and betablockers. However, many of these were developed for other conditions and have been repurposed for migraine. They often have severe and unwanted side-effects. For example, topiramate is very poorly tolerated in greater than 50% of patients and the Medicines and Healthcare products Regulatory Agency (MHRA) warns that sodium valproate causes learning disability in approximately 40% of babies born to mothers using it. Our CGRP Patient Experience Survey found that 90% of respondees had experienced adverse side-effects from migraine preventives, excluding CGRP. They told us: ““Propranolol side-effects were so bad that I had to take a month off of work.” “Low blood pressure from beta blockers and horrendous brain fog from Topamax. It was so intense that I had to come off the drug.” “I tried Botox and had a reaction to it. My throat swelled and I had a hard time breathing.” “Some preventives have caused me to have brain fog, taste changes, musculoskeletal pain, and sleepiness during the day.” Regardless of these side-effects, it is also important to stress that these ‘first line’ preventives also don’t work for everyone with migraine or they can stop working relatively quickly. Our CGRP Patient Experience Survey shows that 78% of respondees had tried more than five different preventives and 70% had also failed to respond to more than five different preventives. Patients told us: “No preventives have been successful, apart from topiramate which works for a couple of months and then stops completely.”

	"I have tried everything there is to try! Anti-depressants, anti-convulsants, HRT, etc. I experienced unpleasant side-effects to a greater or lesser extent from everything and no relief from migraine at all." **What do patients think of botulinum toxin type A (Botox) for the prevention of migraine?** NICE technology appraisal guidance 260 also recommends botulinum toxin type A (Botox) for preventing migraine for adults with chronic migraine who have not responded to at least three prior preventives. Botox is an effective preventive, but is hugely demanding of healthcare professional time and resource and, for some patients, difficult to access (see more below). While uncertainty remains over whether erenumab is more clinically effective than Botox, our findings from patients who have taken both a CGRP inhibitor for their migraine and Botox can shed some light on the real-world patient experience of comparative effectiveness and tolerability. Our CGRP Patient Experience Survey shows that for patients who have received both Botox and a CGRP inhibitor for their chronic migraine, 78% agree or strongly agree that the CGRP drug that they are currently taking (or have taken in the past) is more effective at managing their migraine than Botox, 76% agree or strongly agree that the CGRP drug they are currently taking (or have taken in the past) has improved their quality of life more than Botox, and 95% agree or strongly agree that the CGRP drug they are currently taking (or have taken in the past) is easier to administer than Botox. Our snap poll of neurologists and headache nurses shows that 62% of those surveyed believe that CGRP drugs are as or more effective than Botox based on their real-world experience of treating migraine patients. None of the neurologists or headache nurses we surveyed believed that CGRP drugs are less effective than Botox. 75% of those surveyed agree that their patients would prefer to receive CGRP drugs for their migraine over Botox. **Fremanezumab (Ajovy) for the prevention of migraine**

	On 12 March 2020 NICE granted approval to a CGRP drug, fremanezumab, for chronic migraine patients who had failed to respond to at least three other preventives. This is the first CGRP drug that NICE has approved. At the time of writing this approval has not yet taken effect, so its use is not widespread.
8. Is there an unmet need for patients with this condition?	As referenced above, there is an unmet need for patients who experience intolerable side-effects from the preventives currently available. There is also a considerable unmet need for patients with migraine who will fail to respond to oral preventives and botulinum toxin type A (Botox). These chronic migraine patients currently have no preventive option that works for them. We are not aware of the total size of the UK Botox non-responder population for migraine and our understanding is that no one else knows with certainty either. However, our snap poll of neurologists and headache nurses sheds some light on the size of this population. Of the 9,490 chronic migraine patients the health professionals polled have seen in their clinic in the past year, 5,085 patients have also received Botox injections. Of those 5,085 patients, an estimated 801 (15.7%) failed to respond to that therapy. This means that an estimated 8.4% of chronic migraine patients are not having their treatment needs met by current treatment options. Our CGRP Patient Experience Survey shows that CGRP drugs are answering a significant unmet need in this sub-group, delivering an effective and well-tolerated treatment that many report as 'life changing.' For example, of the patients we surveyed who had failed to respond to Botox, 76% agree or strongly agree that the CGRP drug they are currently taking (or have taken in the past) has improved their quality of life. There is also an unmet need for patients who experience difficulties in accessing Botox injections, which must be administered at a specialist centre by a trained healthcare professional on a quarterly basis. Our snap poll of neurologists and headache specialists shows that over the past year, 9% of their patients receiving Botox (437) have been forced to skip or delay a course of Botox injections due to access, availability, or capacity issues.

	These findings chime with the results of our CGRP Patient Experience Survey, which shows that 12% of eligible respondees had to wait over one year to receive their first course of injections from the time they were first prescribed it. This survey also found that 27% of respondees who had received Botox injections had to pay privately in order to do so.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Erenumab is a specific preventive treatment designed for migraine that has a very tolerable side-effect profile and can be administered in the patient's own home. 80% of respondees to our CGRP Patient Experience Survey agree or strongly agree that using a CGRP drug has improved their quality of life. Their reasons for saying this varied, but most have referenced reduced frequency of migraine attacks, reduced severity of attacks, being able to break the cycle of medication overuse headache, less stress, improved performance at work, being able to spend time with family, and improved mental health. It was not unusual for respondees to report that taking a CGRP drug like erenumab has been 'life changing' for them. Respondees told us: "My number of migraine days has reduced from up to 20 days per month to 5 days. Plus the migraines I still have are less severe and more responsive to triptans. My quality of life has returned to near normal for the first time in 14 years….I could weep with the relief of my life now." "I have gone from 20 plus migraines a month to 3-4. This has been life-changing for me. I was able to start driving a car again. All aspects of my life have improved after having this treatment: work, life, mental health, social life, home life, etc." "My quality of life is transformed."

	"My life has changed beyond recognition. I have been given the opportunity to live again. I can make plans, go places, do things, see people; none of this was possible before. For 45 years my life has been controlled by migraines, my personality, my identity…has been defined by this illness. Now I am free to find out who I am and how I should live." "I am able to leave my house for the first time in over 20 years with no fear of being stranded somewhere, possibly with a migraine attack so bad that I would be unable to open my eyes, walk, or even talk to anyone coherently. I can look after my grandchildren on my own for the first time ever." "Yesterday, for the first time in 15 months I felt well enough to drive my car and take my little boy out." "One injection and my life has improved massively. My mood is better, daily life is better, I've started being involved in physical activity again because my pain is managed effectively." "For the first time in 12 years, I am having pain free days, out of my darkened quiet bedroom." "It has changed my life beyond recognition. I no longer feel isolated. I have a new full time job that I can travel to on public transport and with confidence. I am not spending my life lying in a quiet, dark room. My migraines have gone from 17 per month to 3…AMAZING." "This is life-changing; a resurrection. I can see better, have clarity of thought, can make decisions and have fun again. I now have hope that I can resume work again." "I see friends, I can eat and enjoy food, spend time with family, appreciate my home, go outside!!!! Just to be in daylight and not see the inside of a toilet bowl hour after hour with no end in sight - I cannot tell you what that means to me." "Since taking the CGRP drug, I have not once been sick. I have not had to go into A&E to stop intractable migraine….Previously, I had to give up work because I could not function….Now my migraine episodes are much less frequent."

	"I have been given my life back, after suffering for over 20 years. I actually feel human again." "I have my life back. I still get headaches, but they are nothing compared. I can plan things now, help with my grandchildren, meet up with friends, work again. It's miraculous." Overwhelmingly, respondees to our CGRP Patient Experience Survey indicate that taking a CGRP drug for their migraine has had a positive impact on their family and/or carers. Respondees report that they are able to spend more time with their children, spouse/partner, or grandchildren. They say that their mood has dramatically improved, which in turn has led to a happier life at home. They also report that family members no longer need to act as carers. Respondees wrote: "My husband and I no longer live our lives completely dictated by migraine. We do things together and make plans. My family no longer have to see me in the depths of depression and with no hope that life will ever get better again." "The hope for my husband is palpable. He's seen me disabled and in pain for so long that he's overjoyed to see his former wife back." "Since starting the CGRP drug, my 80-year-old parents have not had to come and take care of me and my son. They have not had to carry me to the doctor or to A&E." "It has had an immeasurable effect. I can be fully present for my family. I can help support my siblings with their numerous small children. My own 16-year-old child can rely on me to be able to do stuff/support her without her having to feel guilty about asking me when I'm clearly struggling." "My parents are much happier as they don't have to worry about me so much. They don't have to do so much for me anymore, like cooking for me, going shopping for me, or driving me to various appointments."

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There are few disadvantages when compared to current standard treatments, although it's important to highlight that not all patients will respond to CGRP drugs. Some people with migraine may have a needle phobia which could be a problem as the drug is administered via an injection. Respondees to our CGRP Patient Experience Survey confirm these few disadvantages, with most indicating in the free text commentary for our survey that there are no disadvantages when compared to standard treatment. A small minority of respondees did indicate that there were disadvantages, which includes: the cost, injection site rashes, constipation, and needing to keep the drug refrigerated (which can make travelling difficult).
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so,	As detailed above, patients who have failed to respond to three oral preventives and also failed to respond to Botox may benefit more from this therapy than others.

please describe them and explain why.	
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). According to our latest research, migraine patients who are under consideration for this therapy (they have failed to respond to at least three preventives and also to Botox) are particularly disabled by the condition.
Other issues	
13. Are there any other issues that you would like the committee to consider?	As a fast, effective, and well-tolerated preventive, erenumab is able to not only reduce the number of headache days that patients experience, but also their use of acute treatments. This will help prevent the onset of medication overuse headache and also save resources elsewhere. 73% of respondees to our CGRP Patient Experience Survey report that they were able to stop or reduce their use of other migraine treatments while they were taking the CGRP medicine. The most common treatments respondees were able to reduce or stop include: triptans, codeine, and anti-sickness medicines.

	Respondees told us: "Before having the CGRP drug I was taking either triptans or painkillers for approximately 6 days of the week. I now generally have only needed medication for migraines approximately once a week." "I now only use only sumatriptan and cyclizine for the sickness. I use no other drugs which is wonderful. My triptan use has gone from the max allowed of 10 per month to max of 3 per month." "I managed to stop taking triptans and I drastically reduced my intake of over the counter medications."

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Migraine is a complex brain disease that greatly impacts the day-to-day lives of people who live with the condition. In particular, people with migraine say it impacts their ability to work or progress in their career, spend time with their family, socialise with friends, and live up to their potential. It also has a significant detrimental impact on mental health and wellbeing.
- While there are many acute and preventive treatments currently available on the NHS in England and Wales, most of them have been developed for other conditions and repurposed for migraine. They can have extremely adverse side-effects.
- Erenumab is a specific preventive treatment designed for migraine that has a very tolerable side-effect profile. An overwhelming majority of patients who have used CGRP drugs who we surveyed (80%) report that the drug has improved their quality of life. Many say using this kind of drug has been ‘life changing.’ Patients report very few disadvantages.
- There is significant unmet need for patients who cannot tolerate currently available oral preventives and/or who have failed to respond to Botox therapy. According to our research, this sub-group of patients represents 8.4% of all chronic migraine patients. Additionally, there is an unmet need for patients who cannot access Botox injections due to capacity, resource, or travel issues.
- 62% of the specialist neurological community in the UK (neurologists and headache nurses) believe that CGRP drugs, like erenumab, are as or more clinically effective than Botox. None believe that this class of drugs are less effective.

-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

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

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

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

……

NICE National Institute for Health and Care Excellence

Professional organisation submission

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	Association of British Neurologists headache and pain advisory group

3. Job title or position	Consultant Neurologist, [redacted] headache and pain advisory group
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).	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.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and	N/A

purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	N/A
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• To reduce the impairment and improve disability caused by migraine and improve associated disease-related quality of life 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 • 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
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.)	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
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	• As a group, we strongly believe there is a very significant unmet need • 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?	
9. How is the condition currently treated in the NHS?	Low frequency episodic migraine is usually self-managed in the community or through primary care. Patients with disabling or high frequency migraine are 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 (beta-blockers, 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 ***update 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?	• Erenumab 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.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Erenumab will only be used in patients with chronic migraine who have failed to respond to Botox. Considering patients receiving Botox treatment have already failed at least three treatments, erenumab will be a 5th line intervention
• 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 treatment should be commenced in a specialist headache centres to establish appropriate eligibility (starting criteria), 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.)	As the treatment will be given in patients with Botox failure, no additional investments will be required. Patients will be self-administering treatment at home, following an initial clinic visit
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, especially in 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?	no
• 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
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate)	Likely to be most effective in those with chronic migraine and in those intolerant of, or with poor compliance to, conventional preventative treatments.

than the general population?	
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.)	Yes - probably easier. Compared to botulinum toxin for chronic migraine, it does not need the time needed for 31 botulinum toxin injections that need to be repeated in a specialist clinic every 3 months.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Patients with Chronic Migraine who fail to respond to Botox treatment will be given erenumab initially for a period of three months. In those with <30% response in either severity or frequency the treatment will be stopped (negative stopping rule). Those that respond will continue the treatment for a year and the need for further treatment will be

Do these include any additional testing?	evaluated. Those successfully converted to low frequency episodic migraine will stop the treatment (positive stopping rule); others will continue and the need for continuing treatment will be evaluated every twelve months.
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?	Clinical studies indicate that a significant proportion of patients show improvements of >75%. This level of improved productivity will in some cases allow patients to return to work, reduce absenteeism from work, and reduce GP and hospital visits. Indirect costs are difficult to measure in QALY assessments.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes: It 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	Better tolerability and side effect profile. Self-administered monthly subcutaneous injections.

condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Patients with chronic migraine who fail Botox treatment may benefit significantly from this treatment, especially considering that they would otherwise be considered for invasive, scarce and expensive treatment options such as intravenous dihydroergotamine, occipital nerve stimulation.
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 very limited side effect profile reported leads to 1. improved compliance (as evidenced by very low drop-out rates in the trials and RWE) 2. contributes to improved quality of life compared to other treatments.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Not entirely: 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) which would be unlikely in clinical practise in which 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?	Trial results are likely to still be 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	Reduction in frequency and severity of headache (>50% in episodic migraine; >30% in chronic migraine).

measured in the trials?	Improvement in quality of life as measured by validated tools such as 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.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not that we are aware of
20. How do data on real-world	**Summary of real world evidence for the efficacy of erenumab (Aimovig) in patients who have failed preventive treatment with onabotulinumtoxin A (Botox).**

experience compare with the trial data?	Following the successful appeal against the decision of NICE not to approve the use of erenumab on the NHS for patients with chronic migraine, headache centres in the UK that have been using erenumab on the existing FOC scheme have provided data on the efficacy of erenumab in patients who have failed preventive treatment with Botox. Given the current emergency, many centres have not been able to provide information, and we have not been able to present information in a standardised format. However, the raw data presented below provides an accurate summary of the real world experience of clinicians using erenumab 140 mg in this highly refractory population. **Guy's & St Thomas's, London** 121 patients (85.1% female, average age 46 yr) who had tried and failed ≥3 preventive medications, and Botox, were treated with erenumab for six months. **At 3 months**: 50% of patients had ≥30% reduction in migraine days, with 36% having ≥50% reduction. **At 6 months:** 56% of patients had ≥30% reduction in migraine days, with 32% having ≥50% reduction in migraine days. 14/121 patients discontinued due to lack of efficacy. 8/121 patients discontinued because of side effects (all minor). **Manchester** 44 patients were treated with erenumab on the FOC scheme. They were a refractory group, having tried a median of 9 different preventative therapies including Botox (range 4-13). **At 10 weeks:** 21/44 had ≥30% reduction in severe headache days**;** 11/44 had ≥30% reduction in total headache days. **At 18 weeks:** 24/44 had ≥30% reduction in severe headache days**;** 15/44 had ≥30% reduction in total headache days. As of 25/03/2020, of 44 patients who started it, 20 remain on it for a median of 55 weeks (mode 55 weeks (range 25-57 weeks)). Reasons for cessation included lack of efficacy, waning of efficacy, and side effects. **Plymouth** 107 patients who had previously tried and received Botox without significant improvement in their headaches, were treated with erenumab, and followed-up for an average of 5 months. The population was predominantly female (80.4%) with a mean age of 50.3. Most had trialled multiple previous migraine treatments, including prescription

	medication (median=6 migraine-specific preventatives), trigger point injections (81.3%) and herbal/holistic therapies (53.3%). By the end of the treatment phase, 31/107 (28.9%) had a ≥50% reduction in migraine days, and 52/107 (48.5%) had a ≥50% increase in pain-free days. There were also significant improvements in triptan days, painkiller days, HIT-6 score, PHQ-9 scores and pain disability index scores. Only 3 patients ceased treatment due to minor side effects. **King's College London** Of the 75 patients treated under the FOC scheme, 43 patients had previously failed to respond to a median of 6 preventive treatments, and Botox. At 3 months, 16/43 (37%) achieved a ≥30% reduction in migraine days. Constipation was the commonest side effect in the entire King's cohort (21%), but all side effects were minor. **Other real world data** the following abstracts were presented at the International Headache Congress, Dublin, 2019: IHC-LB-082 presented the experience of single centre in the Netherlands with erenumab treatment of patients who had failed Botox treatment (Dutch regulations are similar to UK regulations in that Botox treatment can only be undertaken if patients have failed ≥3 other preventive medications). 47/152 chronic migraine patients in this centre were treated with Botox, of who 14 failed to respond. Of these patients 11/14 (79%) improved significantly after 3 months. IHC-PO-405 presented real world data on 109 patients from three centres in Australia. Of these, all patients had tried ≥3 preventive medications, and 105 patients had tried Botox, of whom 35 failed to respond. Of these patients, 21/35 (60%) experienced a ≥50% reduction in monthly migraine days.
Equality	

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Migraine is more common in women (22% versus 8% in men)
21b. Consider whether these issues are different from issues with current care and why.	no

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- There is an unmet need for patients with migraine, resulting 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.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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

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

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

……

NICE National Institute for Health and Care Excellence

Professional organisation submission

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	**British Association for the Study of Headache (BASH)**

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? ☐ 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.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of	**Educational Grant of £ 16000 towards Educational meetings in Penrith and Bristol**

manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	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. 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 fewer 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 are only available to those that have failed to respond to three other treatments. Neuromodulation devices such as GammaCore, Cefaly, and 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 few 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 is 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 Management Guidelines (last updated 2019-20)
• 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 of 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 is of little use if there is lack of expertise in making a proper diagnosis and management plan. Most patients with infrequent or episodic headaches remain in 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, which empowers patient to manage their own care. This reduces 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 Emergency Departments. 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. With regard to this appeal, patients who do not respond to Botox have already tried and failed at least three (and usually many more) previous preventive medications before trying Botox. They have generally exhausted all readily available treatment options, and therefore the only remaining options are invasive and/or scarcely available therapies such as intravenous DHE, occipital nerve stimulation, sphenoid ganglion stimulation, and so on. These are also extremely expensive. This cohort of patients should be given erenumab, which has been shown to be more cost effective than best supportive care in this scenario.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Erenumab will only be used in patients with chronic migraine who have failed to respond to Botox. Considering patients receiving Botox treatment have already failed at least three treatments, Erenumab will be a 5th line intervention.
• 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 should be commenced in a specialist headache centre, with subsequent monitoring in primary or secondary care levels.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As the treatment will be given in patients with Botox failure, no additional investments will be required. Patients will be self-administering treatment at home, following an initial clinic visit.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Current treatments do not work for all patients, and can be limited by tolerability and side effects. The new technology will provide an important option, even if responder rates are similar to existing treatments. Real life data in this scenario is limited but consistent, and provides a valuable insight into its potential benefits.
• 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, because of fewer side effects and better tolerability.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate)	Currently there is a significant unmet clinical need for better treatment in chronic migraine (which carries a very high disability and severely compromises quality of life), particularly in patients refractory to treatment with Botox.

than the general population?	
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.)	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. For example, treatment with Botox requires three monthly clinic visits to a specialist, each involving 31 injections.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Patients with Chronic Migraine who fail to respond to Botox treatment will be given erenumab initially for a period of three months. In those with <30% response in either severity or frequency the treatment will be stopped (negative stopping rule). Those that respond will continue the treatment for a year and the need for further treatment will be

Do these include any additional testing?	evaluated. Those successfully converted to low frequency episodic migraine will stop the treatment (positive stopping rule); others will continue and the need for continuing treatment will be evaluated every twelve months.
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?	Clinical studies indicate that a significant proportion of patients show improvements of >75%. This level of improved productivity will in some cases allow patients to return to work; it will reduce GP and hospital visits, and absenteeism. Indirect costs are difficult to measure in QALY assessments.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The treatment is 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.
• Is the technology a 'step-change' in the management of the	Yes

condition?	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?	Patients with chronic migraine who fail Botox treatment will benefit significantly from this treatment, especially considering that they have been refractory to four treatments and would otherwise be considered for invasive, scarce and expensive treatment options such as intravenous dihydroergotamine, occipital nerve stimulatoion and so on.
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. Drop out rates in the trials and RWE are very low.
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	Reduction in frequency and severity of headache (>50% in episodic migraine; >30% in chronic migraine).

measured in the trials?	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.
• 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 but have come to light subsequently?	The real life data do not show any additional concerning side effects.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not that we are aware of.
20. How do data on real-world experience compare with the	**Summary of real world evidence for the efficacy of erenumab (Aimovig) in patients who have failed preventive treatment with onabotulinumtoxin A (Botox).** Following the successful appeal against the decision of NICE not to approve the use of erenumab on the NHS for

trial data?	patients with chronic migraine, BASH has asked centres that have been using erenumab on the existing FOC scheme to provide data on the efficacy of erenumab in patients who have failed preventive treatment with Botox. Given the current emergency, many centres have not been able to provide information, and we have not been able to present information in a standardised format. However, the raw data presented below provides an accurate summary of the real world experience of clinicians using erenumab 140 mg in this highly refractory population. **Guy's & St Thomas's, London** 121 patients (85.1% female, average age 46 yr) who had tried and failed ≥3 preventive medications, and Botox, were treated with erenumab for six months. **At 3 months**: 50% of patients had ≥30% reduction in migraine days, with 36% having ≥50% reduction. **At 6 months:** 56% of patients had ≥30% reduction in migraine days, with 32% having ≥50% reduction in migraine days. 14/121 patients discontinued due to lack of efficacy. 8/121 patients discontinued because of side effects (all minor). **Manchester** 44 patients were treated with erenumab on the FOC scheme. They were a refractory group, having tried a median of 9 different preventative therapies including Botox (range 4-13). **At 10 weeks:** 21/44 had ≥30% reduction in severe headache days**;** 11/44 had ≥30% reduction in total headache days. **At 18 weeks:** 24/44 had ≥30% reduction in severe headache days**;** 15/44 had ≥30% reduction in total headache days. As of 25/03/2020, of 44 patients who started it, 20 remain on it for a median of 55 weeks (mode 55 weeks (range 25-57 weeks)). Reasons for cessation included lack of efficacy, waning of efficacy, and side effects. **Plymouth** 107 patients who had previously tried and received Botox without significant improvement in their headaches, were treated with erenumab, and followed-up for an average of 5 months. The population was predominantly female (80.4%) with a mean age of 50.3. Most had trialled multiple previous migraine treatments, including prescription

	medication (median=6 migraine-specific preventatives), trigger point injections (81.3%) and herbal/holistic therapies (53.3%). By the end of the treatment phase, 31/107 (28.9%) had a ≥50% reduction in migraine days, and 52/107 (48.5%) had a ≥50% increase in pain-free days. There were also significant improvements in triptan days, painkiller days, HIT-6 score, PHQ-9 scores and pain disability index scores. Only 3 patients ceased treatment due to minor side effects. **King's College London** Of the 75 patients treated under the FOC scheme, 43 patients had previously failed to respond to a median of 6 preventive treatments, and Botox. At 3 months, 16/43 (37%) achieved a ≥30% reduction in migraine days. Constipation was the commonest side effect in the entire King's cohort (21%), but all side effects were minor. **Other real world data** We would also draw the panel's attention to the following abstracts from the International Headache Congress, Dublin, 2019: IHC-LB-082 presented the experience of single centre in the Netherlands with erenumab treatment of patients who had failed Botox treatment (Dutch regulations are similar to UK regulations in that Botox treatment can only be undertaken if patients have failed ≥3 other preventive medications). 47/152 chronic migraine patients in this centre were treated with Botox, of who 14 failed to respond. Of these patients 11/14 (79%) improved significantly after 3 months. IHC-PO-405 presented real world data on 109 patients from three centres in Australia. Of these, all patients had tried ≥3 preventive medications, and 105 patients had tried Botox, of whom 35 failed to respond. Of these patients, 21/35 (60%) experienced a ≥50% reduction in monthly migraine days.
Equality	

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Migraine is more common in women (22% versus 8% in men)
21b. Consider whether these issues are different from issues with current care and why.	No

Key messages

22. 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.

