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Erenumab for preventing migraine

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Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Sabine Grimm, Xavier Pouwels, Willem Witlox, Svenja Petersohn, Nigel Armstrong and Dhwani Shah acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Shelley de Kock critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse events
BASH	British Association for the Study of Headache
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CGRP	calcitonin gene-related peptide
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effect
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
EQ-5D-5L	European Quality of Life-5 Dimensions, five-level scale
ERG	Evidence Review Group
FDA	Food and Drug Administration
HFEM	High-frequency episodic migraine
HIT-6	Headache impact test
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
HUI	Health utilities index
ITC	Indirect treatment comparison
ICER	Incremental cost effectiveness ratio
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
ITT	Intention to treat
IV	Intravenous
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LFEM	Low-frequency episodic migraine
LSM	Least square method
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
Mg	Milligram
MHD	Monthly headache days
MHRA	Medicines and Healthcare Products Regulatory Agency
MIDAS	Migraine disability assessment
MMD	Monthly migraine days
MPFID	Migraine physical function impact diary
MSQ	Migraine-specific quality of life questionnaire
NA	Not applicable
NHS	National Health Service
NHWS	National health and wellness survey

NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
ONS	Office of National Statistics
OR	Odds ratio
ORR	Overall response rate
PAS	Patient access scheme
PRESS	Peer review of electronic search strategies
PRO	Patient-reported outcome
PROMIS	Patient-reported outcomes measurement information system
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q4W	Every four weeks
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse events
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-6D	Short-form six-dimension
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SNRI	Serotonin and norepinephrine reuptake inhibitor
SPC	Summary of product characteristics
STA	Single technology appraisal
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
UK	United Kingdom
VAS	Visual analogue scale
WHO	World Health Organisation
WPAI	Work productivity and activity impairment

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the NICE scope is people with migraine. Erenumab has received marketing authorisation from the European Medicines Agency (EMA) for the prophylaxis of migraine in adults who have at least four migraine days per month. However, the population in the company's submission represents a subset both of the population in the NICE scope and in the marketing authorisation. The targeted population is adult patients with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed. The population addressed is likely to reflect the expected use of erenumab in the NHS as it targets those with the highest unmet need. Furthermore, erenumab would not be expected to be used in treatment-naïve patients due to the low cost of oral prophylactics. The submission relies, primarily, on four randomised, placebo-controlled trials of erenumab, of which three were conducted in patients with episodic migraine and one in patients with chronic migraine. For all four trials, the data used in the submission were derived from *post-hoc* subgroup analyses of patients for whom ≥3 prior prophylactic treatment categories had failed.

The intervention (erenumab) is in line with the scope. The recommended dosage is 70mg every four weeks administered as a subcutaneous injection using a pre-filled pen for self-injection, although some patients may benefit from a dosage of 140mg every four weeks (Q4W), which is administered as two consecutive injections of 70mg each. The company's model assumed that 50% of patients would receive 70mg and 50% of patients 140mg. However, logically, if not all patients would receive the same dose then there must be variation in those patients such that some would benefit more from one dose than another. This would imply two different populations but the company did not explicitly differentiate any such populations and neither were such populations described in the scope. Therefore, it follows that both doses are indicated for the same population and therefore should be considered as comparators to each other. The implications of this are discussed in the economic modelling sections of this report.

The description of comparators in the NICE scope is: "Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies". For the main comparator, best supportive care (BSC), the company considered the placebo arms of the main erenumab trials to be representative of BSC and provided full details of concomitant treatment. No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus BSC. Although these comparators are appropriate for the patients addressed in the company's submission (for whom ≥3 prior prophylactic treatment categories had failed), any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s).

Relevant outcomes were described in the submission, although it is noted that the double-blind phases of the included trials are only up to 24 weeks. Data from open label phases of the trials are available up to 52 weeks but the effectiveness of erenumab as a long-term prophylaxis of migraine requires extrapolation from the data available.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company's submission (CS) included four key erenumab studies. Study 295 was the only erenumab study conducted in patients with chronic migraine. Three studies (STRIVE, ARISE and LIBERTY) were conducted in patients with episodic migraine. Across the four trials, a total of 2,445 patients were included (full intention-to-treat [ITT] population). Of these only 515 are directly relevant to the decision

problem as they had failed ≥3 prior prophylactic treatments. All erenumab trials were randomised, double-blind, placebo-controlled, parallel-group studies and all trials had open-label or active treatment extensions. Double-blind phases were either 12 or 24 weeks in duration. Eligible patients were adults, defined as 18 to 65 in all trials. The trials were international and, with the exception of the ARISE trial, all had a small number of UK sites. Overall, [redacted] patients from the UK were included across the four trials. Although all trials compared erenumab to placebo, dosages varied (70mg and/or 140mg). All outcomes related to change in the number of migraine days as a primary outcome but this was measured differently and at different time points across the trials.

In Study 295 (chronic migraine) the optimised population (≥3 prior prophylactic treatments have failed) had statistically significantly better outcomes in the erenumab 70mg and 140mg groups than in the placebo group. More specifically, at week 12 patients experienced approximately two and a half fewer migraine days whilst taking erenumab 70mg and four fewer whilst taking erenumab 140mg than on placebo. In total, 34.8% of patients taking 70mg of erenumab and 38.5% of patients taking 140mg erenumab achieved a ≥50% reduction in monthly migraine days (MMDs) from baseline, compared to 15.3% of patients on placebo. In studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks, and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. With the exception of change in MMDs in the LIBERTY trial, these effects were statistically significant. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed for any of the outcomes assessed.

Across all four trials, the vast majority of adverse events experienced by patients in the erenumab treatment arms were of mild or moderate severity and very low numbers of patients experienced any serious adverse events.

In the absence of direct evidence comparing erenumab to botulinum toxin, the company conducted three indirect treatments comparisons (ITCs) using erenumab data from Study 295 and botulinum toxin data from PREEMPT. In the optimised population (≥3 prior prophylactic treatments have failed) there was no significant difference between erenumab 70mg and botulinum toxin for ≥50% responder rate (based on monthly headache days) with an OR = [redacted]), this result was similar when using the full trial population (OR [redacted]). There were also no significant differences between erenumab 140mg and botulinum toxin in either the optimised population (OR [redacted]) or full trial populations (OR 1.19, 95% CI 0.74 to 1.92). The indirect comparison results also showed no significant differences between treatments when the outcome of ≥50% responder rate was calculated from monthly migraine days and monthly headache days (MHDs).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company conducted a systematic review to identify studies reporting the efficacy and safety of erenumab and botulinum toxin (as the only active comparator) for the prophylaxis of migraine in adults. The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches. A wide range of databases were searched, and additional searches of conference proceedings, HTA websites and a trials register were conducted. Relevant systematic literature reviews (SLRs) and

network meta-analyses (NMAs) identified through database and grey literature searches were also reference checked. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.

The ERG notes that the evidence for erenumab is based on four international RCTs investigating patient-relevant outcomes. However, only one trial was conducted in patients with chronic migraine and the number of trial participants for whom ≥3 prior prophylactic treatments had failed is relatively low (approximately 20% of the total studied population). Furthermore, three of the four studies had a double-blind phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was mean monthly migraine days. It is certainly inadequate to show the effect on a condition that would be expected to last far beyond this period, thus the long-term effectiveness of erenumab treatment remains unknown.

The ERG also questions the use of the more stringent (≥50% reduction in MMDs vs. ≥30% reduction in MMDs) definition of responder; it seems unlikely that patients in this population would consider a reduction in their MMDs of between 30 and 49% to be not clinically meaningful. Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <30% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 20% reduction in MMDs which they considered to be beneficial.

Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented. This observation applies to both the whole study populations and to the subgroups which are relevant to this submission. There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

With respect to the definitions of chronic and episodic migraine used in the included studies, there is a potential population group (≥15 headache days per month of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population.

With respect to the ITC of erenumab versus botulinum toxin in the chronic migraine population, the ERG notes that there is a lack of evidence to support the company's assertion that the difference in the time point at which the primary outcome was measured, between the erenumab and botulinum toxin studies used in the ITC, would be likely to favour botulinum toxin. The effect of this difference is unclear. The ERG does not have any concerns about the methods or results of the ITC analyses.

1.4 Summary of cost effectiveness evidence submitted by the company

The company developed a decision-tree plus state transition model. The decision tree represented the assessment period. At the end of the assessment period, the probability of treatment response was estimated. Thereafter, responders and non-responders were modelled as separate health states in the post-assessment period using a state transition model. The costs and quality-adjusted life years (QALYs) associated with these health states were calculated conditional on the MMD frequency distributions.

Erenumab, as per marketing authorisation, is indicated for the treatment of all migraine patients who experience ≥4 MMDs. However, the company assessed the cost effectiveness of erenumab in adults with migraine with ≥4 MMDs for whom ≥3 prior prophylactic treatments have failed. This subgroup was further separated into three populations:

- Whole population base-case (patients with ≥4 MMDs)
- Episodic migraine population (patients with <15 MHDs and ≥4 to <15 MMDs)
- Chronic migraine population (patients with ≥15 MHDs and ≥8 MMDs)

The whole population was based on a weighted average of chronic and episodic migraine (66% and 34% respectively; based on market research from the UK). In addition, the high-frequency episodic migraine (HFEM) (8-14 MHDs) subgroup was considered.

As per the licensed posology, the recommended dose for erenumab (self-administered subcutaneously) is 70mg Q4W. However, some patients may benefit from the higher 140mg Q4W dosage (given as two injections of 70mg). The company therefore assumed in their base-case that 50% of patients started treatment on erenumab 140mg and the remaining 50% starting on erenumab 70mg (named blended dose). Erenumab was modelled to be used in combination with BSC.

BSC was defined as continued treatment with acute medication and healthcare resource use in line with the MMD frequency being experienced. The company stated that the placebo arms in Study 295, STRIVE, ARISE and LIBERTY can be considered as reasonably representative of BSC in the UK.

Botulinum toxin was modelled as a comparator for patients having chronic migraine for whom ≥3 prior prophylactic treatments have failed, in line with its recommended use.

The analysis took an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was 12 weeks with a 10-year time horizon and a half-cycle correction was applied.

Clinical parameters were mainly derived from the subgroup of patients for whom ≥3 prior treatments had failed in the pivotal trials (i.e. Study 295 for chronic migraine and ARISE, STRIVE and LIBERTY for episodic migraine). The main treatment effectiveness parameters were the proportion of responders, the MMD frequency distributions (at baseline, after response and after non-response), treatment discontinuation and general population mortality (no excess mortality was assumed). The treatment effectiveness was extrapolated by assuming that the transition probabilities (i.e. probability of treatment discontinuation) as well as the MMD frequency distributions would be constant over time.

Adverse events were accounted for in terms of treatment discontinuation, but the impact on costs and health-related quality of life (HRQoL) was not explicitly modelled.