Your privacy

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

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

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

……

NICE National Institute for Health and Care Excellence

Organisation submission template

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	Allergan Ltd
3. Job title or position	HTA Lead UK/IR

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): Employee of Allergan Ltd
5a. Brief description of the organisation (including who funds it).	Allergan Ltd manufacturers onabotulinumtoxinA
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Not applicable. Allergan Ltd manufacturers onabotulinumtoxinA

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to reduce the frequency, severity or duration of migraine and improve quality of life (TA10339). Also, the American Headache Society states that evidence of treatment benefits may be provided by at least 1 of the following: 1. A reduction in mean monthly headache days of 50% or more relative to the pretreatment baseline 2. A clinically meaningful improvement in a validated migraine-specific patient-reported outcome measure, including but not limited to: ▪ A reduction of at least 5 points or more in MIDAS score for those whose baseline score was between 11-20 ▪ A 30% reduction in MIDAS score for those with baseline scores above 20 ▪ Reduction of 5 or more points on the MPFID ▪ Reduction in the scores on the HIT-6 of at least 5 points ▪ Other document benefits reported by clinician and patient
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	▪ For chronic migraine, a 30% reduction in migraine frequency is considered a clinically meaningful response to treatment (TA10339). ▪ Please also see section 6 for clinically significant treatment responses

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	▪ NICE has already recommended two therapies for the management of chronic migraine: onabotulinumtoxinA (TA260) and Fremanezumab (TA10339). ▪ OnabotulinumtoxinA is a well-tolerated and safe therapy in chronic migraine as demonstrated by a wealth of long-term evidence beyond the registration trials PREEMPT 1 and 2: ▪ RCT: Two-year outcomes from the REPOSE study - over 600 patients in seven European countries, including 94 from the UK – demonstrated that the long-term use of onabotulinumtoxinA is effective and well tolerated, with sustained reductions in headache-day frequency and significant improvement in quality of life. ▪ RCT: The long-term safety and tolerability of onabotulinumtoxinA was demonstrated over 108 weeks and nine cycles of treatment in phase IV COMPEL study and no new safety concerns were identified. ▪ RWE: HULL Migraine Clinic provide the largest consolidated source of UK real-world evidence for the effect of onabotulinumtoxinA in chronic migraine prophylaxis, and results extend for up to seven years of treatment. In this dataset, all patients had failed at least three prior preventive treatments (except for 14 patients who initiated treatment before the NICE guidance came into effect in 2012). This makes the evidence from HULL Migraine Clinic particularly relevant to the decision problem in this appraisal. ▪ 2-year data: HULL Migraine Clinic reported 294 patients with an initial response to onabotulinumtoxinA of which 87.4% (n=257) experienced a successful treatment response over two

	years of follow up: patients were either still on treatment or had successfully withdrawn treatment without relapse to chronic migraine. ▪ 5-year data: HULL Migraine Clinic reported that over five years of follow up, 80.2% (n=101) of initial responders (n=126) experienced a successful treatment response, i.e., were either still on treatment or had successfully withdrawn treatment without relapse to chronic migraine. ▪ 7-year data: HULL Migraine Clinic reported 56.4% responders (388 out of 687) based on Hull Criteria with a good safety profile. ▪ RWE: A multicentre, retrospective chart review of 211 patients from 7 private neurology practices in Australia demonstrated that onabotulinumtoxinA is an effective, safe and well-tolerated therapy at 2 treatment cycles and beyond in adults with inadequately controlled CM. ▪ RWE: PREDICT - a Canadian, multicentre, prospective, observational study in adult 196 patients with CM demonstrates that onabotulinumtoxinA treatment for up to 2 years (7 treatment cycles) improved health-related quality of life and reduced headache days, with high physician and participant satisfaction.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	▪ Patients with chronic migraine who receive onabotulinumtoxinA are generally treated in a hospital setting, often within specialist headache clinics in either secondary or tertiary care, or under the supervision of a general neurologist. In March 2020, the MHRA granted a licence update for onabotulinumtoxinA across all its indications making clear that appropriately trained and qualified healthcare professionals, including specialist nurses and physiotherapists, are now able to administer the product to patients. The licence previously stated that the treatment could only be administered by physicians.
• Are any clinical guidelines used in the treatment of the	▪ Headache clinics generally follow CG150 (Headaches in over 12s: diagnosis and management) although there is a great deal of variety of care in terms diagnosis and treatment.

condition, and if so, which?	▪ The British Association for the Study of Headache (BASH) updated its Guidelines on headache management in 2019. The European Headache Federation created Guidelines (published Jan. 2019) on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention.
• 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.)	▪ Headache clinics generally follow CG150 (Headaches in over 12s: diagnosis and management) although there is a great deal of variety of care in terms diagnosis and treatment
• What impact would the technology have on the current pathway of care?	▪ There are two therapies already approved by NICE in chronic migraine patients: onabotulinumtoxinA (TA260) and Fremanezumab (TA10339).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	▪ We would anticipate that this technology would be used similarly to fremanezumab although NICE guidance for fremanezumab has not yet been issued and it is not currently in routine NHS use. ▪ It is expect that clinicians only to use fremanezumab in patients who are properly managed for medicines overuse headache, even though this is not specified in its proposed guidance.

• How does healthcare resource use differ between the technology and current care?	▪ All patients treated with erenumab would require injector training ▪ All patients would be expected to be initiated on erenumab within a hospital setting, typically a headache clinic, before being able to progress to self-administration. A proportion are unlikely to be able to self-administer at all ▪ A number of patients will need their treatment to be administered for them ▪ Patients to be monitored by specialists in order to ensure compliance with monthly erenumab and to evaluate response to the treatment. This is in line with EHS consensus statement which recommends an evaluation of response to onabotulinumtoxinA after each treatment cycle.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	▪ Mix of hospital and home care as described above
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	▪ Training of HCPs, nurses and patients for administering erenumab

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There is a high degree of uncertainty in the evidence base of erenumab in chronic migraine populations and particularly in the sub-population of patients of interest to this appraisal, ie patients who have failed on onabotulinumtoxin A. Subgroup of patients who have failed onabotulinumtoxinA: ▪ The European Public Assessment Report (EPAR) for erenumab highlighted that "onabotulinumtoxinA treatment failures resulted in such small subgroups that the results of the subgroups could not be analysed in a meaningful way". ▪ To demonstrate the value of erenumab in patients with chronic migraine who have failed onabotulinumtoxinA, this would require a post-hoc analysis of the sub-group analysis of Study 295 (n=69 patients). This will introduce more uncertainty where the uncertainty is already considerable. The NICE appraisal committee has acknowledged this publicly in the evidence it gave at the hearing for the appeal against the previous FAD for erenumab. Subgroup of patients when onabotulinumtoxinA is unable to be tolerated: ▪ OnabotulinumtoxinA is a well-tolerated and safe therapy in chronic migraine as demonstrated by a wealth of long-term evidence beyond the registration trials PREEMPT 1 and 2 (see response in section 8 above).
• Do you expect the technology to increase length of life more than current care?	▪ No therapy in chronic migraine has shown to increase the length of life

• Do you expect the technology to increase health-related quality of life more than current care?	▪ During the development of TA10302, the manufacturer of erenumab has not provided evidence to support the use of erenumab as a fifth line therapy in chronic migraine. ▪ Clinically meaningful improvements from baseline in quality of life (QoL) and disability were experienced after onabotulinumtoxinA treatment for CM in both clinical trials as well as large real-world studies across different clinical settings: ▪ In PREEMPT 1 and 2, onabotulinumtoxinA significantly reduced headache severity (as measured by improved HIT-6 scores at all time points) compared with placebo. ▪ In the REPOSE study, MSQ scores showed significant reductions from baseline in Role Function-Restrictive domain at each follow-up session. ▪ Following treatment with onabotulinumtoxinA, PREDICT participants reported significantly higher MSQ scores, exceeding MIDs for all three domains: role restrictive, role preventive, and emotional function. Consistent with previous clinical and observational studies, onabotulinumtoxinA treatment significantly improved quality of life in individuals with CM (as determined by MSQ). ▪ In Santoro et al. 2017 (Italy) onabotulinumtoxinA effectively reduced headache-related disability and improved patients' quality of life. ▪ In the Sant Andrea Hospital study, onabotulinumtoxinA reduced the mean HIT-6 score during all the treatment period up to 2 years. ▪ In the Australian RWE study, reductions in the adverse impact of headaches, reflected in significant mean (SD) changes in HIT-6 scores of –11.7 (9.8) after 2 treatment cycles (n=80; p<0.001) and –11.8 (12.2) at final follow-up (n=68; p<0.001), respectively, represent a clinically meaningful reduction in HIT-6 scores. ▪ In a retrospective study of 94 patients in Taiwan onabotulinumtoxinA significantly improved MIDAS score from 60 at baseline to 30 at 12 weeks.

	▪ OnabotulinumtoxinA treatment for CM reduced symptoms of comorbid conditions such as depression and anxiety: ▪ Results from the COMPEL study show that approximately 80% of patients treated with onabotulinumtoxinA experience a clinically meaningful improvement in comorbid depression and anxiety. ▪ OnabotulinumtoxinA treatment for CM is associated with reductions in the impact of headache on daily activities and work productivity: ▪ Analysis of secondary endpoints in the FORWARD study showed mean baseline scores on the WPAI-SHP were 4.8 in the onabotulinumtoxinA group and 5.1 in the topiramate group. At Week 12, the scores had improved to 3.3 and 4.4 respectively, and at Week 36, to 3.5 and 4.4, respectively, a significant and clinically meaningful difference.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is a high degree of uncertainty in the evidence base of erenumab in chronic migraine populations. This is especially true for the sub-population of interest to this appraisal. ▪ In the development of TA10302 the manufacturer submitted evidence of a small post-hoc subgroup analysis of 295 Study (n=69 patients) to support the value of erenumab in patients with chronic migraine who have failed >3 previous treatments (the target population in TA10302 submission). This was because Study 295 which enrolled patients with chronic migraine has excluded people with no therapeutic response to >3 previous treatments. The underlying uncertainty from this small patient cohort makes it challenging to derive meaningful conclusions about the value of erenumab in chronic migraine patients who have failed ≥3 previous treatments including onabotulinumtoxinA.
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	▪ Patient preference

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.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	▪ The focus of this appraisal is expected to be on the use of erenumab in patients who are not adequately responding to onabotulinumtoxinA treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) - TA260 ▪ Allergan wants to bring to the Committee's attention the evolving evidence which has shown that onabotulinumtoxinA patients who were deemed non-responders (based on analysis of headache frequency alone) experienced clinically meaningful relief from headache intensity in the second and third cycles of treatment with onabotulinumtoxinA (pooled analysis of the PREEMPT clinical trial programme)
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	▪ During the development of TA10302, the manufacturer of erenumab has not provided evidence to support the use of erenumab as a fifth line therapy in chronic migraine.

quality-adjusted life year (QALY) calculation?	
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?	▪ Same response as above
• Is the technology a 'step-change' in the management of the condition?	▪ Same response as above
• Does the use of the technology address any particular unmet need of the patient population?	▪ Same response as above
17. How do any side effects or adverse effects of the technology affect the	▪ Unknown

management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	There is a high degree of uncertainty in the evidence base of erenumab in chronic migraine populations. ▪ In the development of TA10302 the manufacturer submitted evidence of a small post-hoc subgroup analysis of 295 Study (n=69 patients) to support the value of erenumab in patients with chronic migraine who have failed >3 previous treatments (the target population in TA10302 submission). This was because Study 295 which enrolled patients with chronic migraine had excluded people with no therapeutic response to >3 previous treatments. The underlying uncertainty from this small patient cohort makes it challenging to derive meaningful conclusions about the value of erenumab in chronic migraine patients who have failed ≥3 previous treatments including onabotulinumtoxinA. ▪ In addition, during the development of TA10302 the manufacturer of erenumab did not provide evidence to support the use of erenumab as a fifth line therapy in chronic migraine.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	▪ No
20. How do data on real-world experience compare with the trial data?	▪ During the development of TA10302, the manufacturer of erenumab did not provide evidence to support the use of erenumab as a fifth line therapy in chronic migraine. ▪ OnabotulinumtoxinA is a well-tolerated and safe therapy in chronic migraine as demonstrated by a wealth of long-term real-world evidence (see section 8)
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	▪ No

21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

- 22. In up to 5 bullet points, please summarise the key messages of your submission.

1. There is a high degree of uncertainty in the evidence base of erenumab in chronic migraine populations and especially in the subpopulation (patients who were not responsive to or unsuitable for onabotulinumtoxinA) which is expected to be the focus of this appraisal. In the development of TA10302 the manufacturer submitted evidence of a small post-hoc subgroup analysis of 295 Study (n=69 patients) to support the value of erenumab in patients with chronic migraine who have failed >3 previous treatments. This was because Study 295 which enrolled patients with chronic migraine has excluded people with no therapeutic response to >3 previous treatments. The underlying uncertainty from this small patient cohort makes it challenging to derive meaningful conclusions about the value of erenumab in chronic migraine patients who have failed ≥3 previous treatments including onabotulinumtoxinA.
2. During the development of TA10302, the manufacturer of erenumab did not provide evidence to support the use of erenumab as a fifth line therapy in chronic migraine. To demonstrate the value of erenumab as a fifth line therapy (non-responders to onabotulinumtoxinA after two treatment cycles), a subgroup analysis of the small post-hoc subgroup analysis of 295 Study will be required (n=69 patients) therefore introducing more uncertainty to the evidence submitted where uncertainty is already considerable. The European Public Assessment Report (EPAR) for erenumab stresses that “the results of these subgroups could not be analysed in a meaningful way”.
3. OnabotulinumtoxinA is a well-tolerated, safe and effective therapy in chronic migraine as demonstrated by a wealth of long-term evidence beyond the registration trials PREEMPT 1 and 2
4. OnabotulinumtoxinA therapy also results in clinically meaningful improvements from baseline in quality of life (QoL) and disability in CM as demonstrated in clinical trials and large real-world studies across different clinical settings
5. OnabotulinumtoxinA is the only therapy in chronic migraine with evidence of greater clinical utility versus 1st line treatment topiramate (FORWARD STUDY)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

NICE National Institute for Health and Care Excellence

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

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

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

……

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Erenumab for preventing migraine (post-appeal addendum)

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

Authors
Marie Westwood, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK
Bram Ramaekers, Health Economist, Maastricht UMC
Svenja Petersohn, Health Economist, Maastricht UMC
Sabine Grimm, Health Economist, Maastricht UMC
Xavier Pouwels, Health Economist, Maastricht UMC
Willem Witlox, Health Economist, Maastricht UMC
Debra Fayter, Systematic Reviewer, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Gill Worthy, Statistician, KSR Ltd
Shelley de Kock, Information Specialist, KSR Ltd
Manuela Joore, Health Economist, Maastricht UMC
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to
Marie Westwood,
Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

Date completed 29/05/2020

Source of funding This report was commissioned by the NIHR HTA Programme.

Declared competing interests of the authors
None.

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.

This report should be referenced as follows:
Westwood M, Ramaekers BLT, Petersohn S, Grimm S, Pouwels X, Witlox W, Fayter D, Armstrong N, Worthy G, de Kock S, Joore MA, Kleijnen J. Erenumab for preventing migraine: A Single Technology Assessment (post-appeal addendum). York: Kleijnen Systematic Reviews Ltd, 2020.

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 and Nigel Armstrong 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

BASH	British Association for the Study of Headache
BSC	Best supportive care
CI	Confidence interval
CM	Chronic migraine
CS	Company's submission
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
HIT-6	Headache impact test
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IHS	International Headache Society
ITT	Intention to treat
KSR	Kleijnen Systematic Reviews
LSM	Least square method
Mg	Milligram
MMD	Monthly migraine days
MSQ	Migraine-specific quality of life questionnaire
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
OR	Odds ratio
PAS	Patient access scheme
PSS	Personal Social Services
Q4W	Every four weeks
QALY(s)	Quality-adjusted life year(s)
SD	Standard deviation
SE	Standard error
UK	United Kingdom

Table of Contents

Table of tables

1. Summary

1.1 Background

This addendum to the Evidence Review Group (ERG) report, Erenumab for preventing migraine: A Single Technology Assessment, summarises and appraises the additional evidence submitted by the company post-appeal.

Following the final appraisal determination (FAD), *'Erenumab is not recommended, within its marketing authorisation, for preventing migraine in adults who have at least 4 migraine days per month,*' an appeal was submitted jointly by the British Association for the Study of Headache (BASH) and the Association of British Neurologists (ABN). The appeal was made under ground 2 of NICE's appeal procedures, *'The recommendation is unreasonable in light of the evidence submitted to NICE'.*

The appeal panel upheld the appeal on the ground that: '*The Committee unreasonably failed to consider the cost-effectiveness of erenumab versus best supportive care in those who had failed to benefit from the comparator drug in patients with chronic migraine.'*

The appeal panel concluded that: *'The appraisal is remitted to the appraisal committee who must now take all reasonable steps to address the failure to request any available data to enable it to consider the role of erenumab in alternative parts of the treatment pathway for chronic migraine, specifically, following the failure of treatment with botulinum toxin or when botulinum toxin is contra-indicated. Whether in the light of such data (if any) the recommendation should be amended will be a matter for the committee to consider.'*

This addendum provides a description and critique of the additional evidence submitted in relation to these patient subgroups.

1.2 Summary of the additional clinical effectiveness evidence submitted

The company provided evidence about the clinical effectiveness of erenumab in patients with chronic migraine, for whom at least four prior prophylactic treatments, including botulinum toxin, had failed (CM ≥4 TF, including botulinum toxin subgroup). These data were derived from a *post-hoc* subgroup analysis of Study 295. The subgroup analysis included [redacted] patients in the placebo group and [redacted] patients in the erenumab 140 mg treatment group. Patients in the erenumab 140 mg group experienced a numerically greater reduction in mean monthly migraine days (MMDs), from baseline to week 12, compared to placebo least squares mean (LSM) difference [redacted] days (95% CI: [redacted]; p=[redacted]) and a statistically significantly higher response rate, where response was defined as a ≥30% reduction in MMDs at week 12, odds ratio (OR) [redacted] (95% CI: [redacted]; p=[redacted]).

The company also presented the results of a further *post-hoc* subgroup analysis of Study 295, for patients with chronic migraine who had failed three or more prior prophylactic treatments, but who had not previously received botulinum toxin (CM ≥3 TF, no prior botulinum toxin subgroup). This subgroup analysis was submitted as a proxy for patients in whom botulinum toxin is contraindicated, as no direct evidence was available for this patient group. The subgroup analysis included [redacted] patients in the placebo group and [redacted] patients in the erenumab 140 mg treatment group. Patients in the erenumab 140 mg group experienced a statistically significantly greater reduction in MMDs, from baseline to week 12, compared to placebo LSM difference [redacted] days (95% CI: [redacted]; p=[redacted]) and a statistically significantly higher response rate, where response was defined as a ≥30% reduction in MMDs at week 12, OR [redacted] (95% CI: [redacted]; p=[redacted]).

1.3 Summary of the additional cost effectiveness evidence submitted

The company's economic model, used to conduct cost effectiveness analyses for this post-appeal submission, is identical to the original model i.e. latest model submitted to NICE prior to the third Appraisal Committee meeting in August 2019. The only post-appeal update is the incorporation of clinical effectiveness subgroup data from Study 295 for chronic migraine patients by prior or no prior use of botulinum toxin and for chronic migraine patients with ≥4 prior prophylactic treatment failures.

In the deterministic base-case analysis of the subgroup of adults with chronic migraine and ≥4 prophylactic treatment failures including botulinum toxin, total QALYs gained and total costs were larger for erenumab than for BSC. The deterministic ICER amounted to [redacted] per QALY gained. Also, in the deterministic base-case analysis of the subgroup of adults with chronic migraine and ≥3 prophylactic treatment failures who are ineligible for botulinum toxin, total QALYs gained and total costs were larger for erenumab than for BSC. The deterministic ICER amounted to [redacted] per QALY gained.

The company conducted scenario analyses for both subgroups in which patients who discontinue treatment were assumed to rebound to baseline MMDs, rather than maintain the non-responder MMD improvement achieved at week 12 (as in the base-case). In the subgroup of adults with chronic migraine and ≥4 prophylactic treatment failures including botulinum toxin, this resulted in an ICER of [redacted] per QALY gained. In the subgroup of adults with chronic migraine and ≥3 prophylactic treatment failures who are ineligible for botulinum toxin, this resulted in an ICER of [redacted] per QALY gained.

1.4 Summary of additional cost-effectiveness analyses conducted by the ERG

The new base-case proposed by the company is consistent with most of the original ERG adjustments. The only relevant difference is the assumption of no treatment effect waning but this is now, given the Committee's preferences, consistent with the ERG preferences. Therefore, the ERG analyses consisted only of probabilistic results of the company base-case as well as probabilistic results of the scenario analyses 1) assuming patients who discontinue treatment were assumed to rebound to baseline MMDs (as presented by the company) and; 2) assuming treatment waning over five-year (for completeness).

The ERG's probabilistic results are in line with the deterministic results reported by the company. The company base-case (and now also the ERG's preferred analysis) indicates probabilities of [redacted] for erenumab 140mg to be cost effective at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively in the CM ≥4 TF, including botulinum toxin subgroup while for the CM ≥3 TF, no prior botulinum toxin subgroup these probabilities were [redacted] respectively. The treatment waning scenarios, added by the ERG, substantially increased the estimated ICER to [redacted] per QALY gained for the CM ≥4 TF, including botulinum toxin subgroup and the CM ≥3 TF, no prior botulinum toxin subgroup respectively.

1.5 ERG conclusions on the additional evidence submitted and remaining areas of uncertainty

The new company base-case is consistent with most of the original ERG adjustments. The only relevant difference is the assumption of no treatment effect waning but this is now, given the Committee's preferences, consistent with the ERG preferences. The ERG preferences and the company base-case are now aligned and resulted in probabilistic ICERs of [redacted] per quality-adjusted life year (QALY) gained for the CM ≥4 TF, including botulinum toxin subgroup and the CM ≥3 TF, no prior botulinum toxin subgroup respectively. Nevertheless, it is important to consider the limitations in the clinical evidence when interpreting these results. These limitations include the sample size of the subgroups considered; consistent with the European Public Assessment Report (EPAR) for erenumab

it can be debated whether these small subgroups can be analysed in a meaningful way. Moreover, Study 295 (focussed on patients with chronic migraine) excluded people with no therapeutic response to >3 previous treatments (i.e. potentially excluded the most refractory patients). Given the selected population, the representativeness of the Study 295 results and thus the calculated ICERs to the UK clinical patients (which includes people with no therapeutic response to >3 previous treatments) are considered uncertain. In addition, the CM ≥4 TF, including botulinum toxin subgroup appears to have included some patients ([redacted]) who had discontinued botulinum toxin for reasons other than treatment failure. Non-receipt of botulinum toxin treatment, for patients with chronic migraine and three or more prior prophylactic treatment failures, has questionable validity as a proxy for botulinum toxin being contraindicated. There are a number of possible reasons, other than contraindications, for non-receipt of botulinum toxin treatment, including variations in the availability/provision of botulinum toxin treatment services within the UK NHS. Finally, as was the case for the subgroup presented in the original CS, the post-appeal CS did not include any data on the long-term (>12 weeks) effectiveness of erenumab compared to placebo in either the CM ≥4 TF, including botulinum toxin subgroup or the CM ≥3 TF, no prior botulinum toxin subgroup.

In conclusion, despite the company base-case and the ERG preferences being aligned, there remains uncertainty (that is not quantified in the health economic analyses) regarding the evidence used (from Study 295) and thus the interpretation of these results.

2. Background

This addendum to the Evidence Review Group (ERG) report, Erenumab for preventing migraine: A Single Technology Assessment,[1] summarises and appraises the additional evidence submitted by the company[2] and other stakeholders,[3, 4] post-appeal.

Following the final appraisal determination (FAD), '*Erenumab is not recommended, within its marketing authorisation, for preventing migraine in adults who have at least 4 migraine days per month'*,[5] an appeal was submitted jointly by the British Association for the Study of Headache (BASH) and the Association of British Neurologists (ABN). The appeal was made under ground 2 of NICE's appeal procedures, *'The recommendation is unreasonable in light of the evidence submitted to NICE'.*

The appeal panel upheld the appeal on the ground that: '*The Committee unreasonably failed to consider the cost-effectiveness of erenumab versus best supportive care in those who had failed to benefit from the comparator drug in patients with chronic migraine'*.[6]

The appeal panel concluded that: '*The appraisal is remitted to the appraisal committee who must now take all reasonable steps to address the failure to request any available data to enable it to consider the role of erenumab in alternative parts of the treatment pathway for chronic migraine, specifically, following the failure of treatment with botulinum toxin or when botulinum toxin is contra-indicated. Whether in the light of such data (if any) the recommendation should be amended will be a matter for the committee to consider.'*[6]

This addendum provides a description and critique of the additional evidence submitted in relation to these patient subgroups and the associated alternative positioning of erenumab in the treatment pathway. The section dealing with the alternative model, follows the structure of the equivalent sections in the main ERG report[1] for the model submitted in the original company submission (CS).

3. Clinical effectiveness

3.1 Critique of the company's adherence to the alternative positioning of erenumab, in the treatment pathway for patients' chronic migraine, specified in the appeal decision

The company's post-appeal submission presents evidence in support of the use of erenumab in two subgroups:

1. Patients with chronic migraine (CM) and four or more prior prophylactic treatment failures, including prior receipt of botulinum toxin (CM ≥4 TF, including prior botulinum toxin).

The company stated that: '*this represents a subgroup of patients for whom at least four prior prophylactic treatments have failed. All patients in this subgroup have a history of treatment with botulinum toxin, which was discontinued due to lack of efficacy, unacceptable tolerability and/or other reasons'*.[2]

ERG comment: The ERG questions whether patients discontinuing botulinum toxin treatment for *'other reasons'* should be included in the definition of treatment failure. In respect of the additional evidence submitted, no information was provided about how many of the patients in the relevant subgroup, who had previously received treatment with botulinum toxin, had discontinued this treatment for reasons other than lack of efficacy or unacceptable tolerability, or about the other reasons for discontinuation.

The company were asked to provide clarification on the reasons for discontinuation included in the category 'other' and to provide the number of patients, included in the subgroup analysis, who had discontinued botulinum toxin for each of the reasons, lack of efficacy, unacceptable tolerability and 'other reasons'. The following response was provided: *'In the 'CM ≥4 TF, including prior botulinum toxin' subgroup, the large majority of patients had discontinued prior treatment with botulinum toxin due to treatment failure ([redacted] out of [redacted] patients ([redacted]%) in the erenumab 140 mg group; [redacted] out of [redacted] patients ([redacted]%) in the placebo group), mostly due to lack of efficacy ([redacted]% of patients in the erenumab 140 mg group; [redacted]% of patients in the placebo group). Few patients had a treatment failure due to an adverse reaction to botulinum toxin. Of note, patients could state more than one reason for discontinuation of each prior prophylactic treatment. The most common reason for discontinuation due to reasons other than treatment failure was that prophylactic medication was no longer clinically necessary. Within the "Other" category, the most frequently mentioned reasons related to affordability issues.*'[7] Further details of the reasons for botulinum toxin discontinuation are provided in Table 3.1.

Table 3.1: Prior botulinum toxin discontinuation reasons in post-hoc 'CM ≥4 TF, including prior botulinum toxin' subgroup

	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Botulinum toxin discontinuation reason - n (%)		
Treatment failure	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Adverse reaction	[redacted]	[redacted]
Discontinue due to reason other than treatment failure	[redacted]	[redacted]
Prophylactic medication no longer clinically necessary	[redacted]	[redacted]
Other	[redacted]	[redacted]

	Placebo (n=[redacted])	Erenumab 140 mg (n=[redacted])
Botulinum toxin discontinuation reason - n (%)		
Source: Table 4, Response to clarification[7] Note: Categories are not mutually exclusive and subjects may contribute to more than one category		

The ERG notes that, from the information provided above, it appears that [redacted] of patients included in the CM ≥4 TF, including prior botulinum toxin subgroup did not meet the definition of having failed botulinum toxin treatment, i.e. these patients had discontinued botulinum toxin for reasons other than treatment failure.

2. Patients with chronic migraine and three or more prior prophylactic treatment failures, but no prior receipt of botulinum toxin (CM ≥3 TF, no prior botulinum toxin).

The company stated that: '*evidence from this subgroup is provided as a proxy for the clinical and cost-effectiveness of erenumab in a subgroup of patients with chronic migraine who are not eligible to receive botulinum toxin due to contraindication/unsuitability. It should be noted that data are not available specifically for patients treated with erenumab who are known to have a contraindication/unsuitability for botulinum toxin; the presented subgroup data in patients with chronic migraine who have three or more prior treatment failures and no prior receipt of botulinum toxin is considered to act as a proxy for this population'*.[2]

ERG comment: The ERG questions the validity of non-receipt of botulinum toxin treatment, for patients with chronic migraine and three or more prior prophylactic treatment failures, as a proxy for botulinum toxin being contraindicated. There are a number of possible reasons, other than contraindications, for non-receipt of botulinum toxin treatment, including variations in the availability/provision of botulinum toxin treatment services within the UK NHS. The submission from the Migraine Trust included the following statement: *'Our snap poll of neurologists and headache specialists shows that over the past year, 9% of their patients receiving Botox (437) have been forced to skip or delay a course of Botox injections due to access, availability, or capacity issues'*.[4] The ERG acknowledges the unmet need of patients who experience difficulties in accessing botulinum toxin treatment services, but notes that this patient group is not equivalent to those for whom botulinum toxin is contraindicated.

3.2 Critique of the targeted literature review

The company conducted a targeted literature review (TLR) to identify real-world evidence from the UK for the clinical effectiveness of erenumab in the 'patients with chronic migraine and four or more prior prophylactic treatment failures, including prior receipt of botulinum toxin' subgroup. The inclusion criteria for this TLR are provided in Table 3.2. The targeted review did not search for studies on best supportive care (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 TLR is described, in detail, in Appendix A of the post-appeal CS.[2]

Table 3.2: Inclusion criteria used in the TLR of 'real world evidence'

Category	Inclusion criteria
Population	• Adult patients who have chronic migraine with 4 or more prior preventive/prophylactic treatment failures, one of which is botulinum toxin
Intervention	• Erenumab
Comparators	• Any or none
Outcomes	• Any effectiveness outcomes
Study design	• Real-world evidence such as prospective or retrospective observational studies, database/registry studies or cross-sectional studies
Other considerations	• Records with abstract or full text in English • Journal articles from any date, conference abstracts published since 2018, and ClinicalTrials.gov records from any date • Studies conducted in the United Kingdom
Source: Table 5, post-appeal CS[2]	

ERG comment: The ERG questions the validity of restricting the inclusion of 'real-world evidence' to studies conducted in the UK. Efficacy data from clinical trials were not restricted to the UK. Study 295,[8] the only randomised controlled trial included in the post-appeal CS,[2] was an international study in which only [redacted] of the total of 667 participants were recruited at UK sites. The number of UK participants included in the subgroup analyses was not reported. Given the general paucity of data for the subgroups under consideration, the ERG considers that 'real-world evidence' from countries other than the UK should also have been considered.

With respect to the population inclusion criterion, 'adult patients who have chronic migraine with four or more prior preventive/prophylactic treatment failures, one of which is botulinum toxin,' it is not clear whether the initial (title and abstract) stages of screening considered the possibility that studies may have reported data for this population as a subgroup analysis. It is also unclear why the TLR did not look for 'real-world evidence' about the population with three or more prior preventive/prophylactic treatment failures, for whom botulinum toxin is contraindicated, given that there are no trial data for this population.

3.2.1 Searches

A targeted literature search was undertaken to identify real-world evidence for the clinical effectiveness of erenumab. Details of the search strategy and resources searched were provided in Appendix A and were clearly documented, transparent and reproducible. Electronic databases searched were MEDLINE and Embase via the Ovid SP platform with no date limit. Additional supplementary searches from the previous two years were performed in the following resources:

- European Headache Federation (EHF)
- International Headache Society (IHS)
- Association of British Neurologists (ABN)
- European Academy of Neurology (EAN)
- European Association of Neurosurgical Societies (EANS)
- World Congress of Neurology (WCN)
- American Academy of Neurology (AAN)
- American Headache Society (AHS)

- Migraine Trust International Symposium (MTIS)

A search for observational studies with no date limit was also undertaken in ClinicalTrials.gov. All searches included a sufficient range of terms and synonyms for erenumab and the ERG is satisfied that relevant studies would not have been missed.

3.2.2 Review methods

The description of the TLR, in Appendix A of the post-appeal CS,[2] includes the statement that: *'records were reviewed in three stages (titles, abstracts, full-text articles) by a single reviewer, with a second senior reviewer checking all included records and 10% of excluded records at each stage.'*

ERG comment: It is good practice that all stages of inclusion screening should be performed independently by at least two reviewers. Checking of a partial sample, as described in the TLR methods, may result in erroneous exclusion of relevant studies.

As noted in the TLR methods, Appendix A of the post-appeal CS,[2] no formal data extraction process or assessment of the methodological quality of the 'real-world evidence' identified was undertaken.

3.3 Summary and critique of the clinical effectiveness evidence submitted for erenumab for the treatment of chronic migraine, following the failure of treatment with botulinum toxin

The company provided a further subgroup analysis of Study 295,[8] in addition to that provided in section B.2.6.1 of the original CS.[9] The original subgroup analysis was for patients for whom ≥3 prior prophylactic treatment categories had failed. The subgroup analysis presented in the post-appeal CS[2] was for patients for whom ≥4 individual prophylactic treatments, including botulinum toxin, had failed.

Clinical data were presented for the erenumab 140 mg and placebo groups from Study 295[8] only; data for patients treated with erenumab 70 mg are not included in the post-appeal submission.[2] This reflects the Committee's conclusion from the erenumab FAD (paragraph 3.12) that *'it was acceptable to consider only the 140 mg dose in the cost-effectiveness model.'*[5]

The key efficacy outcomes presented in the post-appeal submission[2] were mean change from baseline in monthly migraine days (MMDs) at week 12 and proportion of patients with ≥30% reduction in MMDs from baseline at week 12. This is a change from the original CS,[9] where the key outcomes were mean change from baseline in monthly migraine days (MMDs) at week 12 and proportion of patients with ≥50% reduction in MMDs from baseline at week 12.

ERG comment: The ERG agrees with the company's statement that a subgroup definition based on prior individual treatments ensures consistency between the clinical and economic analyses and is more in line with clinical practice. NICE guidance on botulinum toxin type A for the prevention of headaches in adults with chronic migraine (TA260)[10] recommends the use of botulinum toxin for the prophylaxis of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse, i.e. the definition of treatment failure is based on individual therapies rather than categories of treatment.

The ERG notes that patients in the CM ≥4 TF, including prior botulinum toxin subgroup may not be fully representative of the relevant target population, because Study 295[8] excluded patients with chronic migraine who were refractory to treatment, defined as having no therapeutic response (reduction in frequency, duration or severity of headache) to ≥3 treatment categories.

The ERG agrees that the focus on the erenumab 140 mg versus placebo comparison was appropriate.

The ERG notes that the change in efficacy outcome is in line with the view expressed by the Appraisal Committee that ≥30% reduction in MMD would be considered a clinically meaningful response to treatment in chronic migraine (erenumab FAD, paragraph 3.3).[5]

3.3.1 Baseline characteristics of Study 295

The company reported that baseline characteristics were comparable for the CM ≥4 TF, including prior botulinum toxin subgroup and the whole intention to treat (ITT) population in Study 295.[2, 8] As might be expected, patients in the CM ≥4 TF, including prior botulinum toxin subgroup had, on average, longer disease duration, were more likely to have received prior topiramate, and had slightly higher monthly usage of acute migraine-specific drugs, than the overall study population. The company further stated that, considering the small numbers of patients, baseline characteristics remained relatively well balanced across the treatment groups. Baseline characteristics, for the subgroup and ITT populations, are summarised in Table 3.3.

ERG comment: The ERG agrees with the company's statement that the overall baseline characteristics were comparable between the ITT population and the CM ≥4 TF, including prior botulinum toxin subgroup. However, the ERG notes that the lack of evidence about the effectiveness of erenumab in males and in non-white populations, identified in the ERG report,[1] is exacerbated in this very small subgroup.

The ERG notes that the original CS (Table 32, Section B.2.6.1)[9] gives the number of patients, in Study 295,[8] for whom ≥3 prior prophylactic treatment categories had failed as n=[redacted] in the placebo group and n=[redacted] in the erenumab 140 mg group, with n=[redacted] the placebo group and n=[redacted] in the erenumab 140 mg group having previously received treatment with botulinum toxin. The number of patients in the post-appeal subgroup analysis of Study 295 (CM ≥4 TF, including prior botulinum toxin) is lower, n=[redacted] in the placebo group and n=[redacted] in the erenumab 140 mg group.[2] This might appear counterintuitive, as patients who have failed ≥3 prior prophylactic treatment categories must, by definition, also have failed ≥3 prior individual prophylactic treatments. The company were asked to provide an explanation for this apparent discrepancy and, if the discrepancy arose from patients included in Study 295 who had received treatment with botulinum toxin before the fourth-line, to provide the number of patients who had failed botulinum by line of therapy. The company confirmed that, of the patients included in Study 295 for whom ≥3 prior prophylactic treatment categories had failed and who had previously received botulinum toxin, [redacted] in the placebo group and [redacted] in the erenumab 140 mg group had failed three prior prophylactic treatments including botulinum toxin, i.e. these patients had received botulinum toxin treatment before the fourth-line and hence were not included in the CM ≥4 TF, including prior botulinum toxin subgroup.[7] The company further noted that: *'As a multinational trial, study 295 was conducted at 69 centres in Canada, Czech Republic, Denmark, Germany, Finland, Norway, Poland, Sweden, United Kingdom, and the United States of America. The fact that some patients included in the trial had received botulinum toxin before having failed at least 3 oral prophylactic treatments may be a reflection of differing clinical practice and local reimbursement criteria in the participating countries.'*[7]

Table 3.3: Baseline characteristics of patients in post-hoc 'CM ≥4 TF, including prior botulinum toxin' subgroup compared to the ITT population in Study 295

Characteristic	Placebo		Erenumab 140 mg	
	Subgroup (n=[redacted])	ITT population (n=286)	Subgroup (n=[redacted])	ITT population (n=190)
Mean age, years (SD)	[redacted]	42.1 (11.3)	[redacted]	42.9 (11.1)
Range	[redacted]	18t to 66	[redacted]	18 to 64
Sex, n (%)				
Women	[redacted]	226 (79)	[redacted]	160 (84)
Men	[redacted]	60 (21)	[redacted]	30 (16)
BMI, kg/m^2 (SD)	[redacted]	26.3 (5.1)	[redacted]	26.0 (5.4)
Race, n (%)				
White	[redacted]	268 (94)	[redacted]	184 (97)
Black or African American	[redacted]	11 (4)	[redacted]	6 (3)
Asian	[redacted]	4 (1)	[redacted]	0
Other	[redacted]	3 (1)	[redacted]	0
Age at migraine onset, years (SD)	[redacted]	20.4 (10.0)	[redacted]	21.5 (10.6)
Disease duration, years (SD)	[redacted]	22.2 (12.6)	[redacted]	21.9 (11.8)
History of migraine with aura, n (%)	[redacted]	124 (43)	[redacted]	71 (37)
Ever used preventative drug topiramate, n (%)	[redacted]	150 (52)	[redacted]	97 (51)
Ever used botulinum toxin, n (%)	[redacted]	62 (23)	[redacted]	43 (23)
Baseline period, mean (SD)				
Monthly migraine days	[redacted]	18.2 (4.7)	[redacted]	17.8 (4.7)
Monthly headache days	[redacted]	21.1 (3.9)	[redacted]	20.7 (3.8)
Monthly migraine attacks	[redacted]	4.2 (1.7)	[redacted]	4.3 (1.6)
Monthly acute migraine-specific drug use days	[redacted]	9.5 (7.6)	[redacted]	9.7 (7.0)

Source: Table 1, post-appeal CS[2] and Table 8, original CS[9]
BMI: body mass index; ITT: intention to treat; SD: standard deviation

3.3.2 Clinical effectiveness results from Study 295

Patients in the erenumab 140 mg group experienced a numerically greater reduction in MMDs, from baseline to week 12, compared to placebo least squares mean (LSM) difference [redacted] days (95% CI: [redacted]; p=[redacted]) and a statistically significantly higher response rate, where response was

defined as a ≥30% reduction in MMDs at week 12, odds ratio (OR) [redacted] (95% CI: [redacted]; p=[redacted]).[2] Clinical effectiveness results for erenumab 140 mg compared to placebo, in the CM ≥4 TF, including botulinum toxin subgroup, are summarised in Table 3.4.

ERG comment: The ERG notes that, as stated by the company, *'Study 295 was not designed or powered to assess the efficacy of erenumab specifically in the CM ≥4 TF, including botulinum toxin subgroup and the data presented for this subgroup are from a post-hoc analysis.'*[2]

The ERG further notes that, as was the case for the subgroup presented in the original CS,[9] the post-appeal CS[2] did not include any data on the long-term (>12 weeks) effectiveness of erenumab compared to placebo in the CM ≥4 TF, including botulinum toxin subgroup.

Table 3.4: Clinical efficacy results from Study 295 post-hoc CM ≥4 TF, including prior botulinum toxin subgroup

Outcome	Placebo (n=[redacted])	Erenumab 140mg (n=[redacted])
Change from baseline in MMDs at Week 12[a]		
Baseline, mean (SD)	[redacted]	[redacted]
LSM (SE)	[redacted]	[redacted]
LSM difference versus placebo (95% CI)	NA	[redacted]
p-value	NA	[redacted]
Proportion of patients with ≥30% reduction in MMDs from baseline at Week 12[b]		
n (%)	[redacted]	[redacted]
Difference versus placebo (%)	NA	[redacted]
Odds ratio (95% CI)	NA	[redacted]
p-value	NA	[redacted]

Source: Tables 1 and 3, post-appeal CS[2]

[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.

[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 region and medication overuse.

CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; SE: standard error.

3.3.3 Adverse events

The post-appeal CS[2] did not include any information about adverse events for the CM ≥4 TF, including prior botulinum toxin subgroup of patients with chronic migraine, treated with erenumab 140 mg.

3.3.4 'Real-world evidence'

The TLR, conducted by the company,[2] identified one 'real-world' study conducted in the UK.[11] This ongoing, open-label, prospective study was presented at the 2019 International Headache Congress. The study included 75 patients with chronic migraine, who had failed at least three prophylactic treatments and failed botulinum toxin,[11] (equivalent to the CM ≥4 TF, including prior botulinum toxin subgroup population from Study 295) who received at least one erenumab 70 mg treatment. Thirty-seven patients completed the three-month trial period; no reasons for non-completion were reported.

The baseline MMD was 20.3 and the MMD at three months was 14.2 (mean change -6.1 days).[11] Nineteen patients (51.4%) achieved a reduction in migraine days ≥30%.[11] Adverse events were reported by 24/37 (64.9%) of patients and these were described as *'mostly mild'*.[11]

BASH provided additional information from a survey of UK centres that have been using erenumab under the existing free-of-charge (FOC) scheme. BASH asked UK centres to provide data on the efficacy of erenumab 140 mg in patients who have failed preventive treatment with botulinum toxin and the submission includes the following responses from four centres:[3]

'Guy's & St Thomas's, London - 121 patients (85.1% female, average age 46 yr) who had tried and failed ≥3 preventive medications, and Botox, were treated with erenumab for six months. At 3 months, 50% of patients had ≥30% reduction in migraine days, with 36% having ≥50% reduction. At 6 months, 56% of patients had ≥30% reduction in migraine days, with 32% having ≥50% reduction in migraine days. 14/121 patients discontinued due to lack of efficacy. 8/121 patients discontinued because of side effects (all minor).'

'Manchester - 44 patients were treated with erenumab on the FOC scheme. They were a refractory group, having tried a median of 9 different preventative therapies including Botox (range 4-13). At 10 weeks, 21/44 had ≥30% reduction in severe headache days; 11/44 had ≥30% reduction in total headache days. At 18 weeks, 24/44 had ≥30% reduction in severe headache days; 15/44 had ≥30% reduction in total headache days. As of 25/03/2020, of 44 patients who started it, 20 remain on it for a median of 55 weeks (mode 55 weeks (range 25-57 weeks)). Reasons for cessation included lack of efficacy, waning of efficacy, and side effects.'

'Plymouth - 107 patients who had previously tried and received Botox without significant improvement in their headaches, were treated with erenumab, and followed-up for an average of 5 months. The population was predominantly female (80.4%) with a mean age of 50.3. Most had trialled multiple previous migraine treatments, including prescription medication (median=6 migraine-specific preventatives), trigger point injections (81.3%) and herbal/holistic therapies (53.3%). By the end of the treatment phase, 31/107 (28.9%) had a ≥50% reduction in migraine days, and 52/107 (48.5%) had a ≥50% increase in pain-free days. There were also significant improvements in triptan days, painkiller days, headache impact test (HIT-6) score, PHQ-9 scores and pain disability index scores. Only 3 patients ceased treatment due to minor side effects.'

'King's College London - Of the 75 patients treated under the FOC scheme, 43 patients had previously failed to respond to a median of 6 preventive treatments, and Botox. At 3 months, 16/43 (37%) achieved a ≥30% reduction in migraine days. Constipation was the commonest side effect in the entire King's cohort (21%), but all side effects were minor.'

The submission from BASH[3] also noted two further, non-UK, 'real-world' studies,[12, 13] presented at the 2019 International Headache Congress.

A single-centre, retrospective, database study, conducted in the Netherlands assessed the efficacy and safety of erenumab in patients with chronic migraine who had failed at least three prophylactic treatments and failed botulinum toxin.[12] In the Netherlands, national guidelines recommend topiramate as the first-line prophylactic therapy for chronic migraine, with botulinum toxin recommended as second-line therapy. However, reimbursement for botulinum toxin requires failure of at least three prior prophylactic treatments. 47/152 chronic migraine patients were treated with botulinum toxin, of whom 14 (30%) failed to respond and were treated with erenumab (dose not specified.[12] At three months follow-up there was a *'significant improvement'* in 11/14 (79%) of erenumab-treated patients and the remaining three patients discontinued due to lack of efficacy.[12] No definition of *'significant improvement'* was provided.

A cohort of 109 refractory migraine patients from three Australian headache centres, all of whom had failed ≥3 prophylactic treatments, were treated with erenumab (dose not specified).[13] 105/109 (96%) of patients had tried botulinum toxin, of whom 38/105 (36.2%) failed to respond. An erenumab response rate (≥50% reduction in MMD) of 21/35 (60%) was reported for the failed botulinum toxin subgroup.[13]

ERG comment: The ERG acknowledges that the 'real-world' evidence, summarised above, provides some additional support for the efficacy of erenumab treatment in the highly refractory population of patients with chronic migraine who have failed at least three prophylactic treatments and have also failed botulinum toxin treatment (see summary in Table 3.5). The ERG also notes that the 'real-world' evidence from UK centres participating in the FOC scheme, provided by BASH, includes some indication of longer-term efficacy (18-weeks to six months). Although the ERG also notes that the response from the Manchester centre lists *'waning of efficacy'* among the reasons for discontinuation, this is not demonstrated in the apparent increase in the number of responders, between 10 weeks and 18 weeks, reported by this centre.