For the company's base-case analysis, treatment independent utility values for each MMD frequency were estimated based on Study 295, STRIVE, and ARISE. Utility values were estimated using multilevel models depending on the MMD frequency distributions. For this purpose, Migraine-Specific Quality of life questionnaire (MSQ) mapped utility values were used. The company stated that the advantage of the MSQ over the European Quality of Life-5 Dimensions (EQ-5D) is its recall period of four weeks, which makes it more likely to capture the impact of experiencing migraine on quality of life than with the European Quality of Life-5 Dimensions, three-level scale (EQ-5D-3L), which was collected in LIBERTY.

The cost categories included in the model were treatment costs and costs of disease management. Treatment costs included drug costs, administration costs and initiation costs. Costs for disease management contained visits to the emergency department, general practitioner, nurse practitioner and neurologist, hospitalisations, migraine-specific medication (assumed to be represented by triptan use) and other medication (assumed to be represented by analgesics). Unit prices stemmed from the

manufacturer, the British National Formulary (BNF) 2017, the National Health Service (NHS) Tariff 2017 and the Personal Social Services Research Unit (PSSRU) 2017. Resource use data from the National health and wellness survey (NHWS) of 2017 and 2018 were used.

The company presented their base-case results separately for the whole migraine, the chronic migraine and the episodic migraine populations, within the subgroup of patients for whom ≥3 prior prophylactic treatments had failed; and separately for the blended dose (50% of patients receiving erenumab 70mg and 50% erenumab 140mg), the 140mg dose and the 70mg dose. The deterministic base-case cost effectiveness results of erenumab (with patient access scheme [PAS]) compared with BSC for the blended dose amount to an incremental cost effectiveness ratio (ICER) of £22,446 per QALY gained in the whole migraine population, to £18,893 per QALY gained in the chronic migraine population, and to £35,787 per QALY gained in the episodic migraine population.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

Cost effectiveness searches in the CS and in the response to clarification were well documented and easily reproducible and were carried out in line with the NICE guide to the methods of technology appraisal. Searches were reported for a wide range of databases and additional searches of conference proceedings, grey literature sources and reference checking were also reported.

The model structure proposed by the company did not fully capture natural progression of migraine. The ERG believes the justification provided by the company, not to model natural progression of migraine, is reasonable. However, the impact of this simplification is not fully known and hence increases the uncertainty regarding the cost effectiveness results. The exact definition of response to treatment might be another source of uncertainty. The company used a ≥50% reduction in baseline MMDs to define response, however, guidelines state that a ≥30% reduction can be clinically meaningful in patients with chronic migraine. For NICE TA260 on botulinum toxin in chronic migraine the committee stated that a 30% (MHD) response rate was the most clinically relevant and reasonable negative (due to no response) stopping rule on which to base its decision.

Patients with ≥15 MHDs and ≥4 to <8 MMDs were not included in either the pivotal trials on chronic migraine or those on episodic migraine. However, these patients are included in the definition of the overall model population (migraine patients with ≥4 MMDs). The company assumed that data from chronic and episodic patients will be applicable to this patient group. As no justification was provided for this assumption and the characteristics of the excluded population are unknown, the ERG finds this assumption not well-founded and considers the evidence for the cost effectiveness of erenumab in patients with ≥15 MHDs and ≥4 to <8 MMDs to be lacking.

The base-case presented by the company used a blended dose of erenumab 70mg and erenumab 140mg for the intervention arm, assuming a dose mix of 50% and 50%, respectively. The use of the blended dose and the 50%/50% distribution are not appropriately justified. Therefore, the ERG included erenumab 70mg and erenumab 140mg separately in its base-case analysis (instead of the blended dose).

In their base-case, the company used a 10-year time horizon for the cost effectiveness analysis of erenumab versus BSC and botulinum toxin, which is not in accordance with the NICE reference case. To adhere to the NICE reference case, the ERG extended the time horizon to a lifetime horizon in their ERG base-case analysis.

There is a lack of evidence related to the extrapolation of (comparative) treatment effectiveness. Although the company provided data from open-label extension studies, these studies did not provide comparative effectiveness data and the follow-up of these studies was also limited (52 weeks for chronic

migraine and 64 weeks for episodic migraine). After this period there was no evidence to inform the extrapolation of treatment effectiveness.

Regarding adverse events, the main concerns of the ERG relate to not explicitly modelling the impact of adverse event on costs and HRQoL.

Whilst treatment effectiveness was based on the population with ≥3 prior prophylactic treatments failed, utility values in the model were informed by the full trial population. According to the company, using the population with ≥3 prior prophylactic treatments failed, the number of patients available in the analysis would be significantly reduced, particularly for STRIVE and ARISE. In response to clarification question B14.b, the company implemented a scenario using utility values estimated from the population with ≥3 prior prophylactic treatments, but only for the whole migraine population (not separately for chronic and episodic migraine) due to small sample sizes. Since the company only provided this analysis in the whole migraine population, the ERG maintained the company's base-case analysis using the full trial population in the ERG base-case. This ensures consistency in the derivation of utilities and resource use, but results in inconsistencies between utility and effectiveness estimates.

Similarly, all estimates of resource use and costs were obtained from patient populations not specified to have ≥3 prior failures of prophylactic treatment. The company provided no evidence that prior treatment failure does not impact the costs of migraine treatment. Hence, the ERG cannot rule out that the estimates presented are subject to bias. Additionally, the company assumed sumatriptan injections to have the same price as oral sumatriptan, without appropriate justification.

The main concerns related to the results presented by the company were the lack of full incremental analyses separately including both the erenumab 140mg and 70mg doses, and the failure to include all important parameters in the probabilistic sensitivity analyses.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The searches in the CS were well presented and easily reproducible. A good range of databases and grey literature sources were searched and reference checking was also undertaken. Recognised study design filters were applied to all clinical effectiveness searches and searches for costs, resource use and HRQoL. Furthermore, relevant terms were added to the study design filters to increase sensitivity. Reference checking was also undertaken by the company in order to identify additional studies not retrieved by the main searches. The clinical evidence is based on four multinational RCTs in a relevant patient group. Relevant outcomes are assessed.

The model developed by the company provides granularity with respect to MMD frequency. By reproducing the patient distributions across MMDs for each treatment for multiple time-points, the economic model retains a strong faithfulness to the trial data and captures information that would otherwise be lost through grouping patients.

1.6.2 Weaknesses and areas of uncertainty

The evidence for erenumab in the submission population (adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed) is based on *post-hoc* subgroup analyses of data from four RCTs involving approximately 20% of the total studied population (n=515). Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented in the erenumab studies, both with respect to the whole study population and to the subgroup relevant to this submission. There is also a lack of

evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age. Given the definitions of chronic (≥15 headache days per month, of which ≥8 were migraine days) and episodic (≥4 and <15 migraine days per month with <15 headache days per month) migraine used in the included studies, there is a population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population.

There is a lack of long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, for either the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed or the wider population covered by the marketing authorisation.

The ERG is concerned that a separate search for adverse events (AEs) was not undertaken. In response to clarification the company reported that AEs were identified by screening the results of database searches. However, clinical effectiveness searches applied a study design filter to identify randomised clinical trials (RCTs) and guidance by the Centre for Reviews and Dissemination (CRD) recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure AEs that are long-term, rare or unanticipated are not missed. It is possible that some relevant evidence may not have been identified as a consequence of this.

There is no direct evidence to compare the effectiveness of erenumab to botulinum toxin.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has incorporated various adjustments to the company base-case. The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that erenumab 140mg was cost effective at willingness to pay thresholds higher than £16,905 and £38,[illegible] per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period respectively (erenumab 70mg was dominated). For the episodic population the probabilistic ERG base-case results indicated that erenumab 70mg would be cost effective at willingness to pay thresholds higher than £10,047 per QALY gained, when assuming a constant treatment effect over time (erenumab 140mg is dominated). When assuming treatment effect waning over a five-year period, this would be £95,227 per QALY gained for erenumab 70mg (erenumab 140mg became cost effective at a willingness to pay threshold of £267,487 per QALY gained).

It should, however, be noted that the increased effectiveness (in terms of QALYs) of erenumab 70mg versus erenumab 140mg (when assuming constant treatment effectiveness), in the episodic migraine population, is inconsistent with the clinical effectiveness evidence presented in chapter 4 (Table 4.9). In Section 4.2.3, the ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed. Indeed, there is a numerically larger difference vs. placebo in change from baseline MMD for 140mg than for 70mg; only the former is statistically significant, and this only in the STRIVE trial. The favourable cost effectiveness of erenumab 70mg for the episodic population seems driven by the MMD frequency distribution for non-responders that is lower than for erenumab 140mg and BSC. It is questionable whether, given the above results for all patients, there would be an advantage for 70mg vs. 140mg for those patients who do not respond. It is also questionable whether extrapolating this benefit for non-responders (or any benefit in MMD frequency distribution for responders) is plausible given the changing response over time. This is to some extent mitigated in

the treatment waning scenarios given benefits in terms of MMD frequency distributions are decreased over time.

In conclusion, the cost effectiveness of erenumab in the chronic and episodic migraine populations largely depends on the assumptions related to the extrapolation of treatment effectiveness. Based on willingness to pay thresholds of £20,000 and £30,000 per QALY gained, erenumab 140mg and erenumab 70mg may be cost effective for the chronic and episodic migraine populations respectively if a constant treatment effect over time is assumed. However, as mentioned above, the plausibility of this assumption may be questionable. The estimated ICERs for erenumab increased above these willingness to pay thresholds of £20,000 and £30,000 per QALY gained if a treatment effect waning with a five-year period is assumed. Finally, it is unclear whether these results can be extrapolated to the population with ≥15 MHDs and ≥4 to <8 MMDs as no cost effectiveness evidence is provided for this population.

2. BACKGROUND

In this section, the Evidence Review Group (ERG) provides a review of the background evidence submitted by Novartis in support of erenumab, trade name Aimovig®, for the treatment of migraine. We outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken mainly from Chapter B.1 of the company's submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem.