Table 3.5: Comparison between Study 295 and real-world evidence

Outcome	Erenumab 140mg outcome
Change from baseline in MMDs at Week 12	
Study 295, week 12	[redacted]
Published RWS[a]	-6.1
Proportion of patients with ≥30% reduction in MMDs from baseline at approximately Week 12	**N(%)**
Study 295[b] - week 12	[redacted]
Published RWS[a] - 3 months	19 (51.4)
Guy's & St Thomas's, London[c] -3 months	(50)
Manchester[c] – 10 weeks; 18 weeks	21 (47.7); 24 (54.5)
King's College London[c] – 3 months	16/43 (37.2)

Source: [a]published real world study[11]: note that does of erenumab was 70mg; [b]Tables 1 and 3, post-appeal CS[2]; [c]BASH[3]: note that reported outcome for Manchester is ≥30% reduction in severe headache days.

CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; RWS: real world study; SE: standard error.

3.4 Summary and critique of the clinical effectiveness evidence submitted for erenumab for the treatment of chronic migraine, in people for whom botulinum toxin is contraindicated

The post-appeal CS[2] included a third subgroup analysis of Study 295,[8] in addition to those described above (Section 3.3) and in section B.2.6.1 of the original CS.[9] This third subgroup analysis was for patients for whom ≥3 individual prophylactic treatments had failed and who had not received botulinum toxin (CM ≥3 TF, no prior botulinum toxin). The company stated that: '*evidence from this subgroup is provided as a proxy for the clinical and cost-effectiveness of erenumab in a subgroup of patients with chronic migraine who are not eligible to receive botulinum toxin due to contraindication/unsuitability. It should be noted that data are not available specifically for patients treated with erenumab who are known to have a contraindication/unsuitability for botulinum toxin; the presented subgroup data in patients with chronic migraine who have three or more prior treatment failures and no prior receipt of botulinum toxin is considered to act as a proxy for this population.* '[2]

As was the case for the CM ≥4 TF, including botulinum toxin subgroup, clinical data were presented for the erenumab 140 mg and placebo groups from Study 295 only; data for patients treated with erenumab 70 mg are not included in the post-appeal submission.[2] This reflects the Committee's conclusion from the erenumab FAD (paragraph 3.12) that *'it was acceptable to consider only the 140 mg dose in the cost-effectiveness model.'*[5]

Similarly, as was the case for the CM ≥4 TF, including botulinum toxin subgroup, the key efficacy outcomes presented in the post-appeal submission[2] were mean change from baseline in monthly migraine days (MMDs) at week 12 and proportion of patients with ≥30% reduction in MMDs from baseline at week 12. This is a change from the original CS,[9] where the key outcomes were mean change from baseline in monthly migraine days (MMDs) at week 12 and proportion of patients with ≥50% reduction in MMDs from baseline at week 12.

ERG comment: As stated in section 3.1, the ERG questions the validity of non-receipt of botulinum toxin treatment, for patients with chronic migraine and three or more prior prophylactic treatment failures, as a proxy for botulinum toxin contraindicated. The ERG questions the underlying assumption that contraindication was the only reason why any patient in Study 295, with three or more prior prophylactic treatment failures, had not previously received botulinum toxin.

The ERG also notes that, irrespective of the validity of the proxy, patients in the CM ≥3 TF, no prior botulinum toxin subgroup may not be fully representative of the relevant target population, because Study 295[8] excluded patients with chronic migraine who were refractory to treatment, defined as having no therapeutic response (reduction in frequency, duration or severity of headache) to ≥3 treatment categories.

The ERG agrees that the focus on the erenumab 140 mg versus placebo comparison was appropriate.

The ERG notes that the change in efficacy outcome is in line with the view expressed by the Appraisal Committee that ≥30% reduction in MMD would be considered a clinically meaningful response to treatment in chronic migraine (erenumab FAD, paragraph 3.3).[5]

3.4.1 Baseline characteristics of Study 295

The company reported that baseline characteristics were comparable for the CM ≥3 TF, no prior botulinum toxin subgroup and the whole intention to treat (ITT) population in Study 295.[2, 8] As might be expected, patients in the CM ≥3 TF, no prior botulinum toxin subgroup were more likely to have received prior topiramate and had slightly higher monthly usage of acute migraine-specific drugs, than the overall study population. The company further stated that, considering the small numbers of patients, baseline characteristics remained relatively well balanced across the treatment groups. Baseline characteristics, for the subgroup and ITT populations, are summarised in Table 3.6.

ERG comment: The ERG agrees with the company's statement that the overall baseline characteristics were comparable between the ITT population and the CM ≥3 TF, no prior botulinum toxin subgroup. However, the ERG notes that the lack of evidence about the effectiveness of erenumab in males and in non-white populations, identified in the ERG report,[1] is exacerbated in this very small subgroup.

Table 3.6: Baseline characteristics of patients in post-hoc 'CM ≥3 TF, no prior botulinum toxin' subgroup compared to the ITT population in Study 295

Characteristic	Placebo		Erenumab 140 mg	
	Subgroup (n=[redacted])	ITT population (n=286)	Subgroup mg (n=[redacted])	ITT population (n=190)
Mean age, years (SD)	[redacted]	42.1 (11.3)	[redacted]	42.9 (11.1)
Range	[redacted]	18t to 66	[redacted]	18 to 64
Sex, n (%)				
Women	[redacted]	226 (79)	[redacted]	160 (84)
Men	[redacted]	60 (21)	[redacted]	30 (16)
BMI, kg/m^2 (SD)	[redacted]	26.3 (5.1)	[redacted]	26.0 (5.4)
Race, n (%)				
White	[redacted]	268 (94)	[redacted]	184 (97)
Black or African American	[redacted]	11 (4)	[redacted]	6 (3)
Asian	[redacted]	4 (1)	[redacted]	0
Other	[redacted]	3 (1)	[redacted]	0
Age at migraine onset, years (SD)	[redacted]	20.4 (10.0)	[redacted]	21.5 (10.6)
Disease duration, years (SD)	[redacted]	22.2 (12.6)	[redacted]	21.9 (11.8)
History of migraine with aura, n (%)	[redacted]	124 (43)	[redacted]	71 (37)
Ever used preventative drug topiramate, n (%)	[redacted]	150 (52)	[redacted]	97 (51)
Ever used botulinum toxin, n (%)	[redacted]	62 (23)	[redacted]	43 (23)
Baseline period, mean (SD)				
Monthly migraine days	[redacted]	18.2 (4.7)	[redacted]	17.8 (4.7)
Monthly headache days	[redacted]	21.1 (3.9)	[redacted]	20.7 (3.8)
Monthly migraine attacks	[redacted]	4.2 (1.7)	[redacted]	4.3 (1.6)
Monthly acute migraine-specific drug use days	[redacted]	9.5 (7.6)	[redacted]	9.7 (7.0)

Source: Table 2, post-appeal CS[2] and Table 8, original CS[9]
BMI: body mass index; ITT: intention to treat; SD: standard deviation

3.4.2 Clinical effectiveness results from Study 295

Patients in the erenumab 140 mg group experienced a statistically significantly greater reduction in MMDs, from baseline to week 12, compared to placebo LSM difference [redacted] days (95% CI: [redacted]; p=[redacted]) and a statistically significantly higher response rate, where response was

defined as a ≥30% reduction in MMDs at week 12, OR [redacted] (95% CI: [redacted]; p=[redacted]).[2] Clinical effectiveness results for erenumab 140 mg compared to placebo, in the CM ≥3 TF, no prior botulinum toxin subgroup, are summarised in Table 3.7.

ERG comment: The ERG notes that, as was the case for the subgroup presented in the original CS,[9] the post-appeal CS[2] did not include any data on the long-term (>12 weeks) effectiveness of erenumab compared to placebo in the CM ≥3 TF, no prior botulinum toxin subgroup.

Table 3.7: Clinical efficacy results from Study 295 post-hoc CM ≥3 TF, no prior botulinum toxin subgroup

Outcome	Placebo (n=[redacted])	Erenumab 140mg (n=[redacted])
Change from baseline in MMDs at Week 12[a]		
Baseline, mean (SD)	[redacted]	[redacted]
LSM (SE)	[redacted]	[redacted]
LSM difference versus placebo (95% CI)	NA	[redacted]
p-value	NA	[redacted]
Proportion of patients with ≥30% reduction in MMDs from baseline at Week 12[b]		
n (%)	[redacted]	[redacted]
Difference versus placebo (%)	NA	[redacted]
Odds ratio (95% CI)	NA	[redacted]
p-value	NA	[redacted]

Source: Tables 1 and 4, post-appeal CS[2]

[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.

[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 region and medication overuse.

CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; NA: not applicable; SE: standard error.

3.4.3 Adverse events

The post-appeal CS[2] did not include any information about adverse events for the CM ≥3 TF, no prior botulinum toxin subgroup of patients with chronic migraine, treated with erenumab 140 mg.

4. Cost effectiveness

The company's economic model, used to conduct cost-effectiveness analyses for this post-appeal submission, is identical to the latest model submitted to NICE prior to the third Appraisal Committee meeting in August 2019. As mentioned in ERG addendum 3 (in response to the e-mail from NICE on February 11th, 2019), the base-case proposed by the company at that time was consistent with most of the adjustments suggested by the ERG. The only relevant difference was the assumption of no treatment effect waning but in the post-appeal submission this is now, given committee preferences, consistent with the ERG preferences (see Section 4.11 below). The only post-appeal update is the incorporation of clinical effectiveness subgroup data from Study 295 for chronic migraine patients by prior or no prior use of botulinum toxin and for chronic migraine patients with ≥4 prior prophylactic treatment failures.

4.1.1 Model structure

The company developed a decision-tree plus state transition model in Microsoft Excel. 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.

4.1.1 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.

Response was assessed at the end of the assessment period and was defined as a ≥30% reduction from baseline MMD.

4.1.2 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, 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 (or death). Patients who discontinued treatment were assumed to rebound to the non-responder MMDs distribution.

In the Final Appraisal Document (FAD) it was stated that the Committee concluded that the company's updated model using a lifetime time horizon was appropriate.

4.2 Population

In their post-appeal submission, the company assessed the cost effectiveness of erenumab in two subgroups of patients with chronic migraine (15 headache days a month or more of which at least eight are migraine):

- Adults with chronic migraine and ≥4 prophylactic treatment (e.g. topiramate, propranolol and amitriptyline) failures including botulinum toxin. In this subgroup, all patients have a history

of botulinum toxin, which was discontinued due to lack of efficacy, unacceptable tolerability and/or other reasons (CM ≥4 TF, including botulinum toxin subgroup).

- Adults with chronic migraine and ≥3 prophylactic treatment failures without prior receipt of botulinum toxin. This subgroup is used as a proxy for the clinical and cost effectiveness of erenumab in patients with chronic migraine who are not eligible for botulinum toxin due to contraindication/unsuitability (CM ≥3 TF, no prior botulinum toxin subgroup).

4.3 Interventions and comparators

Erenumab is self-administered subcutaneously and is modelled using the 140mg every four weeks (Q4W) dosage in combination with BSC. BSC was defined as continued treatment with acute medication.

In the FAD, the Committee concluded that it was acceptable to consider only the 140 mg dose in the cost-effectiveness model.

4.4 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 lifetime time horizon, and a half-cycle correction was applied.

4.5 Treatment effectiveness and extrapolation

In the model, response was defined as a ≥30% reduction from baseline MMD at week 12. Applying the negative stopping based on ≥30% reduction was considered appropriate by the Committee. 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. 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).

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. 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 (Table 4.1).

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 (i.e. assuming not treatment waning over time).

In the FAD it is stated that the long-term comparative effectiveness of erenumab is unknown and the Committee was aware that in other chronic conditions the effects of monoclonal antibodies can wane over time. Nevertheless, based on evidence available, the Committee considered that while people stay on treatment, it is reasonable to assume that the treatment effect does not wane over time.

Table 4.1: Response probability and mean MMD

		CM ≥4 TF, including botulinum toxin subgroup	CM ≥3 TF, no prior botulinum toxin subgroup
Probability of response			
Erenumab 140mg		[redacted]	[redacted]
BSC		[redacted]	[redacted]
Mean MMD by health state			
Baseline MMD	Treatment independent	[redacted]	[redacted]
Responder MMD	Erenumab 140 mg	[redacted]	[redacted]
	BSC	[redacted]	[redacted]
Non-responders MMD	Erenumab 140 mg	[redacted]	[redacted]
	BSC	[redacted]	[redacted]
BSC: best supportive care; CM: chronic migraine; MMD: monthly migraine days			

4.6 Adverse events

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. 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 [redacted] in Study 295, ARISE, STRIVE and LIBERTY). However, 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 from the original submission, the serious adverse events may be as high as [redacted] and [redacted] for erenumab 70 mg and 140 mg respectively.[14] 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.

In the FAD, the Committee concluded that the adverse events in the trials with erenumab were generally not severe and were comparable with placebo, and erenumab was generally well tolerated in the studied populations.

4.7 Health-related quality of life

Treatment independent utility values for each MMD frequency were estimated based on Study 295. Utility values were subsequently estimated based on the MMD frequency distributions.

For estimating the utility values for each MMD frequency the company mapped migraine-specific quality of life questionnaire (MSQ) data collected in Study 295 to EQ-5D-3L utility values using the mapping algorithm described by Gillard et al. 2012[15]. 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 (collected in LIBERTY).

The mapped MSQ utility values were used to fit multilevel models estimating disutility values associated with each MMD frequency. Subsequently the coefficients of the multilevel model (β0, intercept = [redacted]; β1, utility reduction per MMD = [redacted]) can be used to estimate utility per MMD frequency (i.e. utility = 1- (β0 + (β1×MMD frequency))). Health state utility values were subsequently

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 4.2.

Table 4.2: Health state utility values (conditional on MMD distributions)

		CM ≥4 TF, including botulinum toxin subgroup	CM ≥3 TF, no prior botulinum toxin subgroup
Health state utility values (conditional on MMD distributions)			
Baseline MMD	Treatment independent	[redacted]	[redacted]
Responder MMD	Erenumab 140 mg	[redacted]	[redacted]
	BSC	[redacted]	[redacted]
Non-responders MMD	Erenumab 140 mg	[redacted]	[redacted]
	BSC	[redacted]	[redacted]
BSC: best supportive care; CM: chronic migraine; MMD: monthly migraine days			

In the FAD, the Committee agreed that the rationale for using MSQ instead of direct EQ-5D-5L data was plausible. However, the Committee considered that the actual utility values generated from mapping the MSQ data to EQ-5D-3L may be underestimates. Moreover, the Committee noted that the utility data were a key driver of the cost effectiveness estimates and it was concerned about the reliability of the values given the uncertainty of using data from a broader population and mapping this to EQ-5D-3L. On balance, it was concluded that the utility values used in the model may be reasonable but were uncertain.

4.8 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). The costs and resource use related to adverse events were not explicitly included in the cost effectiveness analysis.

The patient access scheme (PAS) price per erenumab 140 mg dose is [redacted] (simple discount).

In the FAD it was mentioned that all relevant costs for implementing erenumab in practice are captured in the model.

4.9 Cost effectiveness results

4.9.1 Company's cost effectiveness results

In the deterministic base-case analysis of the subgroup of adults with chronic migraine and ≥4 prophylactic treatment failures including botulinum toxin, total QALYs gained and total costs were larger for erenumab than for BSC. The deterministic ICER amounted to [redacted] per QALY gained. Also, in the deterministic base-case analysis of the subgroup of adults with chronic migraine and ≥3 prophylactic treatment failures who are ineligible for botulinum toxin, total QALYs gained and total costs were larger for erenumab than for BSC. The deterministic ICER amounted to [redacted] per QALY gained (Table 4.3).

Table 4.3: Deterministic company results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CM ≥4 TF, including botulinum toxin subgroup					
Company base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming rebound to baseline MMDs after discontinuation					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM ≥3 TF, no prior botulinum toxin subgroup					
Company base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming rebound to baseline MMDs after discontinuation					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; CM: chronic migraine; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

4.9.2 Scenario analyses assuming patients who discontinue treatment rebound to baseline MMDs

The company conducted scenario analyses for both subgroups in which patients who discontinue treatment were assumed to rebound to baseline MMDs, rather than maintain the non-responder MMD improvement achieved at week 12 (as in the base-case). In the subgroup of adults with chronic migraine and ≥4 prophylactic treatment failures including botulinum toxin, this resulted in an ICER of [redacted] per QALY gained. In the subgroup of adults with chronic migraine and ≥3 prophylactic treatment failures who are ineligible for botulinum toxin, this resulted in an ICER of [redacted] per QALY gained (Table 4.3).

4.10 Model validity

The ERG (as reported in the original ERG report) was able to independently rebuild the original cohort analysis and recalculate the estimated QALYs for the company base-case. Given the company indicated that the economic model used is identical to the latest model submitted to NICE prior to the third Appraisal Committee meeting in August 2019 (the only update being the incorporation of clinical effectiveness subgroup data from Study 295), this supports the internal validity of the model.

No cross or external validation was reported by the company.

4.11 Evidence review group's cost effectiveness results

In the original ERG report it was highlighted that the main uncertainty in this cost effectiveness assessment is the extrapolation of treatment effectiveness. Consistently, the original ERG report reported the ERG base-case with and without treatment waning. However, given that the Committee considered that, while people stay on treatment, it is reasonable to assume that the treatment effect does not wane over time, the post-appeal ERG preferences include a base-case without treatment waning. Nevertheless, the treatment waning analysis is presented for both subgroups for completeness. In this treatment waning scenario, health state costs and utilities gradually revert to BSC non-responder values (over a specific treatment waning period) to reflect the loss of treatment effect while treatment costs continue to accumulate. Additionally, as mentioned in the original ERG report, it is also questionable whether extrapolating benefits for non-responders (i.e. in MMD frequency distribution) is plausible (for the CM ≥4 TF, including botulinum toxin subgroup the non-responder mean MMD are [redacted] and [redacted] for erenumab and BSC respectively). This is mitigated in the company's scenario analysis assuming rebound to baseline MMDs after discontinuation (see section 4.9) and to some extent mitigated in the treatment waning scenario given the decreased MMD frequency distributions benefits over time.

As mentioned in ERG addendum 3 (in response to the e-mail from NICE on 11 February 2019), the new base-case proposed by the company is consistent with most of the original ERG adjustments. The only relevant difference is the assumption of no treatment effect waning but this is now, given the Committee's preferences, consistent with the ERG preferences (as discussed above). Therefore, the ERG analyses consisted of probabilistic results of the company base-case as well as probabilistic results of the scenario analyses 1) assuming patients who discontinue treatment were assumed to rebound to baseline MMDs (as presented by the company) and; 2) assuming treatment waning over five years.

Table 4.4 indicates that the ERG's probabilistic results are in line with the deterministic results reported by the company. The company base-case (and now also the ERG's preferred analysis) indicates probabilities of [redacted] for erenumab 140 mg to be cost effective at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively in the CM ≥4 TF, including botulinum toxin subgroup while for the CM ≥3 TF, no prior botulinum toxin subgroup these probabilities were [redacted] respectively. The treatment waning scenarios, added by the ERG, substantially increased the estimated ICER to [redacted] per QALY gained for the CM ≥4 TF, including botulinum toxin subgroup and the CM ≥3 TF, no prior botulinum toxin subgroup respectively.

Table 4.4: Probabilistic results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CM ≥4 TF, including botulinum toxin subgroup					
Company base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming rebound to baseline MMDs after discontinuation					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming treatment waning over five-year					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM ≥3 TF, no prior botulinum toxin subgroup					
Company base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming rebound to baseline MMDs after discontinuation					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario assuming treatment waning over five-year					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; CM: chronic migraine; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

5. Conclusions regarding the additional clinical effectiveness and cost effectiveness evidence submitted

The new company base-case is consistent with most of the original ERG adjustments, i.e. those that were recommended by the ERG before the appeal. The only relevant difference is the assumption of no treatment effect waning but this is now, given the Committee's preferences, consistent with the ERG preferences. The ERG preferences and the company base-case are now aligned and resulted in probabilistic ICERs of [redacted] per QALY gained for the CM ≥4 TF, including botulinum toxin subgroup and the CM ≥3 TF, no prior botulinum toxin subgroup respectively. Nevertheless, it is important to consider the limitations in the clinical evidence when interpreting these results. These limitations include the sample size of the subgroups considered; consistent with the European Public Assessment Report (EPAR) for erenumab it can be debated whether these small subgroups can be analysed in a meaningful way. Moreover, Study 295 (focussed on patients with chronic migraine) excluded people with no therapeutic response to >3 previous treatments (i.e. potentially excluded the most refractory patients). Given the selected population, the representativeness of Study 295 results (and thus the calculated ICERs) to UK clinical patients (which includes people with no therapeutic response to >3 previous treatments) are considered uncertain. In addition, the CM ≥4 TF, including botulinum toxin subgroup appears to have included some patients ([redacted]) who had discontinued botulinum toxin for reasons other than treatment failure. Non-receipt of botulinum toxin treatment, for patients with chronic migraine and three or more prior prophylactic treatment failures, has questionable validity as a proxy for botulinum toxin being contraindicated. There are a number of possible reasons, other than contraindications, for non-receipt of botulinum toxin treatment, including variations in the availability/provision of botulinum toxin treatment services within the UK NHS. Finally, as was the case for the subgroup presented in the original CS,[9] the post-appeal CS[2] did not include any data on the long-term (>12 weeks) effectiveness of erenumab compared to placebo in either the CM ≥4 TF, including botulinum toxin subgroup or the CM ≥3 TF, no prior botulinum toxin subgroup.

In conclusion, despite the company base-case and the ERG preferences being aligned, there remains uncertainty (that is not quantified in the health economic analyses) regarding the evidence used (from Study 295) and thus the interpretation of these results.

6. References

[1] Westwood M, Ramaekers BLT, Petersohn S, Grimm S, Pouwels X, Witlox W, et al. *Erenumab for preventing migraine: A Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd, 2018. 118p.

[2] Novartis Pharmaceuticals UK Ltd. *Single technology appraisal (STA). Erenumab for preventing migraine [ID1188]. Post-appeal company evidence submission*. Camberley: Novartis, 2020. 21p.

[3] British Association for the Study of Headache. *Professional organisaiton submission. Erenumab for preventing migraine [ID1188]*. Hull: BASH, 2020. 15p.

[4] The Migraine Trust. *Patient organisation submission. Erenumab for preventing migraine [ID1188]*. London: The Migraine Trust, 2020. 17p.

[5] National Institute for Health and Care Excellence. *Final appraisal document - Erenumab for preventing migraine*. London: NICE, 2019. 27p.

[6] National Institute for Health and Care Excellence. *Single technology appraisal appeal hearing. Advice on erenumab for preventing migraine [ID1188]*. London: NICE, 2019. 11p.

[7] Novartis Pharmaceuticals UK Ltd. *Erenumab for preventing migraine [ID1188] - post-appeal. Response to request for clarification from the ERG*. London: Novartis, 2020. 7p.

[8] Amgen. *A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AMG 334 in chronic migraine prevention. Clinical study report: 20120295*. Thousand Oaks (CA): Amgen, 2016. 868p.

[9] 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*. Camberley: Novartis 2018. 200p.

[10] 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

[11] Lambru G, Hill B, Murphy M, Andreou AP. Erenumab for the treatment of refractory chronic migraine: a UK prospective real world experience. Poster presented at 19th Congress of the International Headahce Society, IHC 2019; 5-8 September 2019; Dublin (Ireland). 2019.

[12] Proot P. How effective is erenumab for patients with chronic migraine who failed on onabotulinum toxin in type A as prophylactic treatment? Poster presented at the 19th Congress of the International Headache Society, IHC 2019; 5-8 September 2019; Dublin (Ireland). 2019.

[13] Jenkins B, Cheng S, Limberg N, Hutton E. Will refractory migraine patiends in the real world respond to erenumab? Poster presented at the 19th Congress of the International Headache Society, IHC 2019; 5-8 September 2019; Dublin (Ireland). 2019.

[14] Novartis Pharmaceuticals UK Ltd. *Erenumab for preventing migraine [ID1188]. Response to request for clarification from the ERG*. Camberley: Novartis, 2018. 147p.

[15] 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.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Erenumab for preventing migraine [ID1188]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Monday 15 June** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Data reporting inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 and page 30: "In addition, the CM ≥4 TF, including botulinum toxin subgroup appears to have included some patients ([redacted]) who had discontinued botulinum toxin for reasons other than treatment failure." Page 12: "The ERG notes that, from the information provided above, it appears that [redacted] of patients included in the CM ≥4 TF, including prior botulinum toxin subgroup did not meet the definition of having failed botulinum toxin treatment, i.e. these patients had discontinued botulinum toxin for reasons other than treatment failure."	Please amend as follows: Page 9 / Page 30: "In addition, the CM ≥4 TF, including botulinum toxin subgroup appears to have included some patients ~~([redacted])~~ ([redacted] ***in the erenumab 140 mg treatment group;*** [redacted] ***in the placebo group)*** who had discontinued botulinum toxin for reasons other than treatment failure." Page 12: "The ERG notes that, from the information provided above, it appears that [redacted] ***([redacted] in the erenumab 140 mg treatment group;*** [redacted] ***in the placebo group)*** of patients included in the CM ≥4 TF, including prior botulinum toxin subgroup did not meet the definition of having failed botulinum toxin treatment, i.e. these patients had discontinued botulinum toxin for reasons other than treatment failure."	Due to the imbalance between the erenumab 140 mg and placebo groups in the trial with regard to the proportion of patients who had discontinued botulinum toxin for reasons other than treatment failure, the data should be stated separately by treatment arm.	Not a factual inaccuracy.
Page 17: "Thirty-seven patients completed the three-month trial period; no reasons for non-completion were reported."	Please amend as follows: "Thirty-seven patients completed the three-month trial period; ~~no reasons for non-completion were reported~~ ***the disposition of the remaining patients (discontinued treatment or not yet completed three-month trial period at time of analysis) was not reported.***"	The status of the study is described as ongoing. The ERG report suggests that all patients not included in the three-month analysis had discontinued erenumab treatment early; however, some or all of these patients might not have been included in the analysis as they had not completed the	Not a factual inaccuracy. Indeed, as the company have identified, it is unclear whether patients have not completed due to insufficient follow-up or not.

		three-month treatment duration at the time of the analysis, given the ongoing nature of the study.	
Page 17: "The baseline MMD was 22.4 and the MMD at three months was 14.2 (mean change -6.1 days).[11]"	Please amend as follows: "The baseline MMD was ~~22.4~~ ***20.3*** and the MMD at three months was 14.2 (mean change -6.1 days).[11]"	The number stated in the ERG report is not the correct figure for baseline MMD.	Corrected.
Page 19: "However, the ERG also notes that the response from the Manchester centre lists *'waning of efficacy'* among the reasons for discontinuation, which seems to be consistent with the apparent decrease in the number of responders, between 10 weeks and 18 weeks, reported by this centre."	Please amend as follows: "However, the ERG also notes that the response from the Manchester centre lists *'waning of efficacy'* among the reasons for discontinuation, ***but no information is provided on the number of patients this applied to*** ~~which seems to be consistent with the apparent decrease in the number of responders, between 10 weeks and 18 weeks, reported by this centre~~."	The second part of the sentence does not seem to be correct, based on the data reported on page 18 and in Table 3.5 on page 19 of the ERG report. Rather than *decreasing*, the reported data indicate that both the proportion of patients who experienced a ≥30% reduction in severe headache days and the proportion of patients who experienced a ≥30% reduction in total headache days *increased* from week 10 to week 18 (from 21/44 to 24/44 and from 11/44 to 15/44, respectively). As the second part of the sentence no longer supports the first, it should be made clear that no information is available on how many	Amended to: 'Although the ERG also notes that the response from the Manchester centre lists 'waning of efficacy' among the reasons for discontinuation, this is not demonstrated in the apparent increase in the number of responders, between 10 weeks and 18 weeks, reported by this centre.'

<table>
<tr>
<td></td>
<td></td>
<td>patients at the Manchester centre discontinued treatment due to waning of efficacy.</td>
<td></td>
</tr>
<tr>
<td>Page 19:

Table 3.1: Comparison between Study 295 and real-world evidence
<table>
<tr><th>Outcome</th><th>Erenumab 140mg outcome</th></tr>
<tr><td>Change from baseline in MMDs at Week 12</td><td></td></tr>
<tr><td>Study 295, week 12</td><td>[redacted]</td></tr>
<tr><td>Published RWS[11]</td><td>[redacted]</td></tr>
<tr><td>Proportion of patients with ≥30% reduction in MMDs from baseline at approximately Week 12</td><td>N(%)</td></tr>
<tr><td>Study 295[a] - week 12</td><td>[redacted]</td></tr>
</table></td>
<td>Please amend as follows:

Table 3.2: Comparison between Study 295 and real-world evidence
<table>
<tr><th>Outcome</th><th>Erenumab 140mg outcome</th></tr>
<tr><td>Change from baseline in MMDs at Week 12</td><td></td></tr>
<tr><td>Study 295, week 12 (baseline MMDs: [redacted])</td><td>[redacted]</td></tr>
<tr><td>Published RWS[b] [11] (baseline MMDs: 20.3)</td><td>[redacted]
-6.1</td></tr>
<tr><td>Proportion of patients with ≥30% reduction in MMDs from baseline at approximately Week 12</td><td>N(%)</td></tr>
</table></td>
<td>1) To put the change from baseline MMDs into context, we propose to state also the baseline MMDs in the table.

2) The reported change from baseline MMDs for the “Published RWS” is incorrect (the stated data represents the LSM difference vs placebo from study 295). The correct number from the published RWS is -6.1 days.

3) The table headers state that all data are for the erenumab 140 mg dose and that the responder rates represent the proportion of patients with ≥30% reduction in MMDs. However, this does not apply to the Published RWS, which reports data for the 70 mg dose of erenumab, and to the responder data from the centre in Manchester, which is for a ≥30% reduction in severe headache days. Explanatory footnotes have been added to the amended</td>
<td>Corrected and footnotes added.</td>
</tr>
</table>

<table><tr><td>Published real world study[b] - 3 months</td><td>19 (51.4)</td></tr><tr><td>Guy's & St Thomas's, London[c] -3 months</td><td>(50)</td></tr><tr><td>Manchester[c] – 10 weeks; 18 weeks</td><td>21 (47.7); 24 (54.5)</td></tr><tr><td>King's College London[c] – 3 months</td><td>16/43 (37.2)</td></tr><tr><td colspan="2">Source: [a]Tables 1 and 3, post-appeal CS[2]; [b]published real world study[11]; [c]BASH[3] CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; SE: standard error.</td></tr></table>	<table><tr><td>Study 295[a] - week 12</td><td>[redacted]</td></tr><tr><td>Published real world study[b] - 3 months</td><td>19 (51.4)</td></tr><tr><td>Guy's & St Thomas's, London[c] -3 months</td><td>(50)</td></tr><tr><td>Manchester[c] – 10 weeks; 18 weeks</td><td>21 (47.7); 24 (54.5)</td></tr><tr><td>King's College London[c] – 3 months</td><td>16/43 (37.2)</td></tr><tr><td colspan="2">Source: [a]Tables 1 and 3, post-appeal CS[2]; [b]published real world study[11] ***Note that dose was erenumab 70 mg***; [c]BASH[3] ***Note that reported outcome for Manchester is ≥30% reduction in severe headache days.*** CI: confidence interval; CMH: Cochran-Mantel-Haenszel; LSM: least squares mean; MMD: monthly migraine day; SE: standard error.</td></tr></table>	version of the table.	
Page 25: "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 [redacted] in Study 295, ARISE, STRIVE and LIBERTY). However, when considering the population for whom ≥3 prior prophylactic treatments have	Please amend as follows: "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 [redacted] in Study 295, ARISE, STRIVE and LIBERTY). ~~However, when~~	The data stated in the section marked for deletion is from episodic migraine trials. The available data from Study 295 as the only chronic migraine trial does not support this statement. The company's response to	Not a factual inaccuracy. This statement is consistent with the original ERG report. Moreover, safety data might still be applicable even if populations are not

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 from the original submission, the serious adverse events may be as high as [redacted] and [redacted] for erenumab 70 mg and 140 mg respectively.[14] 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."	~~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 from the original submission, the serious adverse events may be as high as [redacted] and [redacted] for erenumab 70 mg and 140 mg respectively.[14] 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."~~	clarification question A9 from the original submission also contained serious adverse events (SAE) data for the subgroup of patients with ≥3 prior prophylactic treatment failures from Study 295, but this data is omitted in the ERG report. In this subgroup in the chronic migraine trial Study 295, SAE occurred in [redacted] patients in the placebo group, [redacted] patients in the erenumab 70 mg group, and [redacted] patients in the erenumab 140 mg group. *(Refer to the company response to the clarification questions to the original submission, response to question A9, from October 2018.)*	exactly the same. Particularly given the small sample size when considering patients with ≥3 prior prophylactic treatment failures from Study 295 only. Additionally, we believe the section with statements such as "adverse events may be as high as" and "not possible to draw firm conclusions regarding adverse events for patients for whom ≥3 prior prophylactic treatments have failed" is sufficiently nuanced.

Issue 2 Description of patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 7: "The company provided evidence about the clinical effectiveness of erenumab in patients with chronic migraine, for whom at least four prior treatments, including botulinum	Please amend as follows: "The company provided evidence about the clinical effectiveness of erenumab in patients with chronic migraine, for whom at least four prior ***prophylactic*** treatments, including botulinum toxin, had failed (CM ≥4 TF, including	To provide an accurate description of the subgroup. For the other subgroup included in the post-appeal submission, the treatment failures are accurately described in the ERG report.	Amended.

toxin, had failed (CM ≥4 TF, including botulinum toxin subgroup)."	botulinum toxin subgroup)."		
Page 7: "The company also presented the results of a further *post-hoc* subgroup analysis of Study 295, for patients who had failed three or more prior prophylactic treatments, but who had not previously received botulinum toxin (CM ≥3 TF, no prior botulinum toxin subgroup)." Page 19: "This third subgroup analysis was for patients for whom ≥3 individual prophylactic treatments had failed and who had not received botulinum toxin (CM ≥3 TF, no prior botulinum toxin)."	Please amend as follows: Page 7: "The company also presented the results of a further *post-hoc* subgroup analysis of Study 295, for patients ***with chronic migraine*** who had failed three or more prior prophylactic treatments, but who had not previously received botulinum toxin (CM ≥3 TF, no prior botulinum toxin subgroup)." Page 19: "This third subgroup analysis was for ***chronic migraine*** patients for whom ≥3 individual prophylactic treatments had failed and who had not received botulinum toxin (CM ≥3 TF, no prior botulinum toxin)."	To provide an accurate description of the subgroup. For the other subgroup included in the post-appeal submission, the migraine population is accurately described in the ERG report.	Amended.
Page 9 and page 30: "Moreover, Study 295 (focussed on patients with chronic migraine) excluded people with no therapeutic response to >3 previous treatments (i.e. potentially excluded the most refractory patients)." Page 14: "The ERG notes that patients in the CM ≥4 TF, including prior botulinum toxin subgroup may not be fully representative of the relevant	Please amend as follows: Page 9 / Page 30: "Moreover, Study 295 (focussed on patients with chronic migraine) excluded people with no therapeutic response ***(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))*** to >3 previous treatment~~s~~ ***categories*** (i.e. potentially excluded the most refractory patients)." Page 14: "The ERG notes that patients in the CM ≥4 TF, including prior botulinum toxin	To correctly and consistently reflect the study exclusion criteria with respect to the definition of 'no therapeutic response' and to the number of previous treatments (>3 rather than ≥3) referring to treatment categories. (*Refer to the Study 295 protocol, Amgen 2015, included in the original company submission in September 2018.)*	Not factual inaccuracies.

target population, because Study 295[8] excluded patients with chronic migraine who were refractory to treatment, defined as having no therapeutic response (reduction in frequency, duration or severity of headache) to ≥3 treatment categories." Page 20: "The ERG also notes that, irrespective of the validity of the proxy, patients in the CM ≥3 TF, no prior botulinum toxin subgroup may not be fully representative of the relevant target population, because Study 295[8] excluded patients with chronic migraine who were refractory to treatment, defined as having no therapeutic response (reduction in frequency, duration or severity of headache) to ≥3 treatment categories."	subgroup may not be fully representative of the relevant target population, because Study 295[8] excluded patients with chronic migraine who were refractory to treatment, defined as having no therapeutic response (***no*** reduction in frequency, duration or severity of headache ***after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s)***) to ~~≥~~ **>**3 treatment categories." Page 20: "The ERG also notes that, irrespective of the validity of the proxy, patients in the CM ≥3 TF, no prior botulinum toxin subgroup may not be fully representative of the relevant target population, because Study 295[8] excluded patients with chronic migraine who were refractory to treatment, defined as having no therapeutic response (***no*** reduction in frequency, duration or severity of headache ***after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s)***)) to ≧ **>**3 treatment categories."		
Page 23: "In their post-appeal submission, the company assessed the cost effectiveness of erenumab in two subgroups of patients with chronic migraine (15 headache days a month or more):"	Please amend as follows: "In their post-appeal submission, the company assessed the cost effectiveness of erenumab in two subgroups of patients with chronic migraine (15 headache days a month or more ***of which at least eight are migraine***):"	The provided description of chronic migraine is incomplete.	Amended.

Issue 3 Economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23: "Patients who discontinued treatment were assumed to rebound to the non-responder MMDs distribution."	Please amend as follows: "***In the base case,*** patients who discontinued treatment were assumed to rebound to the non-responder MMDs distribution. ***In a scenario analysis, all patients who discontinued treatment were assumed to rebound to baseline MMDs.***"	The provided description is correct for the base case. We propose to add that information for clarity and to also describe the assumption of the scenario analysis.	Not a factual inaccuracy. Scenario analyses are discussed in a separate section. This scenario is considered in section "4.9.2 Scenario analyses assuming patients who discontinue treatment rebound to baseline MMDs"
Page 28: "Additionally, as mentioned in the original ERG report, it is also questionable whether extrapolating benefits for non-responders (i.e. in MMD frequency distribution) is plausible (for the CM ≥4 TF, including botulinum toxin subgroup the non-responder mean MMD are [redacted] and [redacted] for erenumab and BSC respectively). This is to some extent mitigated in the treatment waning scenario given the decreased MMD frequency distributions benefits over time as well as the company's scenario analysis assuming rebound to baseline MMDs after discontinuation (see section 4.9)."	Please amend as follows: "Additionally, as mentioned in the original ERG report, it is also questionable whether extrapolating benefits for non-responders (i.e. in MMD frequency distribution) is plausible (for the CM ≥4 TF, including botulinum toxin subgroup the non-responder mean MMD are [redacted] and [redacted] for erenumab and BSC respectively). This is ***mitigated in the company's scenario analysis assuming rebound to baseline MMDs after discontinuation (see section 4.9) and*** to some extent mitigated in the treatment waning scenario given the decreased MMD frequency distributions benefits over time ~~as well as the company's scenario analysis assuming rebound to baseline MMDs after discontinuation (see section 4.9)~~."	In the company's scenario analysis, this is fully and not only partially mitigated as all patients who discontinue treatment – including non-responders who discontinue treatment after 12 weeks – rebound to baseline MMDs immediately after stopping treatment. Therefore, no treatment benefit is extrapolated for non-responders beyond the observed 12-week treatment period.	Amended.

Issue 4 Typographical and similar errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13: "It is also unclear why the TLR did not look for 'real-world evidence' about the population with three or more prior preventive/prophylactic treatment failures, for whom botulinum toxin is contraindicated, given that there are no trail data for this population."	Please amend as follows: "It is also unclear why the TLR did not look for 'real-world evidence' about the population with three or more prior preventive/prophylactic treatment failures, for whom botulinum toxin is contraindicated, given that there are no ~~trail~~ ***trial*** data for this population."	Typographical error.	Corrected.
Page 14: "As noted in the TLR methods, Appendix A of the post-appeal CS,[2] no formal data extraction process of assessment of the methodological quality of the 'real-world evidence' identified was undertaken."	Please amend as follows: "As noted in the TLR methods, Appendix A of the post-appeal CS,[2] no formal data extraction process ~~of~~ ***or*** assessment of the methodological quality of the 'real-world evidence' identified was undertaken."	Typographical error.	Corrected.
Page 15/16, header to Table 3.3: **Erenumab 140 mg** **Subgroup mg (n=[redacted])** / **ITT population (n=190)** Page 20/21, header to Table 3.6: **Erenumab 140 mg** **Subgroup mg (n=[redacted])** / **ITT population (n=190)**	Please amend as follows: **Erenumab 140 mg** **Subgroup ~~mg~~ (n=[redacted])** / **ITT population (n=190)** **Erenumab 140 mg** **Subgroup ~~mg~~ (n=[redacted])** / **ITT population (n=190)**	Erroneous inclusion of "mg" in subgroup column of the table.	Corrected.
Page 19: "The ERG also notes that the 'real-world' evidence from UK	Please amend as follows:	The part of the sentence marked for deletion seems to have been	Corrected.

centres participating CM ≥3 TF, no prior botulinum toxin subgroup g in the FOC scheme, provided by BASH, includes some indication of longer-term efficacy (18-weeks to six months)."	"The ERG also notes that the 'real-world' evidence from UK centres participating ~~CM ≥3 TF, no prior botulinum toxin subgroup g~~ in the FOC scheme, provided by BASH, includes some indication of longer-term efficacy (18-weeks to six months)."	included erroneously.	
Page 31: "[11] Lambric G, Hill B, Murphy M, Andreou AP. Erenumab for the treatment of refractory chronic migraine: a UK prospective real world experience. Poster presented at 19th Congress of the International Headahce Society, IHC 2019; 5-8 September 2019; Dublin (Ireland). 2019."	Please amend as follows: "[11] ~~Lambric~~ ***Lambru*** G, Hill B, Murphy M, Andreou AP. Erenumab for the treatment of refractory chronic migraine: a UK prospective real world experience. Poster presented at 19th Congress of the International ~~Headahce~~ ***Headache*** Society, IHC 2019; 5-8 September 2019; Dublin (Ireland). 2019."	Errors in reference.	Corrected.

Single Technology Appraisal (STA)

Erenumab for preventing migraine [ID1188]

Dear company,

We are contacting you in light of the final appraisal document for the galcanezumab appraisal [ID1372] which you will have received this week, as Novartis is a commentator on that appraisal.

In ID1372, the company submitted compelling evidence for differential utilities on and off treatment which demonstrated a statistically significant benefit for their treatment compared to the comparator. They demonstrated a utility benefit beyond that associated with only a decrease in monthly migraine days. The final appraisal document for ID1372 goes into further detail on this (section 3.13).

In the interests of fairness and consistency across appraisals, the appraisal committee are willing to look at evidence related to differential utilities for episodic and chronic migraine in the wider population for ID1188. This would be in addition to the post-appeal evidence Novartis have provided regarding sub-groups, and any further evidence provided would be addressed at the upcoming appraisal committee meeting for ID1188 in November.

If you have any evidence on differential utilities for episodic and chronic migraine in the wider population, please submit a short Word document with this evidence, including redacted versions (as relevant) by **5pm** on **Friday 16 October 2020.**

The document should be consistent with the principles described in sections 3.1.21–30 of Guide to the processes of technology appraisal. As a reminder, confidential marking should be kept to an absolute minimum, and anything that has previously been made public cannot be marked confidential. An amended checklist of confidential information will be required.

Please use this link in NICE Docs to upload:
https://appraisals.nice.org.uk/request/120260

Kind regards,

Jasdeep Hayre
Associate Director, Technology Appraisals

Date: 08/10/2020

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Erenumab for preventing migraine ID1188

Additional information request company evidence submission

October 2020

File name	Version	Contains confidential information	Date
ID1188 Erenumab migraine_Additional information request 2020-10_ACIC	**Final**	**Yes**	**October 2020**

Contents

Tables and figures

Background to the evidence submission

In the appraisal of galcanezumab for preventing migraine [ID1372], the committee acknowledged that there may be important aspects of the burden of migraine that are missed if only considering the frequency of migraine headache days and concluded that there is evidence for the use of differential utility values between treatments (Final Appraisal Document [FAD] 3.13).[1] This conclusion was based on analyses submitted by the company which demonstrated that utility values for galcanezumab were higher across all mean migraine headache day values compared with placebo (difference statistically significant) and results of a correlation study. Differential utilities were thus included in the base case for decision-making in this appraisal.

In the interests of fairness and consistency across appraisals, Novartis was approached by NICE to provide evidence related to differential utilities for erenumab in the wider population of ID1188 for people with episodic and chronic migraine.

The evidence for differential utilities submitted herein focuses on erenumab 140 mg, based on the committee's conclusion that 140 mg is the relevant dose in both episodic migraine (EM; see erenumab FAD, Section 3.7) and chronic migraine (CM; see erenumab FAD, Section 3.12).[2] Cost-effectiveness results incorporating differential utilities are presented for the originally sought positioning in EM and CM after the failure of 3 prior prophylactic treatments and in the post-appeal positioning in CM after failure of 4 prior prophylactic treatments, including botulinum toxin, or after failure of 3 prior prophylactic treatments and a contraindication/unsuitability to botulinum toxin.

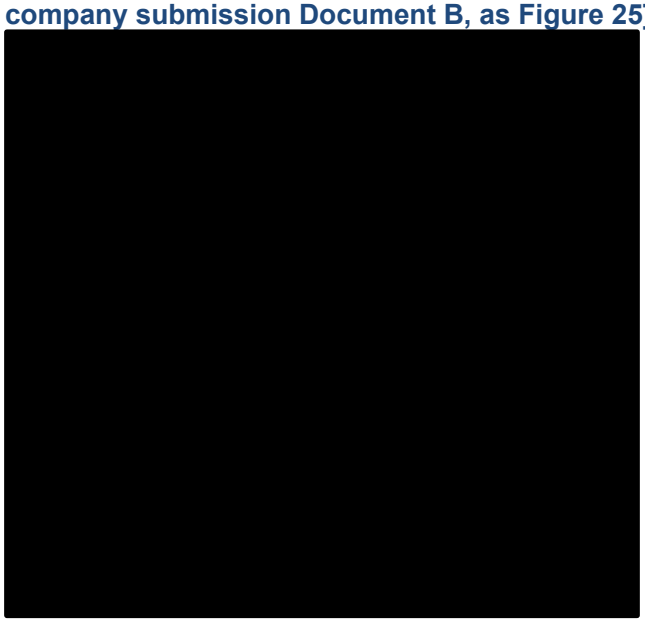
Evidence for differential utilities

Approach to utilities estimation in the original company submission

The economic models submitted in the erenumab appraisal to date included equal health state utility values for all treatments and both on- and off-treatment states. Therefore, a patient experiencing a given number of monthly migraine days (MMDs) would have the same utility value regardless of whether they are treated with erenumab, botulinum toxin, or BSC. As described in the company submission (section B.3.4), utilities were derived from Migraine-Specific Quality of Life Questionnaire (MSQ) data from the erenumab trials Study 295 (CM), STRIVE (EM) and ARISE (EM), mapped onto EQ-5D-3L using the Gillard *et al.* (2012) algorithm.[3] MSQ data were not collected in the LIBERTY (EM) study.

The average MSQ-derived utility values by MMD frequency from Study 295 and STRIVE, which were the only two studies including the erenumab 140 mg dose and the MSQ outcome, are provided in Figure 1 and Figure 2. 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 1: Average MSQ-derived utility for each MMD frequency in Study 295 [included in company submission Document B, as Figure 25]



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

Figure 2: Average MSQ-derived utility for each MMD frequency in STRIVE [included in company submission Document B as Figure 26]

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

Even though the visual inspection of above figures suggested the presence of a treatment effect of erenumab 140 mg on utility values, no treatment effect was assumed in the regression equation, representing a conservative assumption. Estimation of utility values for the original company submission was based on data from all three trials including the MSQ instrument (295, STRIVE, ARISE), all treatment arms and all observations (baseline and post-baseline). MMD frequency was the only covariate included in the multilevel model. Each modelled patient's utility was thus assumed to be determined exclusively by the patient's number of MMDs.