The underlying health problem, addressed by this appraisal, is migraine. Migraine is a serious chronic neurological disorder It has been ranked as the third leading cause of disability in under 50's worldwide,[2] and classified among the most disabling illnesses by the World Health Organisation (WHO), comparable to dementia and active psychosis.[3] Migraine has a high burden of disease; attacks may last for up to 72 hours, with patients experiencing a variety of symptoms, including severe throbbing pain in the head, nausea and vomiting, dizziness, fever and visual disturbances.[4, 5]Around 25% of migraine suffers also experience an aura phase, which usually lasts for under an hour and is characterised by visual disturbances, numbness or weakness, slurred speech and sensitivity to light and sound.[1, 5] In addition to the clinical burden, migraine is the second most frequently cited cause of short-term absence from work, accounting for an estimated 43 million days of work lost each year in the UK.[1, 6]

Migraine is a spectrum disorder with migraine patients distributed across a continuum of monthly migraine and headache day frequencies.[7-10] Some guidelines, e.g. National Institute for Health and Care Excellence (NICE) and International Headache Society (IHS), classify patients as having either chronic or episodic migraine.[4, 11] The International Classification of Headache Disorders (ICHD-III) defines episodic migraine as 0–14 headache days per month, and chronic migraine as 15 or more headache days per month, of which eight or more have features of migraine (with or without aura).[4] Episodic migraine patients may be further categorised into low-frequency episodic migraine (LFEM) and high-frequency episodic migraine (HFEM); the CS (Section B.1.2.1) states that the latter group are "recognised as having a higher burden of migraine more in line with patients who would be classified as having chronic migraine."[1, 12] The CS (Section B.1.2.1) states that "these definitions are used to distinguish patients who have a higher frequency of headaches and migraines, and are likely to suffer more severely from their condition,"[1] but notes that they are not used in all guidelines, e.g. the British Association for the Study of Headache (BASH) guidelines do not clearly define separate chronic and episodic populations,[13] nor are they consistently applied in practice. Patients can experience changes in the frequency of their migraines and hence move between these classifications over time.[7, 14, 15] The decision problem (CS Section B.1.1) considers patients with ≥4 monthly migraine days for whom ≥3 prior prophylactic treatments have failed as a single population of patients across the full spectrum of monthly migraine frequencies, the "whole population base case",[1] but also addresses patients with chronic migraine and episodic migraine, as separate subgroups.[1]

The CS (Section B.1.2.1) states that: "Unpredictable variation in individual responses to prophylactic treatments, currently prescribed in the UK, results in around 30% of patients failing to respond to any particular prophylactic medication, and evidence suggests that up to 20% of migraine patients do not respond to more than three different prophylactic treatment options."[16, 17] Based on Novartis market research data (not provided in the CS): "It is estimated that around 100,000 migraine patients in England and Wales fall under this category, which represents a large and continued unmet clinical need."[1]

ERG comment:
The ERG checked the references cited by the company to support the statements made above and considered the company to have provided an appropriate description of the underlying health problem. However, the estimate of 100,000 migraine patients in England and Wales expected to be eligible for erenumab treatment (based on failure of ≥3 prior prophylactic treatments) was not adequately supported; this estimate was based on unpublished company data, which were not included in the CS. It should also be noted that the article cited in support of the statement that "around 30% of patients fail to respond to any particular prophylactic medication" concerns triptans only. The statement that "up to 20% of migraine patients do not respond to more than three different prophylactic treatment options" is solely supported in un-published Novartis survey of 40 neurologists; summary data provided suggest that the 20% estimate applies specifically to chronic migraine patients.[16]

2.2 Critique of company's overview of current service provision

The company states that the optimised positioning of erenumab within the care pathway is for the prophylaxis of migraine in patients for whom ≥3 prior prophylactic therapies have failed. This optimised positioning reflects the expected use of erenumab in the National Health Service (NHS), given the high burden of disease, the context of the availability of low-cost oral prophylactics as initial treatment options and the high unmet need for these patients; the only currently recommended treatment option at this point in the pathway is botulinum toxin, which is recommended only for chronic migraine patients who have not responded to ≥3 prior prophylactic treatments.

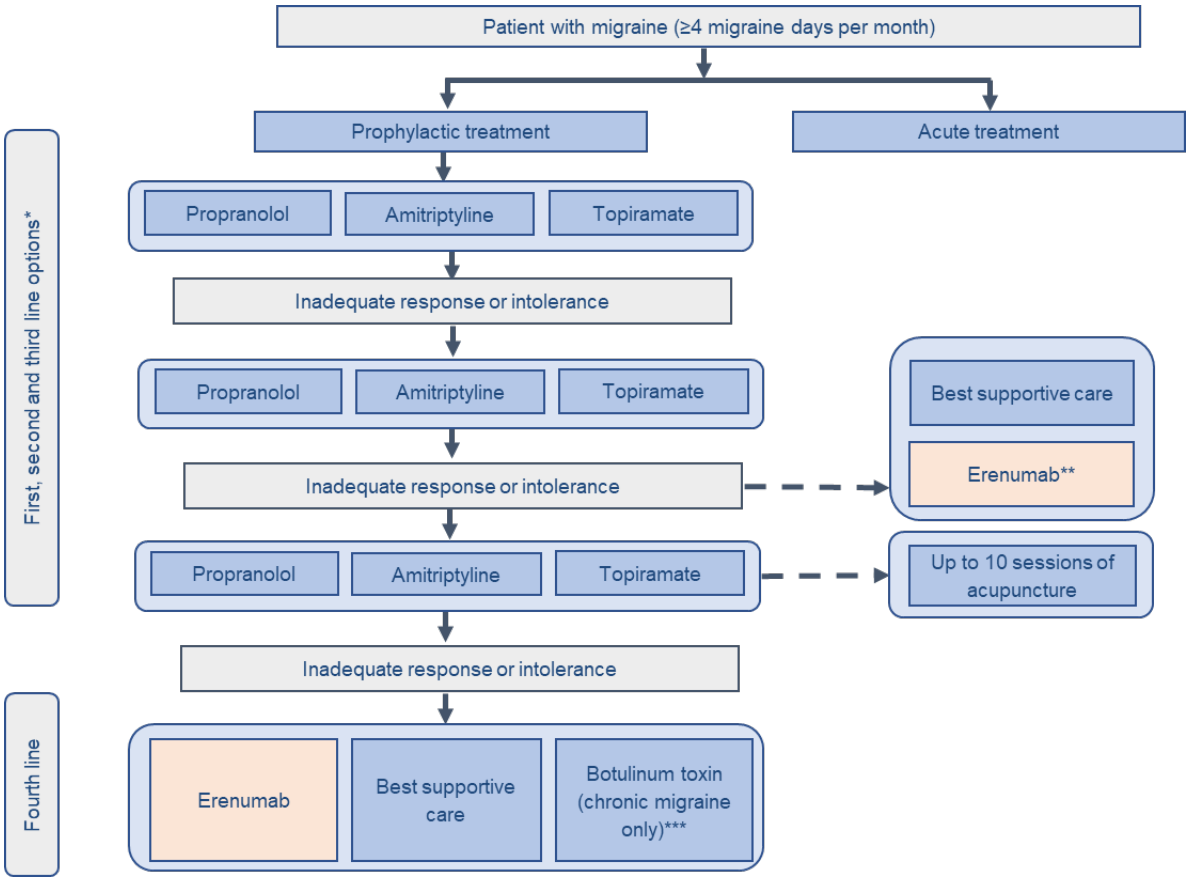
Current NICE clinical guidelines (CG 150) recommend oral prophylactic treatments (typically topiramate, propranolol or amitriptyline) in the first instance for migraine patients.[11] However, these treatments are poorly tolerated, with patients frequently switching, discontinuing or delaying therapies due to a lack of efficacy or adverse events (AEs); reported adherence rates range from 17–20% after one year.[18-20] The CS (Appendix C: Health condition and position of the technology in the treatment pathway) states that, once patients reach a point where ≥3 prophylactic therapies have failed for them, there are no further treatment options for the majority of patients and these patients therefore receive best supportive care (BSC). For some patients, contraindications, special warnings and precautions mean that this point is reached after fewer than three prophylactic therapies have failed. The exception is treatment with botulinum toxin, which is the only NICE-recommended therapy for the prophylaxis of migraine. However, botulinum toxin is only available for patients who have not responded to ≥3 prior prophylactic treatments and who meet the definition of chronic migraine specified in the NICE guidance (TA 260).[21]

ERG comment:

NICE clinical guidelines on diagnosis and management of headaches in over 12s (CG150)[11] include a statement about the possible use of acupuncture in relation to tension-type headache: "Consider a course of up to ten sessions of acupuncture over 5–8 weeks for the prophylactic treatment of chronic tension-type headache." No recommendations about acupuncture are included in the section of the guideline dealing with prophylactic treatment of migraine. Recommendations of the prophylactic treatment of migraine include the following statement on vitamin B2 supplementation: "Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people." The following special consideration is also noted, with respect to women and girls experiencing menstrual-related migraine: "For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) on the days migraine is expected."

Figure 2.1 shows the amended treatment pathway for patients with ≥4 migraine days per month, provided by the company in response to clarification question A14.[22] In the original proposed pathway, the company submission (CS) specified erenumab as fourth-line treatment.[1] The CS (Section B.1.2.2) states that the pathway was based on the NICE clinical pathway for the management of headaches in over 12s (CG150),[11] the section on migraine prophylaxis in BASH guidelines for the diagnosis and management of migraine, tension-type, cluster and medication-overuse headaches,[13] NICE TA260: botulinum toxin type A for the prevention of headaches in adults with chronic migraine,[21] and expert opinion obtained from an advisory board of eight UK neurologists.

Figure 2-1: Proposed treatment pathway for migraine patients with ≥4 migraine days per month



Source: Response to clarification question A14[22]

*If treatment at its maximum tolerated dose in the first-line is ineffective or poorly tolerated, the other two treatment classes may be considered for second-line. The same applies in moving from second-line to third-line treatment. No treatment should be tried twice in the pathway. **There may be clinical desire to use erenumab at an earlier point in the treatment pathway: in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions. This represents the minority of patients for whom ≥2 prior prophylactic treatments have failed. These patients would otherwise receive BSC in clinical practice. ***Botulinum toxin is recommended only for patients classified as having chronic migraine as per the NICE guidance for this therapy.[21]

ERG comment:

The company's description of the treatment pathway and options was based on existing NICE guidance and BASH guidelines, which is appropriate and relevant to the decision problem addressed by their submission. The pathway provided in the CS specified erenumab as fourth-line treatment. However, the proportion of patients in whom erenumab may be considered a treatment option before the fourth-line (e.g. due to contraindications for one or more oral prophylactic treatments) was unclear. The

company were asked to provide an amended pathway (Figure 2.1 above), with an indication of the proportions of patients who may be eligible for treatment with erenumab at each line. The company's response also stated that: "There may be clinical desire to use erenumab at an earlier point in the treatment pathway: in patients for whom ≥2 prior prophylactic treatments have failed and further treatment with a prophylactic therapy is considered inappropriate as a result of contraindications, special warnings and precautions. The exact proportion of patients who would meet this definition is unclear. However, most patients will receive a third oral prophylactic therapy before they reach the point at which BSC is their only option, and therefore the population anticipated to receive treatment with erenumab at this point in the pathway is expected to be small."

The company were also asked to provide further detail on what BSC, in the UK, includes, to elaborate on why the company believes that placebo in the erenumab trials is a good proxy for BSC in the UK, and to provide details of concomitant medication received in the four main trials (Study 295, STRIVE, ARISE and LIBERTY). The company's response stated that:

"The only option for the majority of patients for whom ≥3 prophylactic treatments have failed is BSC, which consists of continued treatment with acute medication. The relevant NICE guideline (CG150), recommends combination therapy with an oral triptan and a non-steroidal anti-inflammatory drug (NSAID), or an oral triptan and paracetamol, as first-line acute treatment options for patients with migraine.[11] Similarly, the British Association for the Study of Headache (BASH) guidelines recommend a stepped management programme comprising NSAIDs, including aspirin and ibuprofen, and triptans as required.[13] Patients in the placebo arms of Study 295, STRIVE, ARISE and LIBERTY were prescribed any treatments deemed necessary to provide adequate supportive care for the duration of the studies (full details are provided in Appendix 1). The majority of patients used acute medications during these trials, with triptan-based migraine medications and non-opioid acute headache medications being the most frequent treatment categories used by patients across all arms of these trials. As these treatment categories align with the acute treatment options recommended in clinical guidelines, the placebo arms of these trials are considered to adequately reflect BSC in UK clinical practice. This is supported by the NICE appraisal for botulinum toxin for chronic migraine (TA260),[21] in which "standard management" (i.e. BSC) was accepted as an appropriate comparator, and was modelled based on the placebo arm of the PREEMPT trials which formed the clinical evidence base for the botulinum toxin appraisal. Similar, to the erenumab studies, patients in both the botulinum toxin and placebo arms were treated with rescue medications such as analgesics and triptans during attacks."