A summary of the utility models used in the original company submission is given in Table 1.

Table 1: Multilevel regression models predicting disutility due to MMD frequency for Study 295, STRIVE and ARISE [included in company submission Document B as Table 54]

	Multilevel Model (Combined Study 295, STRIVE and ARISE; Normal)		Multi-Level Model (Study 295; Normal)		Multi-Level Model (STRIVE and ARISE; Normal)	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	[redacted]		[redacted]		[redacted]	
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD: monthly migraine day.

Estimation of differential utilities

The formal analysis whether a treatment effect for erenumab 140 mg was present in the utility values was based on data from Study 295 (CM) and STRIVE (EM). The other studies offered no relevant evidence as they either did not include the 140 mg dose (ARISE) or the MSQ outcome (LIBERTY). The multilevel regression models presented in this submission used the same approach to estimation of utility values as the models presented in the original company submission (refer to B.3.4.2), the only difference being that treatment effect was introduced as an additional covariate alongside MMD frequency.

All baseline observations were considered as Best Supportive Care (BSC) measurements, since patients were not allowed by the study protocols to use any prophylactic migraine treatments for 2 months before the baseline measurement, and the MSQ has a recall period of 4 weeks. Placebo arm post-baseline observations (Study 295 Week 4, 8, 12; STRIVE Week 4, 8, 12, 16, 20, 24) also contributed as BSC measurements. Post-baseline observations from the erenumab 140 mg arms of Study 295 and STRIVE were considered for the estimation of the erenumab 140 mg utility values.

Same as in the original utility models, one analysis was run incorporating both data from CM and EM patients and two further analyses considered CM and EM utilities separately. In addition to utility models incorporating data from the full trial populations, as presented in the original submission, the analyses for differential utilities were also conducted using only the data from patients with ≥3 previous treatment failures. While the utility analyses for patients with ≥3 previous treatment failures align with the target population and are consistent with the analyses requested in the appraisal of galcanezumab [ID1372], their power to detect statistical significance is limited by a reduced sample size.

Results of the regression models including a treatment covariate are presented in Table 2 (full population) and Table 3 (subgroup with ≥3 prior treatment failures). The treatment effect of erenumab 140 mg is statistically significant in all utility regression models, [redacted].

Table 2: Multilevel regression models including MMD frequency and treatment effect as covariates – Full study population

	Full population – CM+EM (Combined Study 295, STRIVE; Normal)		Full population – CM (Study 295; Normal)		Full population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

Table 3: Multilevel regression models including MMD frequency and treatment effect as covariates – Population with ≥3 prior prophylactic treatment failures

	≥3 prior prophylactic treatment failures population – CM+EM (Combined Study 295, STRIVE; Normal)		≥3 prior prophylactic treatment failures population – CM (Study 295; Normal)		≥3 prior prophylactic treatment failures population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utility values by MMD frequency generated by the regression models are displayed along with the observed mean utility values in 'Appendix A: Differential utility values by MMD'. These tables also present the number of observations for each of the MMD frequencies, and show that in the population with ≥3 prior treatment failures, especially in the analyses that considered CM and EM individually, the sample size for utilities estimation was substantially smaller than in the full population.

In conclusion, all utility models including a treatment effect covariate indicated a treatment effect of erenumab 140 mg beyond the reduction of MMDs; this effect was statistically significant in all regression models [redacted]. In the appraisal of galcanezumab, all regression models providing evidence for differential utilities were based on a combined population of CM and EM patients. A published analysis of erenumab data using a slightly different methodology than this submission also found that mapped utility values were higher for erenumab-treated patients than for patients with the same number of MMDs receiving placebo, "indicating that treating migraine may have benefit beyond simply reducing the number of migraines a patient experiences and may translate into improvements in HRQoL".[4]

Further evidence supporting the use of differential utilities

That there is a benefit of erenumab beyond its effect on monthly migraine days was accepted by the committee in the erenumab appraisal. The FAD states ""The committee recognised that erenumab 140 mg also improved other outcomes compared with placebo, including the severity of migraine pain and the number of headache days each month.".[2]

The primary clinical measure in migraine cost-effectiveness models is the number of MMDs. While reduction in MMDs is a meaningful treatment outcome, research has shown that patients who suffer from migraines experience burden from their condition during a migraine (ictal burden) and between migraines (interictal burden).[5] Therefore, outcomes specific to migraine episodes may not be adequate to understand the condition. Lipton et al., 2020 explores the relationship between measures of interictal and ictal burden based on data from galcanezumab clinical trials.[6]

While improvements were achieved in both interictal and ictal burden, these outcomes were not highly correlated, demonstrating that ictal measures such as the number of MMDs alone do not fully capture all aspects of the burden of migraine.

To explore this finding within the erenumab clinical trials, correlation analyses were conducted between the MMDs, the number of monthly headache days and other patient-reported outcomes (PROs) collected in erenumab clinical trials. In addition to the migraine and headache frequency measures, five PRO instruments were included that assess related aspects:

- HIT-6 – measures the negative effects of headache on normal activity
- MIDAS – measures migraine-related disability
- MSQ – measures the impact of migraines on three essential aspects of a patient's HRQoL
- MPFID – measures the impact of migraines on physical functioning
- PROMIS pain – measures the extent to which pain hinders an individual's engagement with physical, mental, cognitive, emotional, recreational, and social activities.

In addition to these measures more related to ictal burden, a PRO measure related to work productivity and activity impairments specific to the patients' headache condition (WPAI: headache) was collected. This measure provides insights into absenteeism and presenteeism impacts experienced by patients treated for migraines. The absenteeism outcome provides information for the percentage of work time missed and presenteeism provides information related to the percentage of impairment while working. Given the lack of a measure specifically designed to capture interictal burden within the erenumab trials, the WPAI was hypothesised to provide a comprehensive assessment of the impacts of migraine during and between episodes based on days at work and days away from work. Furthermore, it was hypothesised that the six PRO measures related to migraine episodes would be at least moderately correlated post-baseline and for changes from baseline. In addition, a weaker correlation was hypothesised between the MMD and the WPAI outcomes.

As also reported by Lipton et al., 2020 for their study, change from baseline results for the PRO measures were positive in the erenumab analyses and provided evidence to support that erenumab is an efficacious migraine treatment.[6] [redacted]

Overall, the correlation analysis results provide evidence that MMDs alone do not capture the impact of migraine on both ictal and interictal periods. Therefore, inclusion of MMD alone within the economic model may underestimate erenumab's cost-effectiveness compared to best supportive care (BSC). In addition to reduction in monthly migraine days and headache days, clinical trial data in erenumab have demonstrated improvements in treatment effects compared to

placebo (BSC) in work productivity and activity impairment (WPAI), functioning aspects of migraine-specific quality of life (MSQ), migraine disability (MIDAS) and physical functioning (MPFID).[8-10] Hence important benefits not fully captured by the simple reduction in MMDs are being realized but are not being accounted for in an economic model that is based purely on MMD reduction.

Cost-effectiveness results including differential utility values

A new version of the economic model included with this submission incorporates a functionality to switch on differential utilities, using any of the six regression models outlined in Table 2 and Table 3. (Selection of a differential utility model under 'Apply differential treatment utility' on the Settings & Summary Results worksheet overrules the selection under 'Model used for utility values'.)

The differential utility model applies BSC utility values to the BSC comparator arm of the model and to all off-treatment states, irrespective of the prophylactic treatment used in the model prior to discontinuation. Erenumab 140 mg utility values are applied to the erenumab 140 mg on-treatment states as well as botulinum toxin on-treatment states (consistent with our understanding of the approach taken in ID1372, in absence of estimates informing botulinum toxin utility values). In the comparison of erenumab 140 mg and botulinum toxin, the concept of 'differential utilities' hence only refers to different on- and off-treatment utilities.

The regression model using MSQ data from both the CM and EM trials in the subgroup of patients with ≥3 previous prophylactic treatment failures was selected in the differential utility base case analyses. This choice is consistent with the committee-preferred approach in the appraisal of galcanezumab. Cost-effectiveness results using the other differential utility model are presented as scenarios for completeness.

[redacted]. As cost-effectiveness results using equal utilities for all treatments and model states have not been presented [redacted], these results are provided in Appendix B to facilitate the evaluation of the impact of differential utilities on incremental cost-effectiveness ratios (ICERs).

Table 4: Episodic migraine ≥3 prior treatment failures: Base case results with differential utilities (deterministic and probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility model CM+EM – ≥3 treatment failure population					
Deterministic estimates					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic estimates					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utility model: CM+EM – ≥3 treatment failure population.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 5: Episodic migraine ≥3 prior treatment failures: Scenario analyses with alternative differential utility models (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: Utility model CM+EM – Full population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Utility model EM – Full population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Utility model EM – ≥3 treatment failure population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Due to time constraints, presentation of probabilistic results is omitted for scenarios.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 6: Chronic migraine ≥3 prior treatment failures: Base case results with differential utilities (deterministic and probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility model CM+ EM – ≥3 treatment failure population					
Deterministic estimates					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic estimates					
BSC	Estimation not possible for technical reasons (see footnote)				
Botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Estimation of fully incremental ICERs including both botulinum toxin and BSC as comparators is no longer possible in the model following adaptations implemented for the post-appeal evidence submission in April 2020. (Reason: In the post-appeal population of patients with prior failure of or contraindication to botulinum toxin, botulinum toxin is not a relevant comparator.)
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 7: Chronic migraine ≥3 prior treatment failures: Scenario analyses with alternative differential utility models (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: Utility model CM+EM – Full population					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Utility model CM – Full population					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Utility model CM – ≥3 treatment failure population					
BSC	[redacted]	[redacted]			

Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Due to time constraints, presentation of probabilistic results is omitted for scenarios.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 8: Chronic migraine ≥4 prior treatment failures, post-botulinum toxin: Base case results with differential utilities (deterministic and probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility model CM+ EM – ≥3 treatment failure population					
Deterministic estimates					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic estimates					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Given the very small subgroup size, no separate utility analysis was undertaken for patients with CM and ≥4 prior treatment failures, post-botulinum toxin.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 9: Chronic migraine ≥4 prior treatment failures, post-botulinum toxin: Scenario analyses with alternative differential utility models (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: Utility model CM+EM – Full population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Utility model CM – Full population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Utility model CM – ≥3 treatment failure population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Due to time constraints, presentation of probabilistic results is omitted for scenarios.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 10: Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin: Base case results with differential utilities (deterministic and probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility model CM+ EM – ≥3 treatment failure population					
Deterministic estimates					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic estimates					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 11: Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin: Scenario analyses with alternative differential utility models (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: Utility model CM+EM – Full population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Utility model CM – Full population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Utility model CM – ≥3 treatment failure population					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Due to time constraints, presentation of probabilistic results is omitted for scenarios.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

In conclusion, the above results incorporating differential utilities for erenumab and BSC demonstrate that, [redacted], cost-effectiveness results for episodic migraine are all within the range that is commonly accepted as cost-effective. Since the incorporation of differential utilities does not impact the comparison versus botulinum toxin (except for utilities applied in off-treatment states), they are less relevant for fully incremental cost-effectiveness analyses in the chronic migraine population after ≥3 prior treatment failures. However, cost-effectiveness results versus BSC in the chronic migraine subgroups (≥4 prior treatment failures and ≥3 prior treatment failures with contraindication to botulinum toxin) demonstrate improved value with the inclusion of differential utilities.

Scenario analyses addressing further inconsistencies between appraisals

In addition to differences in committee-preferred approaches with regard to differential utilities, further inconsistencies were identified in the appraisals of erenumab [ID1188], fremanezumab [TA631] and galcanezumab [ID1372]. In the interests of fairness and consistency across appraisals, as highlighted in the request from NICE for submission of evidence on differential utilities, these inconsistencies are outlined in Table 12 below and subsequently addressed in scenario analyses.

Table 12: Further inconsistencies in CGRP inhibitor migraine appraisals

	Fremanezumab [TA631]	**Galcanezumab [ID1372]**	**Erenumab [ID1188]**
1) Administration costs for CGRP inhibitor	*Included for 10% of people receiving fremanezumab*[11]	*Included for 10% of people receiving galcanezumab*[12]	Not included (all patients self-administer erenumab after being trained)
2) Age-related disutility	No evidence of inclusion of age-related disutility could be identified	*Included age-related decrements*[13]	Not included
3) Dissipation of placebo effect in BSC responders	*Treatment effect in BSC responders wanes to baseline over 1 year; all patients discontinuing treatment revert to baseline MMDs*[14]	*Treatment effect in BSC responders wanes to baseline over 1 year; all patients discontinuing treatment revert to baseline MMDs;*[15] *no evidence that this assumption was removed in final model*	Treatment effect in BSC responders is maintained throughout the lifetime time horizon of the model; all patients discontinuing treatment maintain the non-responder MMD improvement
4) Treatment effect versus botulinum toxin	Equivalence assumed between fremanezumab and botulinum toxin[16]	*Galcanezumab vs. botulinum toxin treatment effect used in final decision-relevant model*[17]	Equivalence assumed between Erenumab 140mg and botulinum toxin[18]

Abbreviations: BSC: best supportive care; CGRP: calcitonin gene-related peptide; MMDs: monthly migraine days.

1) Administration costs for CGRP inhibitor

Based on experience in the private market and a free-of-charge programme, Novartis estimates that around [redacted] of patients are able to self-administer erenumab which is supplied as a pre-filled autoinjector pen. Both the appraisals of fremanezumab and galcanezumab accounted for administration costs for 10% of patients in their economic models. For consistency, this assumption is therefore implemented in a scenario analysis (#1). As in the galcanezumab appraisal, this was costed as a 30-minute appointment with a Band 5 hospital-based nurse at an hourly rate of £38.00.[19]

2) Age-related disutility

In the galcanezumab appraisal, the final decision-relevant economic model also included age-related disutilities, based on published general population age-related decrements from Ara and Brazier (2011).[19, 20] However, age-related disutilities do not seem to have been included in the fremanezumab appraisal, based on our understanding of the committee papers of this appraisal. The option to include an age-related disutility has been incorporated in the updated economic model provided with this submission and the impact was explored in a scenario analysis (#2), where utility values are weighted based on age-decrements for the UK general population published in Ara and Brazier (2011).[20]

3) Dissipation of placebo effect in BSC responders

In the appraisal of fremanezumab, it was considered implausible that patients responding to BSC – whose data in the economic model was informed by the placebo arms of the clinical trials – would maintain their MMD improvement, driven by the placebo effect of the clinical trial, indefinitely. The treatment effect for people whose migraine responded to BSC was therefore assumed to diminish to baseline over 1 year. In addition, it was assumed that all patients discontinuing treatment would revert to baseline MMDs. The company submission for galcanezumab followed these conclusions. Although the ERG expressed concerns with the removal of a placebo effect exclusively from BSC responders, and not from active treatment arms, due to lack of further discussion in the subsequent parts of the committee papers it appears that this assumption may still have been included in the final decision-relevant economic model. As evidenced by the comparison of the galcanezumab ERG's base case ICER with a scenario analysis where BSC responders were assumed to retain response for the duration of the model time horizon (scenario 9 in the ERG report), the assumption of placebo effect dissipation in BSC responders reduces the ICER significantly.[19] In the erenumab appraisal, a different approach was taken. Placebo response was maintained in the economic model over the lifetime time horizon in all arms, including BSC responders, thus maintaining the overall treatment effect observed in the clinical trials. People discontinuing treatment were assumed to maintain the MMD improvement of non-responders, based on the ERG's preference. This approach can be argued to allow for a consistent inclusion of a placebo effect across all arms and model states, or could also be seen to capture a regression to the mean which is included for all patients in the model irrespective of treatment. In order to permit the assessment of these differences in approaches across appraisals, a scenario analysis (#3) was conducted where BSC responders revert to baseline MMDs at the end of year 1 (sudden and full loss of placebo effect), and all patients discontinuing treatment are assumed to rebound to baseline MMDs. We would like to highlight that due to time constraints, the removal of placebo effect from BSC responders could not be incorporated as an option in a fully probabilistic manner but is assessed in a separate, exploratory version of the Excel model. In this version, all BSC responders move to the discontinuation state (see BSC Markov trace) at a time point that can be set on the Settings & Summary Results worksheet ('Time point of BSC loss of response (years)'). For the presented

scenario analysis, the loss of placebo response was assumed to occur at the end of year 1, which is slightly more conservative than our understanding of the fremanezumab and galcanezumab appraisal assumptions.

4) Treatment effect versus botulinum toxin

In the galcanezumab appraisal, a treatment effect between galcanezumab and botulinum toxin was accepted for use in the final decision-relevant economic model. The galcanezumab FAD notes that "*Most of the results of the indirect treatment comparison were not statistically significant for the all-comers population or the population with 3 or more prior treatment failures, but they did numerically favour galcanezumab. The only statistically significant result was the change in migraine headache days for the population with 3 or more prior treatment failures (results are academic in confidence and cannot be reported here). The company and the ERG noted that because of the limitations of the indirect treatment comparison, these results should be interpreted with caution. Despite this, the ERG advised that the indirect treatment comparison was sufficiently robust for use in the economic model.*".[1] While acknowledging the uncertainty, the committee concluded that it was appropriate to use the clinical-effectiveness estimates from the indirect treatment comparison for decision making.[1]

A similar set of analyses can be presented for erenumab 140 mg (see below, Table 13). In these analyses, unlike the galcanezumab analyses, superiority over botulinum toxin can be demonstrated in a wider population with statistical significance. Equivalently to the galcanezumab analyses, numerical superiority over botulinum toxin type A can be demonstrated in a population with at least 3 prior prophylactic treatment failures. The analyses presented mirror those described in the galcanezumab FAD as closely as possible. In particular:

- For ease of comparison, the 'full trial population' described in the present analysis is equivalent to the 'all-comers' patient population described in the galcanezumab analysis and is defined as patients who are naïve to preventive migraine treatment as well as patients who have previously been unsuccessfully treated with prior preventive migraine treatment. Similarly, the 'TF3+' population in the present analysis is equivalent to the 'difficult-to-treat' patient population in the galcanezumab appraisal, defined as failure on least 3 prior preventive treatments
- Botulinum toxin input data is based on pooled estimates from the PREEMPT 1 and 2 trials
- The Bucher method is employed in a series of indirect treatment comparisons

More details on these analyses can be found in Appendix C.

Table 13: Summary of ITCs of Erenumab 140mg vs. Botulinum toxin type A

	Population	Outcome	Time point of BttA assessment	Treatment effect	p-value	Summary
Full trial population	Total CM	CFB MHDs	Week 12	[redacted]	[redacted]	In the total CM population, erenumab is numerically superior to BttA.
	Total CM	CFB MMDs	Week 12	[redacted]	[redacted]	
	Total CM BttA-naïve	CFB MHDs	Week 12	[redacted]	[redacted]	In the total BttA-naïve CM population, erenumab is superior to BttA with
	Total CM BttA-naïve	CFB MMDs	Week 12	[redacted]	[redacted]	

						statistical significance.
TF3+	CM TF3+	CFB MHDs	Week 24	[redacted]	[redacted]	In the CM TF3+ population, erenumab is numerically superior to BttA in every analysis and is statistically significant at p-value <0.1 in certain analyses. It is likely, based on results from the broader CM population, that with a larger sample size, the clinical superiority of erenumab would also be statistically significant at p-value <0.05.
	CM TF3+	CFB MMDs	Week 24	[redacted]	[redacted]	
	CM TF3+ BttA-naive	CFB MHDs	Week 24	[redacted]	[redacted]	
	CM TF3+ BttA-naive	CFB MMDs	Week 24	[redacted]	[redacted]	
	CM TF3+	50% response MHDs	Week 24	[redacted]	[redacted]	
	CM TF3+	50% response MMDs	Week 24	[redacted]	[redacted]	
	CM TF3+ BttA-naive	50% response MHDs	Week 24	[redacted]	[redacted]	
	CM TF3+ BttA-naive	50% response MMDs	Week 24	[redacted]	[redacted]	

* Statistically significant at p-value threshold of 0.1
** Statistically significant at p-value threshold of 0.05
[1] Relative difference in change from baseline
[2] Odds ratio of 50% response (erenumab vs. BttA)
Abbreviations: BttA: botulinum toxin type A; CFB: change from baseline; CM: chronic migraine; MHD: monthly headache day; MMD: monthly migraine day; TF3+: subgroup with ≥3 prior prophylactic treatment failures;

In totality, the results in Table 13 demonstrate that erenumab 140 mg is more clinically effective than botulinum toxin in the full trial CM population with statistical significance and is consistently numerically superior compared to botulinum toxin type A in TF3+ populations. These latter results are not statistically significant at p-value <0.05 ([redacted]). However, it is likely, given the consistent numerical superiority coupled with the results of the full trial analysis, that erenumab 140 mg is also clinically superior to botulinum toxin in the TF3+ population and would be shown as such with statistical significance were a larger sample available.

Thus, in line with the galcanezumab appraisal, a scenario cost-effectiveness analysis is included in this document whereby a positive treatment effect for erenumab 140mg versus botulinum toxin is considered. This alignment with the conclusion on relative effectiveness versus botulinum toxin drawn in the galcanezumab appraisal is further supported by a statement in the galcanezumab FAD that "the committee heard from the clinical expert that there is no clinical evidence to support any difference in efficacy between the different anti-CGRP drugs", and that two surveys done by the Migraine Trust showing that "most patient and clinical experts consider anti-CGRPs to be more effective than botulinum toxin type A".[1]

In line with the committee's conclusions for galcanezumab we therefore argue that it is plausible that erenumab may be more clinically effective than botulinum toxin type A, and that therefore it is appropriate to use the clinical-effectiveness estimates from the indirect treatment comparison for decision making. For the purposes of this scenario analysis, the same odds ratio has been used as was used for previous analyses submitted within this appraisal that have incorporated an ITC point estimate.

Table 14: Episodic migraine ≥3 prior treatment failures: Scenario analyses addressing other inconsistencies (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including differential utilities; see Table 4)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Inclusion of administration costs for 10% of erenumab patients					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Inclusion of age-related disutility					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Dissipation of placebo effect for BSC responders after 1 year					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Due to time constraints, presentation of probabilistic results is omitted for scenarios.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 15: Chronic migraine ≥3 prior treatment failures: Scenario analyses addressing other inconsistencies (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including differential utilities; see Table 6)					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Inclusion of administration costs for 10% of erenumab patients					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Inclusion of age-related disutility					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Dissipation of placebo effect for BSC responders after 1 year					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Erenumab treatment effect over botulinum toxin (OR=[redacted])					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Due to time constraints, presentation of probabilistic results is omitted for scenarios.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 16: Chronic migraine ≥4 prior treatment failures, post-botulinum toxin: Scenario analyses addressing other inconsistencies (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including differential utilities; see Table 8)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Inclusion of administration costs for 10% of erenumab patients					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Inclusion of age-related disutility					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Dissipation of placebo effect for BSC responders after 1 year					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Due to time constraints, presentation of probabilistic results is omitted for scenarios.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 17: Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin: Scenario analyses addressing other inconsistencies (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including differential utilities; see Table 10)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Inclusion of administration costs for 10% of erenumab patients					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Inclusion of age-related disutility					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Dissipation of placebo effect for BSC responders after 1 year					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Due to time constraints, presentation of probabilistic results is omitted for scenarios.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

As expected based on the analyses in the galcanezumab appraisal, the inclusion of administration costs for 10% of erenumab patients and age-related utility decrements increase the ICERs. But [redacted] the inclusion of these assumptions has a minor impact on ICERs, and would not change conclusions on cost-effectiveness in any of the four subpopulations.

In the comparison versus BSC, the assumption that placebo effect dissipates in BSC responders after 1 year has a substantial positive impact on ICERs. As highlighted, this assumption of maintenance of placebo response for the full first year followed by a sudden and full loss of

placebo effect in BSC responders at the end of year 1 is slightly more conservative than the assumption of gradual loss of efficacy over 1 year which seems to have been included in the base case in the appraisals of fremanezumab and galcanezumab.