The ERG agrees that the placebo arms of the erenumab trials provide a reasonable proxy for BSC in the UK.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with migraine	Adults with migraine with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed. This represents an optimised use of erenumab in clinical practice. Specifically, this submission will address this decision problem by considering three populations: 1. Patients with ≥4 migraine days per month ["whole population base case"] 2. Patients defined as having chronic migraine (≥15 headache days a month of which at least eight are migraine) ["chronic migraine population"] 3. Patients defined as having episodic migraine (4–14 headache days per month) ["episodic migraine population"]	• Migraine is a spectrum disorder with patients distributed across a continuum of monthly migraine day frequencies; it is therefore appropriate to consider the population of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed as a whole • Some guidelines actively classify two populations of migraine (chronic and episodic) by frequency of monthly migraine or headache days,[4, 11] despite difficulties in distinguishing between these patients in practice.[23] It should be noted that these definitions are not universally represented in guidelines, and are of limited relevance in clinical practice. • The clinical trials for erenumab were also conducted in separate chronic and episodic populations in line with clinical trial guidelines, although the licence for erenumab does not distinguish between them as	The population addressed falls within the broader population specified by the scope and is likely to reflect the expected use of erenumab in the NHS. However, it does not fully reflect the final scope, and does not represent the whole population for which erenumab has received marketing authorisation from the EMA (prophylaxis of migraine in adults who have at least 4 migraine days per month when initiating treatment with erenumab).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			these trials showed efficacy in both populations and provided a simplified treatment algorithm • It was thus considered relevant to present evidence for the chronic and episodic migraine populations both together ("whole population base case") and separately	
Intervention	Erenumab	Erenumab 70mg or 140mg once every 4 weeks	NA – in line with NICE final scope	In line with scope
Comparator(s)	Established clinical management for migraine prophylaxis without erenumab	• BSC (for all three populations) • Botulinum toxin (for chronic migraine population only as per NICE recommendation[21])	• For the majority of patients for whom ≥3 prior prophylactic treatments have failed there are no further treatment options. Therefore, these patients would receive BSC • The exception to this is the availability of botulinum toxin, which is the only NICE-recommended therapy in the prophylaxis of migraine indication (and then for prophylaxis of chronic migraine only). Botulinum toxin is therefore a relevant comparator, though it is only recommended in a subset of patients who meet the definition of chronic migraine specified in the NICE guidance. Furthermore, it should	The specified comparators are appropriate for the 'optimised population' addressed in the company submission. However, any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			be noted that the availability of botulinum toxin for these patients is restricted, and must be performed by trained expert physicians with specialist equipment, with only [redacted]% of NHS trusts in the UK estimated to be performing the procedure.[24]	
Outcomes	The outcome measures to be considered include: • Frequency of headache days per month • Frequency of migraine days per month • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days • Reduction in acute pharmacological medication • Adverse effects of treatment	Frequency of migraine days per month Change from baseline in mean monthly migraine days (MMDs) Proportion of patients with ≥50% reduction in mean MMDs from baseline Frequency of headache days per month Change from baseline in mean MHDs Severity of headaches and migraines Change from baseline in monthly average severity of migraine pain Change in pain interference with daily activities and migraine-specific impact from baseline, as measured by PROMIS (chronic migraine only)	NA – in line with NICE final scope	In line with scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• Health-related quality of life	Change from baseline in cumulative monthly headache hours Change from baseline in monthly acute migraine-specific treatment days Adverse effects of treatment Health-related quality of life (EQ-5D-5L, HIT-6, MSQ v2.1, MIDAS and WPAI)		
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	• As per the NICE reference case, the cost-effectiveness of erenumab is expressed in terms of incremental costs per QALY, and costs have been considered from the perspective of the NHS and PSS. • A time horizon of ten years is employed in the base case analysis, as this was considered an appropriate duration over which to fully capture the costs and benefits of erenumab, and is consistent with the time horizon used when evaluating biologics for other chronic diseases.[25-27]	N/A – in line with NICE final scope	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• Costs will be considered from an NHS and PSS perspective.			
Subgroups to be considered/ exploratory analyses	Not specified in final scope	The decision problem includes a subgroup analysis of the episodic migraine population, that considers only those patients within this population who have high frequency episodic migraine (8–14 MHDs). In addition, the submission presents exploratory analyses that consider the use of erenumab at an earlier line of therapy in patients for whom ≥2 prior prophylactic treatments have failed, and who face BSC as their only remaining treatment option due to contraindications, special warnings or precautions precluding use of a third oral prophylactic. As per the analyses in the ≥3 prior treatments population, results of this exploratory analysis are presented for the whole population, the episodic migraine population and the chronic migraine population.	The justification for the subgroup and exploratory analyses included in the submission is as follows: • HFEM is a recognised subgroup of episodic migraine, who are considered to have a clinical burden similar to those classified as having chronic migraine. However, these patients are unable to access botulinum toxin in line with its licensed indication and NICE recommendation, and therefore face a particularly high unmet need • Subgroup analyses are also presented in patients for whom ≥2 prior prophylactic treatments have failed, and who face BSC as their only remaining treatment option due to contraindications, special warnings or precautions precluding use of a third oral prophylactic, following feedback from UK clinicians, which has indicated that there would be clinical desire to use erenumab	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
		Finally, analyses are presented in all three populations where all patients start treatment on the 140mg dose of erenumab. The base case models a 50/50 split between patients receiving the 140mg and 70mg dose on initiation, which represents an assumption in the absence of long-term clinical experience of erenumab dosing in UK NHS clinical practice.	at an earlier point in the treatment pathway • In the absence of long-term UK NHS clinical experience with erenumab, a conservative assumption, whereby 50% of patients would initiate treatment on erenumab 140mg, and the remainder on erenumab 70mg, is made in the base case analysis. However, the 140mg dose may be more appropriate for patients for whom ≥3 prior prophylactic treatments have failed, as there is a trend towards better efficacy with the 140mg dose in these more severe patients (see Section 4.2.3). Analyses in which all patients initiate treatment on erenumab 140mg are therefore also presented. Analyses in which all patients initiate treatment on erenumab 70mg are presented in Appendix Z for completeness	

Source: CS, Table 1, page 9
AE: adverse event; BSC: best supportive care; EQ-5D: EuroQol 5 dimensions; HFEM: high-frequency episodic migraine; HIT-6: Headache Impact Test; MHD: monthly headache day; MIDAS: Migraine Disability Assessment; MMD: monthly migraine day; MSQ-v2.1: Migraine-Specific Quality of Life Questionnaire Version 2.1; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PROMIS: Patient-Reported Outcomes Measurement Information System; PSS: Personal Social Services; QALY: quality-adjusted life year; WPAI: Work Productivity and Activity Impairment

3.1 Population

The population defined in the scope is people with migraine and the population in the submission is a subset of this population.

The submission focuses on adult patients with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed (CS, Section B.1.1).[1] The specification of patients with ≥4 migraine days per month is in line with the marketing authorisation from the European Medicines Agency (EMA), issued on 26 July 2018, for the "prophylaxis of migraine in adults who have at least 4 migraine days per month when initiating treatment with erenumab."[1] The CS (Section B.1.1) states that "The optimisation to patients for whom ≥3 prior prophylactic treatments have failed is relevant and appropriate in the context of clinical practice within the National Health Service (NHS); erenumab would not be expected to be used in treatment-naïve patients due to the low cost of oral prophylactics. As such, at this position in the pathway, erenumab targets patients facing the highest unmet need and a lack of treatment options."[1] The population in the submission is likely to reflect the expected use of erenumab in the NHS. However, it does not fully reflect the final scope, and does not represent the whole population for which erenumab has received marketing authorisation from the EMA.

The submission relies primarily, on four randomised, placebo-controlled trials of erenumab, of which three were conducted in studies with episodic migraine (STRIVE,[28] ARISE,[29] and LIBERTY[30]) and one, Study 295,[31] was conducted in patients with chronic migraine. For all four trials, the data used in the submission were derived from *post-hoc* subgroup analyses of patients for whom ≥3 prior prophylactic treatment categories had failed. With regard to the episodic migraine studies, the submission focuses on LIBERTY. The CS (Section B.2.6) states that: "the number of patients who had received ≥3 prior prophylactic treatments in STRIVE and ARISE was small (n=[redacted] and n=[redacted], [redacted]% and [redacted]% of the study populations, respectively). Analyses across all outcome measures in these subgroups are not therefore considered to be meaningful, and are presented in this section for completeness. LIBERTY provides more relevant clinical evidence in this subgroup as this was a study specifically designed to assess the efficacy and tolerability of erenumab in patients who have failed 2–4 previous migraine prophylactic treatments."[1]

The CS (Section B.2.12.2) reports that the trial populations included patients from [redacted] UK sites ([redacted] patients) in Study 295, [redacted] ([redacted] patients) in STRIVE and [redacted] ([redacted] patients) in LIBERTY,[1] however, it is unclear how many (if any) UK patients were included of patients for whom ≥3 prior prophylactic treatment categories had failed; the ARISE study had no UK sites. The CS (Section B.2.12.2) states that: "The study populations were deemed generalisable to the UK migraine population, as validated by expert clinicians at a UK advisory board,"[23] however, the cited report of this advisory board does not include any discussion of the generalisability of trials to the UK population.

Although migraine affects three times as many women as men,[32] and there is also some evidence that migraine prevalence may be lower in non-white populations,[33] both males and non-white populations appear to be under represented in the erenumab trials (See Tables 4.4 and 4.5 in Section 4.2.1 of this report for an overview of all baseline characteristics, for the relevant subgroup, in the four studies). There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

ERG comment:

The company were asked to provide clarification on whether erenumab is expected to be used in patients under 18 or over 65 years of age. The following response was provided:

"Erenumab is not expected to be used in patients under 18 years of age as the licence is for the prophylaxis of migraine in adults, classified as ≥18 years. Erenumab is expected to be used in patients over 65 years. Although this age group were not included in the clinical trials reported in the submission, the licence does not provide an upper age restriction. The Summary of Product Characteristics[34] states:

Aimovig has not been studied in elderly patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age.

However, as migraine most commonly affects people in their 30s–50s, it is anticipated that few patients over 65 years will be initiated on treatment in clinical practice."