Cost-effectiveness versus botulinum toxin in the population with CM and ≥3 prior treatment failures is largely unaffected by variations in assumptions as long as an equal efficacy assumption is maintained (odds ratio for response with erenumab 140 mg vs botulinum toxin set to 1). However, based on the committee's considerations in appraisal ID1372 that it is plausible that galcanezumab may work better than botulinum toxin and the comparison of the evidence presented in ID1372 with the evidence on relative effectiveness of erenumab versus botulinum toxin summarised in this submission, we believe that the assumption of a treatment effect of erenumab 140 mg versus botulinum toxin would be reasonable. At an odds ratio of [redacted], reflecting the point estimate from the indirect comparison included in the original company submission, the ICER of erenumab 140 mg versus botulinum toxin improves dramatically to [redacted]. In a threshold analysis, an odds ratio of [redacted] – indicating a minimal treatment effect of erenumab over botulinum toxin – would already be sufficient to achieve an ICER below <£20,000 ([redacted]) [redacted]; an ICER <£30,000 would result from an odds ratio of [redacted] (ICER [redacted]). Such a minimal treatment effect of erenumab 140 mg versus botulinum toxin is plausible in our view, given the consistent, at least numerical benefit in all outcomes demonstrated in the ITC.

References

1. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]. Final Appraisal Document. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10454/documents [Last accessed: 16/10/2020].
2. National Institute for Health and Care Excellence. Erenumab for preventing migraine [ID1188]. Final Appraisal Document. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10302/documents [Last accessed: 16/10/2020].
3. Gillard PJ, Devine B, Varon SF, et al. Mapping from disease-specific measures to health-state utility values in individuals with migraine. Value Health 2012;15:485-94.
4. Di Tanna GL, Porter JK, Lipton RB, et al. Longitudinal assessment of utilities in patients with migraine: an analysis of erenumab randomized controlled trials. Health and Quality of Life Outcomes 2019;17:171.
5. Buse DC, Rupnow MF, Lipton RB. Assessing and managing all aspects of migraine: migraine attacks, migraine-related functional impairment, common comorbidities, and quality of life. Mayo Clin Proc 2009;84:422-35.
6. Lipton RB, Buse DC, Sandoe CH, Ford JH, Hand AL, Jedynak JP, et al. Interictal burden of migraine: correlations with other measures of migraine burden and effects of galcanezumab migraine-preventive treatment. Migraine Trust Virtual Symposium 2020 (MTIS); Oct 3-9, 2020.
7. Novartis Data on File: Correlation Analyses. .
8. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017;16:425-434.
9. Goadsby PJ, Reuter U, Hallström Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. New England Journal of Medicine 2017;377:2123-2132.
10. Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. The Lancet 2018;392:2280-2287.
11. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [TA631]. Technology Appraisal Guidance - SECTION 3.22. Available at https://www.nice.org.uk/guidance/ta631 [Last accessed: 16/10/2020].
12. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]. Final Appraisal Document - SECTION 3.14. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10454/documents [Last accessed: 16/10/2020].
13. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]. Final Appraisal Document - SECTIONS 3.17, 3.18 and 3.19. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10454/documents [Last accessed: 16/10/2020].
14. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [TA631]. Technology Appraisal Guidance - SECTION 3.16. Available at https://www.nice.org.uk/guidance/ta631 [Last accessed: 16/10/2020].
15. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]. Eli Lilly- Manufacturer Submission - SECTION 3.3. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10454/documents [Last accessed: 16/10/2020].
16. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [TA631]. Technology Appraisal Guidance - SECTION 3.11. Available at https://www.nice.org.uk/guidance/ta631 [Last accessed: 16/10/2020].
17. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]. Eli Lilly- Manufacturer Submission - SECTION 3.12. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10454/documents [Last accessed: 16/10/2020].
18. National Institute for Health and Care Excellence. Erenumab for preventing migraine [ID1188]. Final Appraisal Document - Section 3.13. Available at

https://www.nice.org.uk/guidance/indevelopment/gid-ta10302/documents [Last accessed: 16/10/2020].
19. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]. Evidence Review Group Report. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10454/documents [Last accessed: 16/10/2020].
20. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health 2011;14:539-45.
21. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010;50:921-36.
22. CADTH Common Drug Review for onabotulinumtoxinA in the treatment of chronic migraine. Clinical Report. Available at https://cadth.ca/onabotulinumtoxina-23 [Last accessed 16/10/2020].
23. Scottish Medicines Consortium. Botulinum toxin A. Detailed Advice Document. Available at: https://www.scottishmedicines.org.uk/medicines-advice/botulinum-toxin-a-botox-resubmission-69211/. [Last accessed 16/10/2020].

Appendix A: Differential utility values by MMD

Table 18: Observed and model-predicted utility values by MMD frequency – Full population CM+EM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg
[redacted]						

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

Table 19: Observed and model-predicted utility values by MMD frequency – Full population CM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg
[redacted]						

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

Table 20: Observed and model-predicted utility values by MMD frequency – Full population EM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg
[redacted]						

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

Table 21: Observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population CM+EM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg
[redacted]						

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

Table 22: Observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population CM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg
[redacted]						

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

Table 23: Observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population EM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg	BSC	Erenumab 140 mg
[redacted]						

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

Appendix B: Cost-effectiveness results at equal utility values

Below cost-effectiveness results [redacted] and the same utility values, generated from utility models without a treatment effect covariate, for all treatment arms and model states.

Table 24: Episodic migraine ≥3 prior treatment failures: Cost-effectiveness results using equal utilities for all treatments and model states (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pooled multilevel model: Full population – Study 295, STRIVE, ARISE					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indication-specific multilevel model: Full population –STRIVE, ARISE					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 25: Chronic migraine ≥3 prior treatment failures: Cost-effectiveness results using equal utilities for all treatments and model states (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pooled multilevel model: Full population – Study 295, STRIVE, ARISE					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indication-specific multilevel model: Full population –Study 295					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26: Chronic migraine ≥4 prior treatment failures, post-botulinum toxin: Cost-effectiveness results using equal utilities for all treatments and model states (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pooled multilevel model: Full population – Study 295, STRIVE, ARISE					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indication-specific multilevel model: Full population –Study 295					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 27: Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin: Cost-effectiveness results using equal utilities for all treatments and model states (deterministic)*

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pooled multilevel model: Full population – Study 295, STRIVE, ARISE					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indication-specific multilevel model: Full population –Study 295					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix C: Details of ITCs of Erenumab 140mg vs. Botulinum toxin type A

Total CM population (including BttA-experienced patients)
Outcomes assessed at Week 12 for erenumab trial and at Week 12 for BttA trials

Table 28: Change from baseline in monthly headache days

	295 trial		PREEMPT 1 and 2		Relative difference	
	Erenumab 140mg N = 182 [A]	Placebo N = 267 [B]	Onabotulinum-toxinA N = 688 [C]	Placebo N = 696 [D]	Mean (95% CI) [A - B] - [C - D]	p-value
Change from baseline in monthly headache days, mean (SD)	[redacted]	[redacted]	-7.2 (6.4)	-6.0 (6.4)	[redacted]	[redacted]
Note: In the PREEMPT trials, patients with previous history of onabotulinum toxin A were excluded.						

Table 29: Change from baseline in monthly migraine days

	295 trial		PREEMPT 1 and 2		Relative difference	
	Erenumab 140mg N = 190 [A]	Placebo N = 286 [B]	Onabotulinum-toxinA N = 688 [C]	Placebo N = 696 [D]	Mean (95% CI) [A - B] - [C - D]	p-value
Change from baseline in monthly migraine days, mean (SD)	[redacted]	[redacted]	-7.1 (6.7)	-5.6 (6.3)	[redacted]	[redacted]
Note: In the PREEMPT trials, patients with previous history of onabotulinum toxin A were excluded.						

Data source of BttA trials: Dodick 2010, Figure 2.[21]

Total CM BttA-naïve population
Outcomes assessed at Week 12 for erenumab trial and at Week 12 for BttA trials

Table 30: Change from baseline in monthly headache days

	295 trial		PREEMPT 1 and 2		Relative difference	
	Erenumab 140mg N = 139 [A]	Placebo N = 205 [B]	Onabotulinum-toxinA N = 688 [C]	Placebo N = 696 [D]	Mean (95% CI) [A - B] - [C - D]	p-value
Change from baseline in monthly headache days, mean (SD)	[redacted]	[redacted]	-7.2 (6.4)	-6.0 (6.4)	[redacted]	[redacted]

Table 31: Change from baseline in monthly migraine days

	295 trial		PREEMPT 1 and 2		Relative difference	
	Erenumab 140mg N = 147 [A]	Placebo N = 221 [B]	Onabotulinum-toxinA N = 688 [C]	Placebo N = 696 [D]	Mean (95% CI) [A - B] - [C - D]	p-value
Change from baseline in monthly migraine days, mean (SD)	[redacted]	[redacted]	-7.1 (6.7)	-5.6 (6.3)	[redacted]	[redacted]

Data source of BttA trials: Dodick 2010, Figure 2.[21]

CM TF3+ population (including BttA-experienced patients)
Outcomes assessed at Week 12 for erenumab trial and at Week 24 for BttA trials

Table 32: Change from baseline in monthly headache days

	295 trial		PREEMPT 1 and 2		Relative difference	
	Erenumab 140mg N = 68 [A]	Placebo N = 99 [B]	Onabotulinum-toxinA N = 231 [C]	Placebo N = 248 [D]	Mean (95% CI) [A - B] - [C - D]	p-value
Change from baseline in monthly headache days, mean (SD)	[redacted]	[redacted]	-7.4 (6.6)	-4.7 (6.4)	[redacted]	[redacted]

Table 33: Change from baseline in monthly migraine days

	295 trial		PREEMPT 1 and 2		Relative difference	
	Erenumab 140mg N = 68 [A]	Placebo N = 102 [B]	Onabotulinum-toxinA N = 231 [C]	Placebo N = 248 [D]	Mean (95% CI) [A - B] - [C - D]	p-value
Change from baseline in monthly migraine days, mean (SD)	[redacted]	[redacted]	-7.1 (6.6)	-4.3 (6.5)	[redacted]	[redacted]

Data source of BttA trials: CADTH review report.[22]

CM TF3+ BttA-naïve population
Outcomes assessed at Week 12 for erenumab trial and at Week 24 for BttA trials

Table 34: Change from baseline in monthly headache days

	295 trial		PREEMPT 1 and 2		Relative difference	
	Erenumab 140mg N = 36 [A]	Placebo N = 55 [B]	Onabotulinum-toxinA N = 231 [C]	Placebo N = 248 [D]	Mean (95% CI)	p-value
					[A - B] - [C - D]	
Change from baseline in monthly headache days, mean (SD)	[redacted]	[redacted]	-7.4 ± 6.6	-4.7 ± 6.4	[redacted]	[redacted]

Table 35: Change from baseline in monthly migraine days

	295 trial		PREEMPT 1 and 2		Relative difference	
	Erenumab 140mg N = 36 [A]	Placebo N = 57 [B]	Onabotulinum-toxinA N = 231 [C]	Placebo N = 248 [D]	Mean (95% CI)	p-value
					[A - B] - [C - D]	
Change from baseline in monthly migraine days, mean (SD)	[redacted]	[redacted]	-7.1 (6.6)	-4.3 (6.5)	[redacted]	[redacted]

Data source of BttA trials: CADTH review report.[22]

CM TF3+ population (including BttA-experienced patients)
Outcomes assessed at Week 12 for erenumab trial and at Week 24 for BttA trials

Table 36: 50% responder based on reduction in MHD

	295 trial		PREEMPT 1 and 2		Odds ratio		
	Erenumab 140mg N = 68 [A]	Placebo N = 99 [B]	Onabotulinum-toxinA N = 189 [C]	Placebo N = 207 [D]	Mean (95% CI)	SE	p-value
					[A vs B] vs [C vs D]		
50% responder based on reduction in MHD	[redacted]		76 (40.2%)	51 (24.6%)	[redacted]	[redacted]	[redacted]

Table 37: 50% responder based on reduction in MMD

	295 trial		PREEMPT 1 and 2		Odds ratio		
	Erenumab 140mg N = 68 [A]	Placebo N = 102 [B]	Onabotulinum-toxinA N = 231 [C]	Placebo N = 248 [D]	Mean (95% CI)	SE	p-value
					[A vs B] vs [C vs D]		
50% responder based on reduction in MMD[1]	[redacted]		41.2%	25.5%	[redacted]	[redacted]	[redacted]

Data source of BttA trials: Scottish Medicines Consortium report.[23]

[1] 50% responder rates based on reduction in MMD of BttA and corresponding placebo were estimated by taking the ratio of the 50% responder rate based on reduction in MMD and the 50% responder rate based on reduction in MHD in the overall BttA/placebo population, and applying this ratio to the 50% responder rate based on reduction in MHD for the 3+TF BttA/placebo population

CM TF3+ BttA-naïve population
Outcomes assessed at Week 12 for erenumab trial and at Week 24 for BttA trials

Table 38: 50% responder based on reduction in MHD

	295 trial		PREEMPT 1 and 2		Odds ratio		
	Erenumab 140mg N = 36 [A]	Placebo N = 55 [B]	Onabotulinum-toxinA N = 189 [C]	Placebo N = 207 [D]	Mean (95% CI)	SE	p-value
					[A vs B] vs [C vs D]		
50% responder based on reduction in MHD	[redacted]		76 (40.2%)	51 (24.6%)	[redacted]	[redacted]	[redacted]

Table 39: 50% responder based on reduction in MMD

	295 trial		PREEMPT 1 and 2		Odds ratio		
	Erenumab 140mg N = 36 [A]	Placebo N = 57 [B]	Onabotulinum-toxinA N = 231 [C]	Placebo N = 248 [D]	Mean (95% CI)	SE	p-value
					[A vs B] vs [C vs D]		
50% responder based on reduction in MMD[1]	[redacted]		41.2%	25.5%	[redacted]	[redacted]	[redacted]

Data source of BttA trials: Scottish Medicines Consortium report

[1] 50% responder rates based on reduction in MMD of BttA and corresponding placebo were estimated by taking the ratio of the 50% responder rate based on reduction in MMD and the 50% responder rate based on reduction in MHD in the overall BttA/placebo population, and applying this ratio to the 50% responder rate based on reduction in MHD for the 3+TF BttA/placebo population

Modelling approach

The company's modelling approach consisted of a 12-week decision-tree followed by state transition model (ERG report Figure 5.1). The decision tree represented the response assessment period and the state transition model represented the post-assessment period where patients are subdivided based on the response assessment. 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 best supportive care (BSC; 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, the post-assessment costs and utilities, estimated depending on the MMD frequency distribution were applied. Responders entered the on-treatment health state and were assumed to continue treatment and hence maintain the responder MMD until treatment discontinuation.

Estimated health state utilities in original CS

As mentioned above, the estimated health state utility values was dependent on MMD frequency (and population specific, i.e. episodic migraine, chronic migraine or combined). As the estimated MMD frequency was [redacted] for erenumab 140mg compared with BSC (ERG report Table 5.6) for both responders as well as non-responders, the estimated health state utilities (mapped based on MSQ) were [redacted] for erenumab 140mg compared with BSC (ERG report Table 5.7). Consequently, the original CS approach did already incorporate differential (or treatment dependent) health state utilities [redacted] erenumab 140mg both during treatment as well as after treatment discontinuation (this is illustrated by the health state utility values reported in Table 4.2 of the ERG post-appeal addendum).

Given the above, the company's statement that "The economic models submitted in the erenumab appraisal to date included equal health state utility values for all treatments and both on- and off-treatment states" is therefore incorrect.

Estimation of differential utilities (independent of MMD frequency)

The additional information provided by the company included the estimation of differential (or treatment dependent) utilities independent of MMD frequency (i.e. independent on the treatment dependent health state utilities already included). Based on visual inspection, Figures 1 and 2 illustrate that there seems to be a clear relation between MMD frequency and health state utility, this is however less obvious for the relation between treatment and health state utility (independent of MMD frequency).

Treatment dependent utility values independent of MMD frequency were estimated using data from the two trials including the MSQ instrument and erenumab 140 mg (Study 295 (chronic migraine; CM), baseline week 4, 8, 12; STRIVE (episodic migraine; EM) baseline, week 4, 8, 12, 16, 20, 24). Multilevel regression models were separately estimated for CM, EM as well as for the combined (CM + EM) population. Additionally, next to analyses based on the full trial populations, analyses were also conducted using only the data from patients with ≥3 previous treatment failures (consistent with the target population and the analyses requested in the appraisal of galcanezumab [ID1372]). The multilevel regression included the following covariates:

- MMD frequency (as in the original CS approach)
- Treatment – either erenumab 140 mg or BSC (not included in the original CS approach)

The "treatment" covariate was statistical significant ([redacted]) supporting a differential utility independent of MMD frequency. However, the ERG wishes to highlight that for the treatment covariate all baseline observations, regardless of treatment allocation, were categorised as BSC. The company justified this approach by stating that, according to study protocols, patients were not allowed to use prophylactic migraine treatments for 2 months before the baseline measurement, and the MSQ has a recall period of 4

weeks. The ERG strongly disagrees with the categorisation of baseline observations as BSC. This is mainly because baseline and follow-up observations might differ substantially due to the placebo effect (as for instance illustrated by the MMD frequency at baseline and 12-week follow-up for BSC, ERG report Table 5.6). Therefore, utilities observed on erenumab would be those due to erenumab plus any placebo effect whereas those observed on BSC would include those at baseline, which must exclude the placebo effect. Thus, the estimated differential utility using the "treatment" covariate as defined by the company partly and possibly completely represents the placebo effect rather than the difference between erenumab 140 mg and BSC. Therefore, the analyses presented by the company are not considered plausible by the ERG and should thus not be considered for decision-making as the differential utility for erenumab 140 is likely overestimated. The analyses should be redone while including a separate category for baseline observations. When reconsidering these analyses, it would be informative to explore interaction effects between covariates as well.

Face validity of differential utilities

It is unclear whether the estimated (differential) utilities have been checked for face validity. Ideally, these utilities (or utilities estimated in any additional analyses) should be clearly presented per health state and per treatment as well as checked for face validity.

Further evidence supporting the use of differential utilities

The section "further evidence supporting the use of differential utilities" might support the statement that MMDs alone does not capture the impact of migraine on both ictal and interictal periods. However, it does not provide compelling evidence of a differential utility of erenumab 140 mg versus BSC independent of MMD frequency.

Implementation of differential utilities in the economic model

The implementation of the estimated differential utilities is unclear. For instance, whether these are applied for a specific duration/ lifetime and to both patients on and off treatment (i.e. the alive health states).

Replicating the estimated cost-effectiveness analyses and ERG base-case

Using the newly submitted economic model, the ERG was able to reproduce the results provided by the company for EM and CM. The ERG base-case is similar to the company's base-case while removing the differential utility that has now been introduced by the company. For EM, this would result in an ERG base-case consistent with the ERG base-case in the original ERG report (assuming constant treatment effectiveness). For the CM ≥3 prior treatment failures, contraindication to botulinum toxin and ≥4 prior treatment failures; post-botulinum toxin populations this would be consistent with the post-appeal ERG base-case (Table 1).

The ERG base-case results should however be interpreted while noting the uncertainty (that is not quantified in the health economic analyses) regarding the evidence used as described in the post-appeal ERG addendum. Moreover, as mentioned in the original ERG report and post-appeal addendum, it is also questionable whether extrapolating additional benefits for non-responders (i.e. due to differential MMD frequency) is plausible.

Table 1: Deterministic results (re)produced by the ERG

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Episodic migraine ≥3 prior treatment failures					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility) – consistent with ERG base-case in original ERG report (assuming constant treatment effectiveness)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic migraine ≥3 prior treatment failures					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population)					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility)					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility) – consistent with post-appeal ERG base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic migraine ≥4 prior treatment failures; post-botulinum toxin					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility) – consistent with post-appeal ERG base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; CM: chronic migraine; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Erenumab for preventing migraine ID1188

Response to additional information request in ERG addendum 27 October 2020

29 October 2020

File name	Version	Contains confidential information	Date
ID1188 Erenumab migraine_Response to ERG addendum request_ 20201029_ACIC	Final	Yes	29 October 2020

Contents

Tables and figures

Background to the response document

As requested by NICE via email on 27th October 2020 in conjunction with the ERG addendum on differential utilities, this response document contains revised differential utility analyses as well as further clarification on how the utility values were used in the economic model and their face validity. It also shows cost-effectiveness results including the revised differential utilities.

Revised differential utility analyses

In relation to the ERG's summary of health state utilities in the original company submission for erenumab, we wish to clarify that the term 'differential utilities' has never been used to refer to health state utility values differing by monthly migraine day (MMD) frequency. In the appraisal of fremanezumab [TA631], the term 'differential utilities' referred to different on- and off-treatment utility values, for a given MMD frequency.[1,2] In the appraisal of galcanezumab [ID1372], the term 'differential utilities' referred to different utility values for galcanezumab and the comparator, for a given MMD frequency.[3,4] In the original erenumab submission, a patient with a given MMD frequency had the same utility value irrespective of the treatment they received and on-/off-treatment status. The mean utilities for treatment arms and model states differed only due to differences in the underlying MMD distributions.

In this context, the ERG's statement that the original company submission "*did already incorporate differential (or treatment dependent) health state utilities*" is incorrect. Therefore, we also reject the ERG's conclusion that "*the company's statement that "The economic models submitted in the erenumab appraisal to date included equal health state utility values for all treatments and both on- and off-treatment states" is therefore incorrect*" as factually inaccurate. In the versions of the economic model supplied prior to October 2020, the 'Utilities' worksheet clearly shows that the utility value for a given MMD frequency is identical for all treatments (cell range O12:Q40; for example, in the post-appeal model, the utility value for 10 MMDs is given as [redacted] for erenumab, placebo and botulinum toxin). The formulae for calculation of mean utilities per health state (C11:L19) refer to these – equal – utility values. In the submissions prior to October 2020, the mean utilities by treatment and health state thus differed only due to differences in underlying MMD distributions, which has not been referred to as "differential utilities" in any of the recent CGRP inhibitor migraine appraisals.

In the differential utilities analyses in our 16 October 2020 submission, MSQ measurements of all patients in the clinical trials who were not receiving a prophylactic migraine treatment but only best supportive care (BSC; acute medications and healthcare resource use) contributed to the utility regression models as BSC utility values. This included both baseline observations, as study protocols did not allow patients to use any prophylactic migraine treatments for 2 months before the baseline measurement, and post-baseline observations of placebo arm patients, as these patients did not receive any (active) prophylactic migraine treatment. All patients were allowed acute medications (BSC) during the trials.

Following the ERG's request in the addendum dated 27 October 2020, the revised differential utility analyses supplied in this response document follow the approach taken in the appraisal of galcanezumab [ID1372; company response to clarification question B2 in the published committee papers],[3] where baseline MSQ data were included in one regression model with MMD frequency as the only covariate and post-baseline MSQ data were included in a second

regression model with MMD frequency and treatment as covariates. Therefore, separate regression models have now been used to generate utility values

- from baseline MSQ observations, for patients who did not receive any prophylactic treatment during the 4-week MSQ recall period but BSC only, subsequently referred to as off-treatment utility values, and

- from post-baseline MSQ observations (Study 295 Week 4, 8, 12; STRIVE Week 4, 8, 12, 16, 20, 24), for patients who in the clinical trials received either erenumab 140 mg as an active prophylactic intervention or placebo, in addition to BSC, subsequently referred to as on-treatment utility values, with values differing between erenumab 140 mg and placebo for a given MMD frequency.

As in the submission dated 16 October 2020, all analyses were conducted 1) using data from the full study populations and 2) only using data from patients with ≥3 prior prophylactic treatment failures, with the latter corresponding to the target population for erenumab. In addition, as in the previous submission, analyses were conducted using 1) pooled data from Study 295 (CM) and STRIVE (EM) and 2) individual study data (i.e. considering CM and EM separately).

Results of the off-treatment (baseline) and on-treatment (post-baseline) regression models for the full population and for the ≥3 prior treatment failures population are presented in Table 1 to Table 4. Splitting the data into two regression models for off- and on-treatment reduced the sample size in each individual model, resulting in reduced statistical power compared to the differential utilities analyses in the submission dated 16 October 2020. Nevertheless, the treatment effect of erenumab 140 mg, independent of the reduction in MMDs, remained statistically significant versus placebo in all utility regression models including data from the full trial populations (Table 2). The regression models only utilising data from patients with ≥3 prior treatment failures showed [redacted] (Table 4). Of note, the regression models based on data from patients with ≥3 prior treatment failures only used a fraction of the full study population data, ranging from [redacted]% in the EM-only model to [redacted]% in the CM-only model, and [redacted]% in the combined CM+EM model.

Table 1: Off-treatment (baseline) multilevel regression models including MMD frequency as covariate – Full study population

	Full population – CM+EM (Combined Study 295, STRIVE; Normal)		Full population – CM (Study 295; Normal)		Full population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

Table 2: On-treatment (post-baseline) multilevel regression models including MMD frequency and treatment effect as covariates – Full study population

	Full population – CM+EM (Combined Study 295, STRIVE; Normal)		Full population – CM (Study 295; Normal)		Full population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

Table 3: Off-treatment (baseline) multilevel regression models including MMD frequency as covariate – Population with ≥3 prior prophylactic treatment failures

	≥3 prior prophylactic treatment failures population – CM+EM (Combined Study 295, STRIVE; Normal)		≥3 prior prophylactic treatment failures population – CM (Study 295; Normal)		≥3 prior prophylactic treatment failures population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

Table 4: On-treatment (post-baseline) multilevel regression models including MMD frequency and treatment effect as covariates – Population with ≥3 prior prophylactic treatment failures

	≥3 prior prophylactic treatment failures population – CM+EM (Combined Study 295, STRIVE; Normal)		≥3 prior prophylactic treatment failures population – CM (Study 295; Normal)		≥3 prior prophylactic treatment failures population – EM (STRIVE; Normal)	
No. of observations	[redacted]		[redacted]		[redacted]	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD frequency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

'Appendix A: Differential utility values by MMD' presents the number of observations by MMD frequency that contributed to each of the above regression models. Since off-treatment regression models were based on baseline observations only, no observations were available for lower and/or upper ranges of the MMD frequency range due to the respective study inclusion criteria relating to MMDs. However, as will be explained further below, utility values generated from these regression models were used in the economic model for all patients in negative discontinuation off-treatment states, thus requiring the regression models to predict utility values outside the observed range of MMD frequencies. This provides a strong argument for use of the combined CM+EM utility model, where observations covered a much wider range of MMD frequencies than the separate CM and EM utility models.

As expected, the regression models only using data from patients with ≥3 prior prophylactic treatment failures have fewer observations, especially in the erenumab 140 mg arm in the upper range of MMD frequencies, which reduces the power of this analysis to detect a statistically significant erenumab 140 mg treatment effect compared to the full population regression models.

'Appendix A: Differential utility values by MMD' also shows the mean observed utility values and model-predicted utility values by MMD frequency. Both in the observed and in the modelled utilities, placebo utility values were generally higher than baseline utility values, and erenumab 140 mg utility values were generally higher than placebo utility values, although some face validity issues were present where data was sparse. Face validity relating to the base case differential utility models using data from the combined CM+EM trials and patients with ≥3 prior prophylactic treatment failures, which aligns with the ERG and committee preference in the galcanezumab appraisal, is further discussed in the next section. Utility values by MMD frequency derived from these base case utility regression models are presented in Table 5.

Table 5: Utility values by MMD frequency derived from base case utility regression models ≥3 prior prophylactic treatment failures population – CM+EM

MMD	Off-treatment utility values (baseline observations; MMD as regression covariate)	On-treatment utility values (post-baseline observations; MMD and treatment as regression covariates)	
	Off-treatment (all)	Placebo	Erenumab 140 mg
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]

Assessment of face validity of differential utilities

The assumed starting age of people in the erenumab economic model is 42 years, with 84.5% of the cohort being female. The average utility value in the general population for these cohort characteristics, based on values reported in Ara and Brazier (2010), is estimated as 0.885.[5] The base case utility regression models based on erenumab trial data predict utility values for patients with 0 MMDs of [redacted] (off-treatment, based on baseline observations) to [redacted] (erenumab 140 mg) (see Table 5). In comparison with the estimated general population utility value of 0.885, the base case regression models are thus judged to be of good external validity.

In the galcanezumab appraisal [ID1372], the ERG noted (ERG report p. 74) that the utility values generated from galcanezumab trial data for 0 MMDs were notably lower than the general population value that would be expected for the cohort.[3] (A more in-depth comparison was not feasible as utility values were designated academic in confidence in ID1372.) In the appraisal of botulinum toxin [TA260], utility values for patients with ≥3 prior treatments and 0-3 monthly headache days (MHDs) were reported as 0.691 for botulinum toxin and 0.669 for placebo, which appear to be low in comparison with general population estimates, even when considering that these values are for people with up to 3 MHDs.[6] Predictions of the erenumab utility models might thus have higher face validity than utility values in other migraine NICE appraisals.

For patients with 24+ MHDs, the overview of utility values for patients with ≥3 prior treatments in the botulinum toxin appraisal [TA260] states utility values of 0.501 for patients receiving botulinum toxin and 0.461 for patients receiving placebo.[6] These values are [redacted] than the values generated in the erenumab base case utility model for this range of MMDs (see Table 5). However, MHDs and MMDs are not fully comparable and the utilities reported for patients with ≥3 prior treatments in TA260 seem to suffer from internal validity issues, as utilities for health states

with more MHDs were higher than utilities for health states with fewer MHDs in several instances, which is implausible.[6]

Since off-treatment and on-treatment utility values were derived from the erenumab trial data in two separate regression models in the latest analyses, model-predicted utilities also have to be assessed whether they are plausible relative to each other for a given MMD frequency. As shown in Figure 1, utility values derived from the base case regression models are highest for erenumab 140 mg, followed by placebo, and off-treatment (baseline) utilities, across the entire range of 0 to 28 MMDs. These differences are plausible, given the likely presence of a placebo effect in MSQ measurements while patients received placebo during the trial compared to off-treatment baseline measurements. Higher utilities for a given MMD frequency for patients treated with erenumab 140 mg represent the treatment effect versus placebo over and above the reduction of MMDs. Please refer to our previous differential utilities submission, section “Further evidence supporting the use of differential utilities”, for further discussion.

Figure 1: Utility values by MMD frequency derived from base case utility regression models ≥3 prior prophylactic treatment failures population – CM+EM

Implementation of differential utilities in economic model

As explained in our previous differential utilities submission, in the economic model dated 16 October 2020, BSC utility values were applied to the BSC comparator arm of the model and to all off-treatment states, irrespective of the prophylactic treatment used in the model prior to discontinuation. Erenumab 140 mg utility values were applied to the erenumab 140 mg on-treatment states as well as botulinum toxin on-treatment states. Table 6 provides an overview of where BSC and erenumab 140 mg utilities were applied by intervention and cost-effectiveness model state, in the economic model dated 16 October 2020.

Table 6: Source of differential utility values by intervention and model state in economic model dated 16 October 2020

Cost-effectiveness model state		Source of utility values by intervention and model state		
		Erenumab 140 mg	BSC	Botulinum toxin
Assessment period (decision tree)	Baseline	BSC	BSC	BSC
	Responders	Erenumab 140 mg	BSC	Erenumab 140 mg
	Non-responders	Erenumab 140 mg	BSC	Erenumab 140 mg
Post-assessment period (Markov model)	On treatment	Erenumab 140 mg	BSC	Erenumab 140 mg
	Negative discontinuation (non-response; AE-related; long-term)	BSC	BSC	BSC

Note: BSC utility vales were generated from baseline MSQ observations and placebo arm post-baseline MSQ observations. Erenumab 140 mg utility values were generated from erenumab 140 mg arm post-baseline MSQ observations (on-treatment).
Abbreviations: AE: adverse event; BSC: best supportive care.

In the new differential utilities analyses requested by the ERG, MSQ observations for patients effectively on BSC were split between on-placebo observations and off-treatment (baseline) observations. The updated economic model, dated 29 October 2020 and supplied with this submission, accordingly utilises placebo utility values for the calculation of QALYs for all health states where patients in the clinical trials received placebo, and off-treatment (baseline) utility values for all health states where patients received neither placebo nor an active prophylactic intervention. Again, for botulinum toxin the same on-treatment utility values were assumed as for erenumab 140 mg on-treatment. An overview by intervention and model state is given in Table 7.

From a technical perspective, due to the limited time available, regression coefficients of the previously provided differential utility models were overwritten with the regression coefficients of the new differential utility models in the economic model dated 29 October 2020 ('Utilities' worksheet, cells N90:O107). Regression coefficients from the separate off-treatment (baseline) utility models are given in cells W90:X101, and introduced into the calculation with cells H53:I56 and G59:G88. To facilitate the ERG's review of the inclusion of new differential utility values, all changes on the 'Utilities' worksheet are highlighted in red font. Due to time constraints and as this would have required more extensive rework of the model, off-treatment utility regression coefficients were not included in the parameters for the probabilistic analysis. A probabilistic sensitivity analysis run with the model dated 29 October 2020 will thus not capture the full uncertainty present in the utility estimates.

Table 7: Source of differential utility values by intervention and model state in economic model dated 29 October 2020

Cost-effectiveness model state		Source of utility values by intervention and model state		
		Erenumab 140 mg	BSC	Botulinum toxin
Assessment period (decision tree)	Baseline	Off-treatment	Off-treatment	Off-treatment
	Responders	Erenumab 140 mg	Placebo	Erenumab 140 mg
	Non-responders	Erenumab 140 mg	Placebo	Erenumab 140 mg
Post-assessment period (Markov model)	On treatment	Erenumab 140 mg	Placebo	Erenumab 140 mg
	Negative discontinuation (non-response; AE-related; long-term)	Off-treatment	Off-treatment	Off-treatment

Note: Off-treatment utility vales were generated from baseline MSQ observations. Erenumab 140 mg and placebo utility values were generated from post-baseline MSQ observations (on-treatment).
Abbreviations: AE: adverse event; BSC: best supportive care.

Mean utilities generated by the economic model are presented in Table 8 by population, intervention and model state. Mean utilities differ due to different underlying MMD distributions (as in the original submission), as well as due to differential utility values being used for any given MMD frequency for prophylactic interventions (erenumab 140 mg, botulinum toxin) and BSC, and for on- and off-treatment states (as shown in Table 7).

Table 8: Mean utilities by intervention and model state in economic model dated 29 October 2020, with differential utility model ≥3 treatment failure population – CM+EM

Cost-effectiveness model state		Mean utilities across cohort by intervention and model state		
		Erenumab 140 mg	BSC	Botulinum toxin
Episodic migraine ≥3 prior treatment failures				
Assessment period	Baseline	[redacted]	[redacted]	NA
	Responders	[redacted]	[redacted]	NA
	Non-responders	[redacted]	[redacted]	NA
Post-assessment period	On treatment	[redacted]	[redacted]	NA
	Negative discontinuation	[redacted]	[redacted]	NA
Chronic migraine ≥3 prior treatment failures				
Assessment period	Baseline	[redacted]	[redacted]	[redacted]
	Responders	[redacted]	[redacted]	[redacted]
	Non-responders	[redacted]	[redacted]	[redacted]
Post-assessment period	On treatment	[redacted]	[redacted]	[redacted]
	Negative discontinuation	[redacted]	[redacted]	[redacted]

Chronic migraine ≥4 prior treatment failures, post-botulinum toxin				
Assessment period	Baseline	[redacted]	[redacted]	NA
	Responders	[redacted]	[redacted]	NA
	Non-responders	[redacted]	[redacted]	NA
Post-assessment period	On treatment	[redacted]	[redacted]	NA
	Negative discontinuation	[redacted]	[redacted]	NA
Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin				
Assessment period	Baseline	[redacted]	[redacted]	NA
	Responders	[redacted]	[redacted]	NA
	Non-responders	[redacted]	[redacted]	NA
Post-assessment period	On treatment	[redacted]	[redacted]	NA
	Negative discontinuation	[redacted]	[redacted]	NA

Cost-effectiveness results including revised differential utilities

Cost-effectiveness results including the revised differential utilities are presented in the following tables for all populations of interest. Conclusions on cost-effectiveness from our 16 October 2020 submission remain unchanged for all populations. Compared to the previous differential utilities submission, the base case ICER of erenumab 140 mg versus the relevant comparator slightly decreased in all populations except for the chronic migraine ≥4 prior treatment failures population, where the ICER slightly increased. Scenario analyses with alternative differential utility models demonstrate that the conclusions are robust to changes in the applied differential utilities models.

Compared to the base case differential utility values included in the 16 October 2020 submission, the difference in utility values for a given MMD frequency decreased between erenumab 140 mg and placebo, but increased between erenumab 140 mg and off-treatment (baseline) utilities (as in the previously supplied analyses, BSC utility values were generated from combined baseline and placebo MSQ measurements). The observed changes in the cost-effectiveness results suggest that the positive impact of the larger difference between erenumab 140 mg and off-treatment utility values outweighed the negative impact of the smaller difference between erenumab 140 mg and placebo utility values in all populations except for the chronic migraine ≥4 prior treatment failures population.

Table 9: Episodic migraine ≥3 prior treatment failures: Base case results with revised differential utilities (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility models ≥3 treatment failure population – CM+EM					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 10: Episodic migraine ≥3 prior treatment failures: Scenario analyses with revised alternative differential utility models (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: Utility models full population – CM+EM					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Utility models full population – EM					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Utility models ≥3 treatment failure population – EM					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 11: Chronic migraine ≥3 prior treatment failures: Base case results with revised differential utilities (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility models ≥3 treatment failure population – CM+EM					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 12: Chronic migraine ≥3 prior treatment failures: Scenario analyses with revised alternative differential utility models (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: Utility models full population – CM+EM					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Utility models full population – CM					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Utility models ≥3 treatment failure population – CM					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 13: Chronic migraine ≥4 prior treatment failures, post-botulinum toxin: Base case results with revised differential utilities (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility models ≥3 treatment failure population – CM+EM					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Given the very small subgroup size, no separate utility analysis was undertaken for patients with CM and ≥4 prior treatment failures, post-botulinum toxin.
Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 14: Chronic migraine ≥4 prior treatment failures, post-botulinum toxin: Scenario analyses with revised alternative differential utility models (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: Utility models full population – CM+EM					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario 2: Utility models full population – CM												
BSC		[redacted]			[redacted]							
Erenumab 140 mg		[redacted]			[redacted]			[redacted]			[redacted]	
Scenario 3: Utility models ≥3 treatment failure population – CM												
BSC		[redacted]			[redacted]							
Erenumab 140 mg		[redacted]			[redacted]			[redacted]			[redacted]	

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 15: Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin: Base case results with revised differential utilities (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Utility models ≥3 treatment failure population – CM+EM					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 16: Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin: Scenario analyses with revised alternative differential utility models (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: Utility models full population – CM+EM					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Utility models full population – CM					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Utility models ≥3 treatment failure population – CM					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Cost-effectiveness results addressing further inconsistencies and including revised differential utilities

As highlighted in the 16 October 2020 submission, further inconsistencies were identified in the appraisals of erenumab [ID1188], fremanezumab [TA631] and galcanezumab [ID1372]. For further details, we refer to the section titled “Scenario analyses addressing further inconsistencies between appraisals” in said submission. With regard to age-related disutilities, we noticed that our previous submission included an incorrect reference. We apologise for this error and are providing the correct reference (Ara and Brazier 2010)[5] with this submission.

Cost-effectiveness results for scenario analyses addressing these other inconsistencies and incorporating the latest differential utilities estimates are shown in the tables below. Again,

compared to the previous submission including differential utilities, ICERs slightly improved in all scenarios and populations except for the chronic migraine subgroup with ≥4 prior prophylactic treatment failures, where a minor increase in ICERs was observed in two of the scenarios.

Table 17: Episodic migraine ≥3 prior treatment failures: Scenario analyses addressing other inconsistencies (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including revised differential utilities; see Table 9)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Inclusion of administration costs for 10% of erenumab patients					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Inclusion of age-related disutility					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Dissipation of placebo effect for BSC responders after 1 year					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 18: Chronic migraine ≥3 prior treatment failures: Scenario analyses addressing other inconsistencies (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including revised differential utilities; see Table 11)					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Inclusion of administration costs for 10% of erenumab patients					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Inclusion of age-related disutility					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Dissipation of placebo effect for BSC responders after 1 year					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Erenumab treatment effect over botulinum toxin (OR=[redacted])					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	**Extendedly dominated**
Erenumab 140 mg	[redacted]	[redacted]	[redacted] (vs BSC)	[redacted] (vs BSC)	[redacted] (vs BSC)

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 19: Chronic migraine ≥4 prior treatment failures, post-botulinum toxin: Scenario analyses addressing other inconsistencies (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including revised differential utilities; see Table 13)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Inclusion of administration costs for 10% of erenumab patients					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Inclusion of age-related disutility					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Dissipation of placebo effect for BSC responders after 1 year					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 20: Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin: Scenario analyses addressing other inconsistencies (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (including revised differential utilities; see Table 15)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Inclusion of administration costs for 10% of erenumab patients					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Inclusion of age-related disutility					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Dissipation of placebo effect for BSC responders after 1 year					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

In the population with chronic migraine and ≥3 prior treatment failures, with the latest differential utilities estimates an odds ratio of [redacted] of erenumab 140 mg vs botulinum toxin in the ≥30% MMD reduction outcome would be sufficient to achieve an ICER <£20,000 (£[redacted]); an ICER <£30,000 would result from an odds ratio of [redacted] (ICER £[redacted]). The existence of at least such a minimal treatment effect seems highly plausible, given the consistent, at least numerical benefit of erenumab 140 mg vs botulinum toxin demonstrated in ITCs (refer to our previous submissions).

References

1. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [TA631]. Committee papers 1. Available at https://www.nice.org.uk/guidance/ta631/documents/committee-papers [Last accessed: 29/10/2020].
2. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [TA631]. Committee papers 2. Available at https://www.nice.org.uk/guidance/ta631/documents/committee-papers-2 [Last accessed: 29/10/2020].
3. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]. Committee papers. Available at https://www.nice.org.uk/guidance/gid-ta10454/documents/committee-papers [Last accessed: 29/10/2020].
4. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]. Final Appraisal Document. Available at https://www.nice.org.uk/guidance/gid-ta10454/documents/final-appraisal-determination-document [Last accessed: 29/10/2020].
5. Ara R, Brazier JE. Populating an economic model with health state utility values: Moving toward better practice. Value Health 2010;13(5):509-18.
6. National Institute for Health and Care Excellence. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine [TA260]. Migraine (chronic) - botulinum toxin type A: manufacturer utility correction document. 16 February 2012. Available at https://www.nice.org.uk/guidance/ta260/documents/migraine-chronic-botulinum-toxin-type-a-manufacturer-utility-correction-document2 [Last accessed: 29/10/2020].

Appendix A: Differential utility values by MMD

Table 21: Off-treatment (baseline) observed and model-predicted utility values by MMD frequency – Full population CM+EM model

MMD	Number of observations	Observed mean utility value	Model-predicted utility value
	Baseline	Baseline	Baseline
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: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

Table 22: On-treatment observed and model-predicted utility values by MMD frequency – Full population CM+EM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

Table 23: Off-treatment (baseline) observed and model-predicted utility values by MMD frequency – Full population CM model

MMD	Number of observations	Observed mean utility value	Model-predicted utility value
	Baseline	Baseline	Baseline
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: CM: chronic migraine; MMD: monthly migraine day.

Table 24: On-treatment observed and model-predicted utility values by MMD frequency – Full population CM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; MMD: monthly migraine day.

Table 25: Off-treatment (baseline) observed and model-predicted utility values by MMD frequency – Full population EM model

MMD	Number of observations	Observed mean utility value	Model-predicted utility value
	Baseline	Baseline	Baseline
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: EM: episodic migraine; MMD: monthly migraine day.

Table 26: On-treatment observed and model-predicted utility values by MMD frequency – Full population EM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EM: episodic migraine; MMD: monthly migraine day.

Table 27: Off-treatment (baseline) observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population CM+EM model

MMD	Number of observations	Observed mean utility value	Model-predicted utility value
	Baseline	Baseline	Baseline
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: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

Table 28: On-treatment observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population CM+EM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day.

Table 29: Off-treatment (baseline) observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population CM model

MMD	Number of observations	Observed mean utility value	Model-predicted utility value
	Baseline	Baseline	Baseline
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: CM: chronic migraine; MMD: monthly migraine day.

Table 30: On-treatment observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population CM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; MMD: monthly migraine day.

Table 31: Off-treatment (baseline) observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population EM model

MMD	Number of observations	Observed mean utility value	Model-predicted utility value
	Baseline	Baseline	Baseline
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: EM: episodic migraine; MMD: monthly migraine day.

Table 32: On-treatment observed and model-predicted utility values by MMD frequency – ≥3 prior prophylactic treatment failures population EM model

MMD	Number of observations		Observed mean utility value		Model-predicted utility value	
	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg	Placebo	Erenumab 140 mg
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EM: episodic migraine; MMD: monthly migraine day.

Has the company's new approach to differential utilities resolved the issues the ERG had with the methodology

Yes the current methodology for the multilevel regression model is definitely preferred and seems reasonable. It also appears to support that in the previous analyses, the estimated differential utility (using the "treatment" covariate where baseline observations were categorised as BSC) partly included the placebo effect (as suspected by the ERG) and thus shouldn't be used.

Are the face validity checks reasonable?

As a face validity check, the company compares the general population utility values with the estimated utility values for migraine patients with 0 MMDs. This is a limited face validity assessment but it is appreciated given the time available. In addition, it is really helpful that the company summarises the health state utilities in Table 8 as well as the implementation method in Table 7. The committee might want to discuss the face validity based on these Tables.

Are there outstanding issues?

It is contra intuitive that the ICERs of erenumab 140 mg versus the relevant comparator, in general, slightly decreased (when considering the estimated coefficients for the "treatment" covariate of the 29 October 2020 and the 16 October 2020 submitted regression models). This is likely due to the assumed utilities after discontinuation. As highlighted by the company in Table 7, after discontinuation the company assumes patients are assigned 'off-treatment' i.e. baseline utilities and not BSC utilities. As illustrated by Figure 1 this might have an impact on the estimated QALYs (particularly driven by the difference in discontinuation due to the (proportions of) non-responders). Additionally, this assumption seems inconsistent with the assumptions for MMD frequency after discontinuation. After discontinuation it is assumed that patients maintain the non-responder MMD improvement (and will not rebound back to baseline MMD). The approach described Table 6 (used in the previous analyses) but using the newly estimated utility values might be a reasonable alternative. Therefore, the ERG added a scenario analysis using the company's 16 October 2020 approach while implementing the differential treatment utility ([redacted]) estimated in the 29 October 2020 submitted document by the company (Table below). These results indicate that when adopting a differential treatment utility, the exact approach to implement this is unlikely to be a main driver of the cost-effectiveness of erenumab 140 mg.

Table: Deterministic results ([redacted])

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Episodic migraine ≥3 prior treatment failures					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 16 October 2020					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 29 October 2020[a]					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case 16 October 2020 + differential utility of 29 October 2020 ([redacted])					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility) – consistent with ERG base-case in original ERG report (assuming constant treatment effectiveness)					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic migraine ≥3 prior treatment failures ([redacted])[b]					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 16 October 2020					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 29 October 2020[a]					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case 16 October 2020 + differential utility of 29 October 2020 ([redacted])					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility)					
BSC	[redacted]	[redacted]			
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic migraine ≥3 prior treatment failures, contraindication to botulinum toxin					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 16 October 2020					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 29 October 2020[a]					

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case 16 October 2020 + differential utility of 29 October 2020 ([redacted])					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility) – consistent with post-appeal ERG base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic migraine ≥4 prior treatment failures; post-botulinum toxin					
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 16 October 2020					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case (differential utility; utility model CM+EM – ≥3 treatment failure population) 29 October 2020[a]					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case 16 October 2020 + differential utility of 29 October 2020 ([redacted])					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (no differential utility) – consistent with post-appeal ERG base-case					
BSC	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; CM: chronic migraine; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

[a]Given the time available the ERG did not consider the correctness of the implementation of these analyses

[b]The cost-effectiveness of erenumab 140 mg versus BSC for this population ranged between approximately [redacted] per QALY gained and [redacted] per QALY gained.