3.2 Intervention

Erenumab is a monoclonal antibody calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is a pro-inflammatory vasodilating neuropeptide involved in migraine pathophysiology.[35] Erenumab binds to the CGRP receptor complex. It is designed to specifically inhibit CGRP biological activity through CGRP receptor signal transduction, irrespective of circulating CGRP levels. Therefore, the efficacy of erenumab is not affected by CGRP release or concentration. Binding to the receptor is competitive and can be reversible. By blocking the CGRP receptor, erenumab reduces the frequency and intensity of migraines experienced by patients.[1]

The intervention (erenumab) is in line with the scope. Regulatory approval by the EMA for the prophylaxis of migraine in adults who have at least four migraine days per month when initiating treatment with erenumab was granted on 26 July 2018. The recommended dosage is 70mg Q4W, administered as a subcutaneous injection using a pre-filled pen for self-injection, although some patients may benefit from a dosage of 140mg Q4W, which is administered as two consecutive injections of 70mg each.

ERG comment:

The company were asked to provide clarification on which patients are expected to benefit from the 140mg Q4W dose and how these patients can be identified before initiating treatment with erenumab. The following response was provided:

"The licence for erenumab does not indicate the specific patient population expected to benefit from the 140mg dose of erenumab. However, as discussed in Document B, Section B.2.6 of the CS, numerically superior clinical outcomes were observed for patients treated with erenumab 140mg compared to erenumab 70mg in the subgroup of patients for whom ≥3 prior treatments have failed. Additionally, there is no difference in the safety profiles of the 70mg and 140mg doses. The 140mg dose may therefore be most appropriate for the patient population for whom ≥3 prior treatments have failed: the optimised population considered in this submission. This is supported by feedback from six expert UK neurologists, who considered that starting patients on the 140mg dose may be the most efficient treatment approach for those patients with the greatest unmet need.[23] This patient population can be identified through their usage of prior prophylactic treatments, and it is estimated that overall 19% of patients classified as having chronic migraine and 10% of patients classified as having episodic migraine are in the category of patients for whom ≥3 prior treatments have failed (see Budget Impact Assessment document, Section 3.2)."

The ERG does not consider that this statement provides adequate clarification, since it implies that the whole of the optimised population considered in this submission are expected to benefit from the 140mg Q4W dose.

3.3 Comparators

The description of comparators in the NICE scope is: "Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies."

The company included BSC as a comparator for all populations considered and botulinum toxin as a comparator for chronic migraine population only, in-line with NICE guidance (TA260).[21]) These comparators are appropriate for the population addressed in the company submission (patients for whom ≥3 prior prophylactic treatment categories had failed). However, any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s).

For the main comparator, BSC, the company considered the placebo arms of the erenumab trials to be representative of BSC and provided full details of concomitant treatments, by study arm, for the optimised population (patients for whom ≥3 prior prophylactic treatment categories had failed) and for the exploratory analysis population (patients for whom ≥2 prior prophylactic treatment categories had failed), see Appendix 1 of this report. Hence, the STRIVE, ARISE, LIBERTY and Study 295 studies provided direct head-to-head evidence against this comparator.

ERG comment:

The ERG agrees that the placebo arms of the erenumab trials provide a reasonable proxy for BSC in the UK (see Section 2.2).

No direct head-to-head comparisons of erenumab versus Botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus BSC. Estimates of the clinical effectiveness of Botulinum toxin, in patients for whom ≥3 prior prophylactic treatment categories had failed, were taken from pooled data from two randomised placebo controlled trials (PREEMPT 1 and PREEMPT 2).[36] Full details of the baseline characteristics, including concomitant treatments, of the relevant population (patients with chronic migraine for whom ≥3 prior prophylactic treatment categories had failed) were provided for the erenumab study used in the ITC (Study 295[31]). For PREEMPT,[36] these data were unavailable for the subgroup (patients for whom ≥3 prior prophylactic treatment categories had failed); these patients were assumed to be similar to the whole study population and data were provided for the whole population.

3.3 Outcomes

The NICE final scope lists the following outcome measures:

- frequency of headache days per month
- frequency of migraine days per month
- severity of headaches and migraines
- number of cumulative hours of headache or migraine on headache or migraine days
- reduction in acute pharmacological medication
- adverse effects of treatment
- health-related quality of life (HRQoL)

With the exception of HRQoL, all outcomes were reported, for the relevant population (patients who did not respond to ≥3 previous prophylactic treatments), in at least one of the three erenumab studies

conducted in patients with episodic migraine (STRIVE, ARISE and LIBERTY); HRQoL outcomes were only reported for the whole study populations. There were no safety, tolerability or quality of life outcomes reported in the subgroup who did not respond to ≥3 previous prophylactic treatments for either botulinum toxin (PREEMPT study) or for erenumab in the chronic migraine population (Study 295).

The CS includes response rate, defined as the proportion of patients with ≥50% reduction in mean MMDs from baseline as a primary outcome measure (used in economic modelling).[1] The company were asked to provide justification and supporting references for this definition, and provided the following response:

"The definition of a responder as achieving a ≥50% reduction in MMDs from baseline in the company submission was informed by the definition of responder used in the clinical trials for erenumab. The responder rate defined as a ≥50% reduction in MMDs from baseline was the primary endpoint in LIBERTY, and a key secondary endpoint in Study 295, STRIVE and ARISE. This definition of a responder aligns with the International Classification of Headache Disorders (ICHD) guidelines for controlled trials of drugs in migraine, which state that the proportion of patients with a 50% reduction in number of migraine days (i.e. responder rate), as compared to baseline values, is an important efficacy outcome.[37] Whilst it is acknowledged that the choice of a ≥50% reduction is arbitrary, it is considered to be clinically relevant as most patients with migraine value a ≥50% improvement in headache frequency as the most important attribute of an effective migraine preventive drug.[37] Similarly, International Headache Society (IHS) guidelines for conducting clinical trials in migraine state that responder rates in migraine have traditionally been defined as a ≥50% reduction in MMDs.[37] Whilst these guidelines state that a ≥30% reduction can be clinically meaningful in patients with chronic migraine, the more stringent ≥50% definition was considered to be more appropriate for this submission, where patients across the entire spectrum of migraine patients with ≥4 MMDs are considered, as per the licence for erenumab.[34] Finally, EMA guidelines suggest that the responder rate, where a 'responder' is defined as "*a patient with a 50% or greater reduction in attack frequency during treatment compared to baseline*", is collected as an endpoint in trials of migraine prophylactic therapies.[22]

This is supported further by feedback from six expert UK neurologists who recommended that clinical trials should capture the percentage responder rates rather than MMD frequencies. The advisors considered it more helpful to tell patients the chance of a therapy working, or how many migraine patients usually respond to a therapy, rather than how many fewer MMDs they could expect to experience.[23]"

ERG comment:

The ERG questions the use of the more stringent (≥50% reduction in MMDs vs. ≥30% reduction in MMDs) definition of responder; it seems unlikely that patients in this population would consider a reduction in their MMDs of between 30 and 49% to be not clinically meaningful. Furthermore, with respect to the stopping rule, which defines non-responders as those experiencing a <30% reduction in MMDs, it is unclear whether/how this would be determined in clinical practice and whether practitioners would actually be willing to discontinue treatment in patients who experienced, for example, a 20% reduction in MMDs which they considered to be beneficial.

3.5 Other relevant factors

The company argues that erenumab is innovative because: "it is the only licensed treatment to have been developed specifically for the prophylaxis of migraine, based on an understanding of the

underlying pathophysiology of the disease, and represents a major breakthrough as the first targeted therapy for the prophylaxis of migraine. Erenumab is a highly potent and selective antagonist of the CGRP receptor pathway, which plays a key role in mediating the pain of migraine. This novel mechanism of action compared to current therapies is a 'step change' in the management of migraine, and if recommended, erenumab will provide the first targeted prophylactic migraine therapy recommended for use in the UK."[1]

The company argues that: "The prophylaxis of migraine with erenumab has a potential wider societal value, as a reduction in migraine symptoms may mean that patients are able to return to work, reducing productivity loss from migraine. This would also have a positive impact on the UK economy, with absenteeism due to migraine costing the UK economy approximately £4.4 billion per year."[1]

With respect to the higher (140mg) erenumab dose, [redacted] A simple PAS (confidential discount), making erenumab available at a fixed net price of £[redacted] per 70mg dose was approved by the NHS England Commercial Medicines and Devices Investment Group on 1 May 2018.

[redacted]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify studies reporting the efficacy and safety of erenumab and botulinum toxin (as the only active comparator) for the prophylaxis of migraine in adults. The population defined by the inclusion criteria for this systematic review (see Table 4.1) was broader than the optimised population specified in the company's definition of the decision problem (adults with migraine with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed); it is unclear whether any studies conducted in the broader population were excluded. The systematic review did not search for studies on BSC, as the company considered the placebo arms of the erenumab trials (where acute treatment for migraine attacks was allowed) to be representative of BSC and hence to provide a direct comparison. The systematic review is described, in detail, in Appendix D of the CS.[38]

This section of the ERG report critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis of erenumab and comparator studies.

4.1.1 Searches

The following contains summaries and critiques for all searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidenced based checklist for the peer review of electronic search strategies (PRESS) was used to inform the critique.[39] The submission was checked against the single technology appraisal (STA) specification for company/sponsor submission of evidence.[40]

A SLR was undertaken to identify clinical evidence from RCTs, SLRs and NMAs of erenumab and onabotulinumtoxin A in February 2018 and then updated in July 2018. Searches were reported for Medline, including In-Process, Daily and Epub Ahead of Print, Embase, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effect (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) and the Health Technology (HTA) database. Further searches of congresses, HTA websites and ClinitalTrials.gov were also conducted. Relevant SLRs and NMAs were reference checked. All searches were clearly reported and reproducible, the database name, database date span, and date searched was provided. No language or date limits were applied except for congress searches which were restricted to the previous two years as high-quality studies reported before this time would be expected to have been published. Database searches in Embase and Medline databases included an RCT filter based on one provided by Scottish Intercollegiate Guidelines Network (SIGN) with some adaptions to increase sensitivity.[41]

ERG comment:

- Database searches were clearly structured and documented and contained a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation.
- The ERG noted that the inclusion of the Emtree term for erenumab would have helped make Embase searches more thorough. Some additional synonyms and the use of adjacency for onabotulinumtoxin A would have also helped to increase sensitivity. For example "onabotulinum toxin A" or "botulinum toxin adj2 A".
- Section B.2.9 of the CS states that the safety and tolerability of erenumab was evaluated within Study 295, STRIVE, ARISE and LIBERTY.[1] No separate literature searches to identify other AE data were undertaken. The ERG queried this and in the response to clarification the company stated that results from database searches were screened for AEs.[22] However, the clinical effectiveness searches incorporated a study design filter intended to limit to RCTs.

Guidance by the Centre for Reviews and Dissemination (CRD) [42] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that AEs that are long-term, rare or unanticipated are not missed. The ERG considers that it was possible that some relevant safety data may not have been identified as a consequence of the study design limits applied to the database searches.

4.1.2 Inclusion criteria

The inclusion criteria specified in the systematic review conducted by the company (CS, Appendix D[38]) are provided in Table 4.1.

Table 4.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Domain	Inclusion criteria	Exclusion criteria
Patient population	Adult humans with chronic or episodic migraine	• Non-humans • Humans without migraine • ≥50% children
	Studies with mixed populations (e.g. where some patients have migraine and some have non-migraine headaches, or where both adults and children were included) were included if all or most (≥50%) patients were relevant (i.e. had migraine and were adults), or if separate relevant results were reported for relevant patients.	
Intervention	• Erenumab (Aimovig), previously known as AMG 334 or AMG334 • Onabotulinumtoxin A (also known as botulinum toxin [type] A or Botox)	• Interventions other than erenumab and onabotulinumtoxin A • Non-pharmacological interventions • Acute treatments (i.e. treatments providing symptomatic relief) • Herbal remedies, such as butterbur or feverfew
Comparator	Any	-
Outcomes	• Efficacy outcomes, including but not limited to: o CFB in migraine episodes o CFB in monthly migraine days o CFB in monthly headache days o CFB in monthly migraine-specific acute medication days o Proportion of responders (e.g. participants with ≥50% improvement in migraine	Studies that did not report any outcomes of interest, such as studies reporting only costs or resource use

Domain	Inclusion criteria	Exclusion criteria
	attacks, or any other reported threshold or definition) • Safety and tolerability o All-cause discontinuation o Discontinuation due to AEs o Discontinuation due to lack of efficacy o Adherence o Persistence o Treatment-emergent AEs o Treatment-related AEs o Serious AEs o Serious treatment-related AEs o Specific AEs, including but not limited to: o Depression o Dizziness o Fatigue o Dry mouth o Nausea o Parasthesias o Sleep disturbance o Vomiting o Weight gain • HRQoL o Any generic measures (e.g. SF-36 or EQ-5D) o Any disease-specific measures (e.g. MSQ) o HIT scores o MIDAS score o MPFID score, including “Impact on physical activities” and “Physical impairment” domain scores o Headache severity (VAS)	
	Publications reporting study protocols or baseline characteristics only, without any outcomes of interest, were included at title/abstract review. At full-text review, they were linked to other publications reporting on the same study. If there was at least one publication reporting relevant outcomes (efficacy, safety or HRQoL) for the trial, the protocol or baseline characteristics were included as	

Domain	Inclusion criteria	Exclusion criteria
	a secondary publication for the trial. However, if there were no publications with relevant outcomes, the protocol or baseline characteristics were excluded.	
Study design	RCTs	• Interventional non-randomised controlled trials (non-RCTs), including single-arm studies • Narrative review articles, editorials and letters • Observational studies • Economic analyses or models • Case studies
	SLRs, meta-analyses or NMAs of relevant RCTs were included at title/abstract review for the purpose of identifying any additional studies not identified in the database searches, but were subsequently excluded at full-text review.	
Other	• Full-text or abstract in the English language • If the full-text was non-English, the abstract had to report enough data to be eligible for inclusion in its own right	Non-English abstract

Source: Table 6, Appendix D of the CS

CFB: change from baseline; AE: adverse event; HRQoL: health-related quality of life; EQ-5D: European Quality of Life-5 Dimensions, five-level scale; SF-36: 36-item Short form survey; MSQ: Migraine-Specific Quality of life questionnaire; HIT: Headache Impact Test; MIDAS: Migraine Disability Assessment; MPFID: Migraine Physical Function Impact Diary; VAS: visual analogue scale; RCT: randomised controlled trial; SLR: systematic literature review; NMA: network meta-analysis

ERG comment: Recommended methods were used for inclusion screening: two reviewers independently assessed studies for inclusion in the SLR and any disagreements were resolved through discussion and consensus.

The company were asked to provide clarification on the definition of 'adult patients' and whether erenumab is expected to be used in patients under 18. The following response was provided: "Erenumab is not expected to be used in patients under 18 years of age as the licence is for the prophylaxis of migraine in adults, classified as ≥18 years."

Only English language studies, or studies with an English language abstract reporting sufficient data for inclusion, were included. Although this is widely accepted by NICE within STAs, it is not good practice for systematic reviews, since relevant studies, published in other languages, may be missed. The company were asked to clarify how many papers/studies were excluded solely on the basis of not having an English abstract or full text. The following response was provided: "At the full-text review

stage, one paper was excluded solely on the basis of not having an English full text: *Blumenkron D, Rivera C, Cuevas C. Efficacy of botulinum toxin type A in patients with migraine. Medicina Interna de México. 2006;22(1):25-3.* This paper considered the efficacy of botulinum toxin in patients with migraine. However, the study involved only 30 patients and all patients were recruited from a single hospital in Mexico, limiting generalisability to the UK migraine patient population. In addition, the trial does not specifically state the frequency of migraine attacks, instead characterising patients as mild, moderate, severe and very severe, therefore it is unclear whether results are in patients classified as either chronic or episodic migraine."

The ERG considers that the inclusion criteria for the SLR were in line with the NICE scope, as applied to the optimised population (adult patients with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed) covered by this submission. The full population specified in the scope (people with migraine) would require the SLR to include studies of oral prophylactic treatments for migraine, as well as studies of erenumab and onabotulinumtoxin A.

4.1.3 Critique of data extraction

The CS does not provide any details of how data were extracted from the erenumab studies and the comparator study of botulinum toxin, or how many reviewers were involved in the process. It is therefore not clear whether the data extraction process was adequately designed to minimise error and bias during data extraction.

4.1.4 Quality assessment

No formal, validated quality assessment or risk of bias tools were used to assess the quality of included studies. A seven-question checklist, adapted from CRD's guidance for undertaking systematic reviews in health care,[42] was used to provide quality assessments of the studies included in the submission (erenumab studies and the botulinum toxin study). The checklist adequately covers the key risk of bias issues for randomised controlled trials (randomisation, allocation concealment, blinding, baseline equivalence of treatment groups, drop-outs, selective outcome reporting and missing data). The full results of the quality assessment process, with supporting information, are provided in Appendix D of the CS (Tables 18 and 23).[38] The ERG has assessed the trials included in this report against the criteria provided, and agrees with the quality assessment and supporting information provided in the CS.

4.1.5 Evidence synthesis

The STRIVE, ARISE, LIBERTY and Study 295 studies, individually, provided direct head-to-head evidence for the comparison to BSC. The CS (Section B.2.8.1) states that: "Throughout these trials, patients were prescribed any treatments deemed necessary to provide adequate supportive care, meaning that the placebo arms were considered to be representative of BSC."[1]

The SLR did not identify and direct head-to-head comparisons of erenumab to botulinum toxin in patients with chronic migraine, for whom ≥3 prior prophylactic treatments have failed. The company conducted an ITC, using the methods of Bucher et al.,[35] for change from baseline in mean MMDs, change from baseline in mean MHDs and ≥50% responder rate. Data for erenumab were taken from Study 295 and data for botulinum toxin were taken from PREEMPT (pooled data from the PREEMPT 1 and PREEMPT 2 trials). The ITC is described in Section B.2.8 of the CS[1] and in Appendix D of the CS.[38]

ERG comment: A meta-analysis of erenumab studies was not performed. The CS (Section B.2.7 states that: "Study 295 used a different definition for a "migraine day" and a "headache day" to that of the

studies in episodic migraine (STRIVE, ARISE and LIBERTY), therefore rendering any pooling of these trials inappropriate as outcomes cannot be interpreted as equivalent across trials."

Table 4.2: Definitions of migraine used in erenumab studies

	Study 295	**STRIVE, ARISE and LIBERTY**
Definition of migraine	A qualified migraine headache was determined by the following criteria: • A migraine without aura, lasting for **≥4 continuous hours** and having met criteria a) and/or b): a) ≥2 of the following pain features: o Unilateral o Throbbing o Moderate to severe o Exacerbated with exercise/physical activity b) ≥1 of the associated symptoms: o Nausea and/or vomiting o Photophobia and phonophobia **OR** • A migraine with aura having met criteria c) and d) below, defined as: c) Meeting ≥1 of the following aura symptoms o **Visual** o **Sensory** o **Speech and/or language** o **Retinal** o **Brainstem** d) Aura accompanied, or followed within 60 minutes, by headache lasting for ≥4 continuous hours If the patient took an acute migraine-specific drug on a calendar day, then it was counted as a migraine day regardless of the duration and pain features/associated symptoms.	A qualified migraine headache was defined as a migraine with or without aura, lasting for ≥**30 minutes**, and meeting at least one of the following criteria: • ≥2 of the following pain features: o Unilateral o Throbbing o Moderate to severe o Exacerbated with exercise/physical activity • ≥1 of the following associated symptoms: o Nausea and/or vomiting o Photophobia and phonophobia If the patient took a migraine-specific medication during aura or to treat headache on a calendar day, then it was counted as a migraine day regardless of the duration and pain features/associated symptoms.
Source: CS, Table 7		

STRIVE, ARISE and LIBERTY evaluated different doses of erenumab (STRIVE, 70mg and 140mg Q4W; ARISE, 70mg Q4W; LIBERTY, 140mg Q4W), and STRIVE assessed primary outcomes at 24 weeks, whereas ARISE and LIBERTY had a study duration of 12 weeks. Pooled patient-level data from STRIVE, ARISE and LIBERTY were used to inform the economic analyses.

A critique of the analysis methods used for the ITC is provided in Section 4.4 of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS (Section B.2.1) stated that the SLR identified nine RCTs of erenumab; however, only eight studies were listed. Four main trials (Study 295, STRIVE, ARISE and LIBERTY) were included in the CS clinical effectiveness Section (B.2),[1] two further studies (NCT20130255, a long-term follow-up study of patients enrolled in Study 295, and NCT01952574,[43] a phase II study cited in support of the model assumptions regarding long-term maintenance of erenumab efficacy) provided supporting evidence and were summarised in Appendix L of the CS,[38] Two phase I studies (NCT01688739 and NCT01723514)[44] were identified and excluded from the submission, because they were conducted in healthy individuals and patients with migraine.[1]

ERG comment:

The company was asked to clarify the discrepancy in the number of erenumab studies reported. The following explanatory text was provided:

"Two studies identified in the SLR were omitted in error from Table 4 of the original submission. These are listed below. Neither of these studies informed the clinical evidence base for the economic model.

NCT02630459[45] – this study is ongoing, specific to Japan, and no results are available. The estimated study completion date is 3rd June 2019.

NCT03333109[46] – the EMPOWER study – study of safety and efficacy in episodic migraine patients ongoing in countries other than the US, Europe and Japan. The estimated completion date is 7th February 2020.

In addition, study NCT02174861[47] was included – this study was a long-term follow-up of patients enrolled in Study 295. Results are presented in Section B.2.9 of the CS (long-term safety data). This study is the same as study NCT20130255 originally listed in Table 4, which refers to the additional study ID number for this trial. This study was incorrectly described as NCT20130255, when the actual study ID is NCT02174861 (20130255 is the Novartis study number for this open-label extension). Results have recently been presented at a congress (Tepper et al., Assessment of long-term safety and efficacy of erenumab during open-label treatment of subjects with chronic migraine. Presented at: AHS, San Francisco, CA, USA, June 28–July 1 2018).[48]

It should be noted that that the total number of studies of erenumab in Table 4 when adding these studies is ten."

The ERG agrees that all relevant studies were included in the submission and that the ongoing studies identified could not have been used in the submission.

4.2.1 Details of included erenumab studies

The CS includes four key erenumab studies (see Table 4.3), which are the focus of this report. Study 295 was the only erenumab study conducted in patients with chronic migraine. Three studies (STRIVE, ARISE and LIBERTY) were conducted in patients with episodic migraine. Because the LIBERTY trial included only patients who had failed two to four previous migraine prophylactic treatments, this study contributed the majority of the data on patients with episodic migraine included in this submission (optimised population for whom ≥3 prior prophylactic treatments have failed); the STRIVE and ARISE studies included only small numbers of patients in this subgroup (see Table 4.5). No two studies evaluated the same erenumab dose in comparable populations, with similar outcome measures and follow-up times (see Table 4.3).

Across the four trials, a total of 2,445 patients were included (full ITT population): Study 295 n=667; STRIVE n=955; ARISE n=577; LIBERTY n=246. Of these only 515 are directly relevant to the decision problem as they had failed ≥3 prior prophylactic treatments: Study 295 n=236; STRIVE n=74; ARISE n=56; LIBERTY n=149.

All erenumab trials were randomised, double-blind, placebo-controlled, parallel-group studies and all trials had open-label or active treatment extensions. Double-blind phases were either 12 or 24 weeks in duration. This report will present data from the blinded phases of the trials only. Eligible patients were adults, defined as 18 to 65 in all trials. The trials were international and, with the exception of the ARISE trial, all had a small number of UK sites. Overall [redacted] patients from the UK were included across the four trials. Although all trials compared erenumab to placebo, dosages varied. Study 295 in patients with chronic migraine and STRIVE in patients with episodic migraine allowed patients to receive 70 or 140mg doses. However, in ARISE patients could only receive the 70mg dose and in LIBERTY only the 140mg dose was given. All outcomes related to change in the number of migraine days as a primary outcome but this was measured differently and at different time points across the trials.

Table 4.3: Clinical effectiveness evidence for erenumab in patients with migraine

Study	Study 295	STRIVE	ARISE	LIBERTY
Study design	Phase II	Phase III	Phase III	Phase IIIb
	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study			
Study duration	≤3-week screening phase, 4-week baseline phase			0–2 weeks screening, 4-week baseline phase
	12-week double-blind phase 52-week open-label phase	24-week double-blind phase 28-week active treatment phase	12-week double-blind phase 28-week open-label treatment phase	12-week double-blind phase 52-week open-label
	Subsequent 12-week safety follow-up			
Study location	International: 69 sites UK (four sites, [redacted] patients)	International: 121 centres UK (six sites, [redacted] patients)	International: 69 centres UK 0	International: 68 locations UK (five sites, [redacted] patients)
Population	Adults aged 18–65			
	History of chronic migraine, with or without aura (≥15 headache days per month, of which ≥8 were migraine days)	History of episodic migraine (≥4 and <15 migraine days per month with <15 headache days per month) with or without aura for ≥12 months		History of episodic migraine (4–14 baseline migraine days) with <15 days per month of headache symptoms who have failed 2–4 previous migraine prophylactic treatments
Intervention	Erenumab 70mg or 140mg Q4W		Erenumab 70mg Q4W	Erenumab 140mg Q4W
Comparator	Placebo			
Primary outcome	Mean change in MMDs from baseline to final four weeks of 12-week double-blind phase	Change from baseline in mean MMDs using the MMDs from each of the last three months of 24-week double-blind phase	Mean change in MMDs from baseline to final four weeks of 12-week double-blind phase	At least 50% reduction from baseline in MMDs in Month 3 (the final month) of the double-blind phase

Source: CS Tables 5 and 6

Mg = milligrams; MMD = monthly migraine day; Q4W = every four weeks; UK = United Kingdom

As the population of interest in this submission is patients for whom ≥3 prior prophylactic treatments have failed, we will not describe or comment in detail on the baseline characteristics of the whole study populations in the four included studies, but will focus on the information provided for the relevant subgroups. Baseline characteristics for the population for whom ≥2 prior prophylactic treatments have failed, used in exploratory economic analyses, were provided in Appendix E of the CS and are not reproduced in this report.[38]

ERG comment:

The ERG notes that the evidence for erenumab is based on international RCTs investigating patient-relevant outcomes, however, only one trial was conducted in patients with chronic migraine and the number of trial participants for whom ≥3 prior prophylactic treatments had failed is relatively low (approximately 20% of the total studied population). Furthermore, three of the four studies had a double-blind phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was mean monthly migraine days; evidence is lacking about the long-term effectiveness of erenumab treatment.

Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented (see Tables 4.4 and 4.5); this observation applies to both the whole study populations and to the subgroups which are relevant to this submission. There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

With respect to the definitions of chronic and episodic migraine used in the included studies (see Table 4.3), there is a potential population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population. This was confirmed in the company's response to clarification questions: "Given the definitions of chronic and episodic migraine used in the clinical trial programme, which were based on clinical guidelines, patients falling outside of these definitions were not included in the clinical trials. However, the license for erenumab covers all patients that have ≥4 MMDs, therefore under the terms of this license, erenumab could be used in patients with ≥15 MHDs, and ≥4 to <8 MMDs."[22]

Studies evaluated different doses of erenumab; Study 295 and STRIVE evaluated 70mg and 140mg Q4W, ARISE evaluated 70mg Q4W, and LIBERTY evaluated 140mg Q4W. The company were asked to provide clarification on which patients are expected to benefit from the 140mg Q4W dose and how these patients can be identified before initiating treatment with erenumab. The following response was provided: "The licence for erenumab does not indicate the specific patient population expected to benefit from the 140mg dose of erenumab. However, numerically superior clinical outcomes were observed for patients treated with erenumab 140mg compared to erenumab 70mg in the subgroup of patients for whom ≥3 prior treatments have failed. Additionally, there is no difference in the safety profiles of the 70mg and 140mg doses. The 140mg dose may therefore be most appropriate for the patient population for whom ≥3 prior treatments have failed: the optimised population considered in this submission."

No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus Botulinum toxin, in patients with chronic migraine (see Section 4.4). For the main comparator, BSC, the company considered the placebo arms of the erenumab trials to be representative of BSC and provided full details of concomitant treatments, by study arm, for the optimised population (patients for

whom ≥3 prior prophylactic treatment categories had failed), see Appendix 1 of this report. The ERG agrees that the placebo arms of the erenumab trials provide a reasonable proxy for BSC in the UK (see Section 2.2).

Study 295 (Chronic migraine population)

The company reported that overall baseline characteristics were comparable between the ITT population and the patients for whom ≥ 3 prior prophylactic treatments have failed. Patients in the erenumab 140mg arm were slightly older in the optimised population than in the whole ITT population (44.1 vs. 42.9 years respectively). The age at onset of migraine was slightly lower in the optimised population, for all arms, however, baseline MMDs were comparable.

Additional data from the company indicated that [redacted] of the optimised population subgroup from study 295 had a diagnosis of migraine with aura, at baseline.[22] Information about which medications were used to treat acute migraine, during the study, was requested in the clarification letter and is provided in Appendix 1 of this report.

Table 4.4: Baseline characteristics of patients for whom ≥ 3 prior prophylactic treatments have failed in Study 295

Characteristic	Placebo [redacted]	Erenumab 70mg [redacted]	Erenumab 140mg [redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Women	[redacted]	[redacted]	[redacted]
Men	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]
Age at migraine[b] onset, years (SD)	[redacted]	[redacted]	[redacted]
Disease duration, years (SD)	[redacted]	[redacted]	[redacted]
Previous use of preventative drug topiramate, n (%)	[redacted]	[redacted]	[redacted]
Previous use of botulinum toxin, n (%)	[redacted]	[redacted]	[redacted]
Previous prophylactic treatment failures, n (%)			
Divalproex sodium, sodium valproate	[redacted]	[redacted]	[redacted]

Characteristic	Placebo	Erenumab 70mg	Erenumab 140mg
Topiramate			
Beta-blockers			
Tricyclic antidepressants			
Flunarizine or verapamil			
SNRI			
Lisinopril or candesartan			
Other			
Acute headache medication use, n (%)			
Migraine specific[c]			
Non-migraine specific			
Baseline period, mean (SD)			
Monthly migraine days			
Monthly headache days			
Monthly migraine attacks			
Monthly acute migraine-specific drug use days			

Source: CS Table 32 and additional information provided in response to clarification questions
Footnotes: [a]Other includes American Indian or Alaska native, multiple, native Hawaiian or other Pacific Islander and all other races. [b]Migraine with or without aura. [c]During the baseline phase, 557 patients (58.5%) used triptan-based medications and four patients (0.4) used ergotamine-based medications (safety analysis set).
BMI = body mass index; SD = standard deviation; SNRI = Serotonin and norepinephrine reuptake inhibitor.

ERG comment:
The ERG agrees with the company's statement that the overall baseline characteristics were comparable between the ITT population and the optimised population, for whom ≥3 prior prophylactic treatments have failed. However, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations.

Although all patients in described in Table 4.4 have failed ≥3 prior prophylactic treatments, it is not clear that the treatments failed correspond to the treatments or treatment classes indicated in the care pathway (Figure 2.1), i.e. not all patients have failed to respond to treatment with a beta-blocker, an anti-convulsant and a tricyclic antidepressant.

STRIVE, ARISE and LIBERTY (Episodic migraine population)

As these trials are all in episodic migraine, we present the baseline characteristics of patients for whom ≥ 3 prior prophylactic treatments have failed together in the table below.

The CS (Section B.2.6 states that: "It should be noted that the number of patients who had received ≥3 prior prophylactic treatments in STRIVE and ARISE was small (n=[redacted] and n=[redacted], [redacted]% and [redacted]% of the study populations, respectively). Analyses across all outcome measures in these subgroups are not therefore considered to be meaningful, and are presented in this section for completeness. LIBERTY provides more relevant clinical evidence in this subgroup as this was a study specifically designed to assess the efficacy and tolerability of erenumab in patients who have failed 2–4 previous migraine prophylactic treatments."

For STRIVE, the company reported that baseline characteristics were comparable between the ITT population and the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, but notes that a higher proportion of patients in this subgroup is white, and patients in the subgroup have slightly higher MMDs at baseline. For ARISE, the company reported that baseline characteristics for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed were consistent with those in the full trial population, both in terms of patient demographics and baseline disease characteristics. For both studies, fewer details of the baseline characteristics were provided for the subgroup population than for the whole population, e.g. age at onset of migraine and disease duration were not provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. In addition, baseline data for the secondary outcomes, mean monthly headache days (MHD) and acute migraine-specific drug use outcomes, were not provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in either STRIVE or ARISE.

For LIBERTY, the company reported that baseline characteristics for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed were consistent with those in the full trial population, both in terms of patient demographics and baseline disease characteristics.

Additional data from the company indicated that [redacted] of the optimised population subgroup, from STRIVE, ARISE and LIBERTY respectively, had a diagnosis of migraine with aura, at baseline.[22] Information about which medications were used to treat acute migraine, during the studies, was requested in the clarification letter and is provided in Appendix 1 of this report.

Table 4.5: Baseline characteristics of patients for whom ≥ 3 prior prophylactic treatments have failed in STRIVE, ARISE and LIBERTY

Characteristics	STRIVE			ARISE		LIBERTY	
	Placebo [redacted]	E70mg [redacted]	E140mg [redacted]	Placebo [redacted]	E70mg [redacted]	Placebo [redacted]	E140mg [redacted]
Mean age, years (SD)	[redacted]						
Range							
Sex, n (%)							
Women							
Men							
Weight (kg), mean (SD)							
BMI (kg/m^2), mean (SD)							
Ethnicity, n (%)							

Characteristics	STRIVE			ARISE		LIBERTY	
	Placebo	E70mg	E140mg	Placebo	E70mg	Placebo	E140mg
White	[redacted]						
Black or African American							
Asian							
Other[a]							
Age at migraine[b] onset, years (SD)							
Disease duration, years (SD)							
History of previous prophylactic treatment failure							
3							
4							
>4							
Details of previous prophylactic treatment failures							
Divalproex sodium, sodium valproate							
Topiramate							
Beta-blockers							
Tricyclic antidepressants							
Flunarizine or verapamil							
SNRI							
Lisinopril or candesartan							
Other							
Acute headache medication use, n (%)							
Migraine specific							
Non-migraine specific							
Baseline period, mean (SD)							
Monthly migraine days							
Monthly headache days							
Monthly acute migraine-specific drug use days							

Characteristics	STRIVE			ARISE		LIBERTY	
	Placebo [redacted]	E70mg [redacted]	E140mg [redacted]	Placebo [redacted]	E70mg [redacted]	Placebo [redacted]	E140mg [redacted]
Acute migraine-specific drug use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: CS Tables 33, 34 and 35, and additional information provided in response to clarification questions Footnotes: [a] Other includes Native American, Pacific Islander, unknown and all other races; [b] Migraine with or without aura BMI = body mass index; E = erenumab; kg = kilogrammes; MMD = mean monthly migraine days; SD = standard deviation; NA = not applicable; NR = not reported							

ERG comment:
The ERG agrees with the company's statement that the overall baseline characteristics were comparable between the ITT populations and the optimised populations, for whom ≥3 prior prophylactic treatments have failed. However, it should be noted that some baseline data were not provided, for whom ≥3 prior prophylactic treatments have failed, in STRIVE and ARISE. In addition, the ERG notes that there remains a lack of evidence about the effectiveness of erenumab in males and in non-white populations.

Although all patients in described in Table 4.5 have failed ≥3 prior prophylactic treatments, it is not clear that the treatments failed correspond to the treatments or treatment classes indicated in the care pathway (Figure 2.1), i.e. not all patients have failed to respond to treatment with a beta-blocker, an anti-convulsant and a tricyclic antidepressant.

4.2.2 Risk of bias assessment for included erenumab studies

Full risk of bias assessments, including supporting information for each criterion, were provided in Appendix E of the CS.[38] Table 4.6 provides a summary of the risk of bias assessments conducted for the four included erenumab studies.

Table 4.6: Overview of risk of bias assessments for studies of erenumab

Trial number (acronym)	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT NCT02483585)	LIBERTY (NCT03096834)
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors	Yes	Yes	Yes	Yes

Trial number (acronym)	Study 295 (NCT02066415)	STRIVE (NCT02456740)	ARISE (NCT NCT02483585)	LIBERTY (NCT03096834)
blind to treatment allocation?				
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	No
Source: CS Table 14				

ERG comment:
The ERG agrees with the risk of bias assessment provided in the CS.

4.2.3 Clinical effectiveness results for included erenumab studies

This section focuses on the key clinical effectiveness outcomes, reported in the CS and used to inform economic modelling, change in MMD/MHD from baseline to week 12 and responder rate (proportion of patients achieving ≥50% reduction in MMD/MHD from baseline week 12). As the population of interest in this submission is patients for whom ≥3 prior prophylactic treatments have failed, results are reported for this population rather than for the whole study ITT population; results are also provided for the two populations used in exploratory economic analyses (patients for whom ≥2 prior prophylactic treatments have failed, and patients with HFEM (defined as MMD eight to 14 in all three studies of erenumab for the prophylactic treatment of episodic migraine) for whom ≥3 prior prophylactic treatments have failed).

Table 4.7: Key clinical effectiveness results for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in Study 295

	Study 295		
	Placebo (n=[redacted])	**Erenumab 70mg (n=[redacted])**	**Erenumab 140mg (n=[redacted])**
Change from baseline in MMDs			
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change at Week 12 (SE)	[redacted]	[redacted]	[redacted]

	Study 295		
	Placebo (n=[redacted])	**Erenumab 70mg (n=[redacted])**	**Erenumab 140mg (n=[redacted])**
LSM difference versus placebo (95% CI)	NA	−2.53 (−4.27, −0.78)	−4.09 (−5.83, −2.33)
p-value	NA	0.005	<0.001
≥50% responder rate (MMDs)			
n (%)	15 (15.3)	23 (34.8)	25 (38.5)
Odds ratio (95% CI)	NA	3.0 (1.4, 6.3)	3.5 (1.6, 7.4)
p-value	NA	0.004	0.001
Change from baseline in MHDs			
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Mean change at Week 12 (SE)	[redacted]	[redacted]	[redacted]
LSM difference versus placebo (95% CI)	NA	[redacted]	[redacted]
p-value	NA	[redacted]	[redacted]
≥50% responder rate (MHDs)			
n (%)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NA	[redacted]	[redacted]
p-value	NA	[redacted]	[redacted]

Source: CS Section B.2.6.1 and Table 32

CI = confidence interval; MHDs = mean headache days; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; LSM = Least square method

Table 4.8: Key clinical effectiveness results for the subgroup of patients for whom ≥2 prior prophylactic treatments have failed in Study 295

	Study 295		
	Placebo (n=141)	**Erenumab 70mg (n=90)**	**Erenumab 140mg (n=92)**
Change from baseline in MMDs			
Baseline, mean (SD)	18.2 (4.7)	17.9 (4.4)	17.8 (4.7)
Mean change at Week 12 (SE)	−2.68	−5.3 (NR)	−6.96 (NR)
LSM difference versus placebo (95% CI)	NA	−2.71 (−4.20, −1.21)	−4.28 (−5.75, −2.80)
p-value	NA	<0.05	<0.05
≥50% responder rate (MMDs)			
n (%)	17 (12.1)	24 (26.7)	32 (34.8)
Odds ratio (95% CI)	NA	2.81 (1.39, 5.67)	3.96 (2.01, 7.82)
p-value	NA	0.003	<0.001

Source: CS Table 36

CI = confidence interval; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; LSM = Least square method

ERG comment:

The ERG notes that in Study 295 (chronic migraine) the optimised population (≥3 prior prophylactic treatments have failed) had better outcomes in the erenumab 70mg and 140mg groups than in the placebo group. More specifically, at week 12 patients experienced approximately two and a half fewer migraine days whilst taking erenumab 70mg and four fewer whilst taking erenumab 140mg than on placebo. In total, 34.8% of patients taking 70mg of erenumab and 38.5% of patients taking 140mg erenumab achieved a ≥50% reduction in MMDs from baseline, compared to 15.3% of patients on placebo. Results were similar for the subgroup of patients for whom ≥2 prior prophylactic treatments had failed, however, response rates appeared slightly lower in this expanded population; 26.7% of patients taking 70mg of erenumab and 34.8% of patients taking 140mg erenumab achieved a ≥50% reduction in MMDs from baseline, compared to 12.1% of patients on placebo.

With respect to secondary outcome measures in the population for whom ≥3 prior prophylactic treatments have failed, neither erenumab dose was associated with a statistically significant reduction in monthly migraine severity relative to placebo; Patients in the erenumab 70mg and erenumab 140mg arms achieved mean reductions versus placebo of [redacted] (95% CI: [redacted]; [redacted]) and [redacted] (95% CI: [redacted]; [redacted]), respectively. At week 12, patients treated with either erenumab dose had a significantly greater reduction in the monthly acute migraine-specific treatment days from baseline, compared with placebo; patients achieved a mean reduction of [redacted] and [redacted] days in the erenumab 70mg and 140mg arms, respectively, compared to [redacted] days in the placebo arm. This was associated with an LSM difference versus placebo of [redacted] days (95% CI: [redacted]; [redacted]) for the erenumab 70mg arm, and [redacted] days (95% CI: [redacted]; [redacted]) for the erenumab 140mg arm. This finding is consistent with the greater reduction in MMD observed in patients on the higher dose of erenumab.

The CS did not include any data on the long-term (>12 weeks) effectiveness of erenumab compared to placebo in people with chronic migraine. The open-label extension of study 295 (NCT20130255),[47] described in Appendix L of the CS,[38] provides some information about the longer-term maintenance of the effects, relative to baseline, of erenumab. However, due to a protocol amendment that resulted in the dose of erenumab being altered from 70mg to 140mg, the results provided are averaged across the whole trial population consisting of patients who had received either erenumab 70mg, erenumab 140mg or erenumab 70mg/140mg over the open-label extension follow-up period, and there are no results for the subgroup of patients in whom ≥3 prior prophylactic treatments have failed. The mean (95% CI) change from Study 295 baseline in MMDs was –8.36 (95% CI: –8.92, –7.80) days at week 24 and –9.29 (95% CI: –9.96, –8.62) days at week 52. The group ending the study on the 140mg dose showed numerically higher ≥50% responder rates, with 67.1% achieving the response compared with 53.5% of those who finished the study on 70mg erenumab.

Table 4.9: Key clinical effectiveness results for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in STRIVE, ARISE and LIBERTY

	STRIVE			ARISE		LIBERTY	
	Placebo (n=27)	**Erenumab 70mg (n=24)**	**Erenumab 140mg (n=23)**	**Placebo (n=29)**	**Erenumab 70mg (n=27)**	**Placebo (n=72)**	**Erenumab 140mg (n=77)**
Change from baseline in MMDs							
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change at Week 12 (SE)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus placebo (95% CI)	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
≥50% responder rate (MMDs)							
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
Change from baseline in MHDs							
Baseline, mean (SD)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	[redacted]	[redacted]
Mean change at	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	STRIVE			ARISE		LIBERTY	
	Placebo (n=27)	**Erenumab 70mg (n=24)**	**Erenumab 140mg (n=23)**	**Placebo (n=29)**	**Erenumab 70mg (n=27)**	**Placebo (n=72)**	**Erenumab 140mg (n=77)**
Week 12 (SE)							
Difference versus placebo (95% CI)	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
≥50% responder rate (MHDs)							
n (%)	NR	NR	NR	NR	NR	[redacted]	[redacted]
Odds ratio (95% CI)	NR	NR	NR	NR	NR	NA	[redacted]
p-value	NR	NR	NR	NR	NR	NA	[redacted]

Source: CS Section B.2.6.1 and Tables 33, 34 and 35

*For STRIVE this is mean change to last three months of the double-blind treatment phase

CI = confidence interval; MHDs = mean headache days; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error

Table 4.10: Key clinical effectiveness results for the subgroup of patients for whom ≥2 prior prophylactic treatments have failed in STRIVE, ARISE and LIBERTY

	STRIVE			ARISE		LIBERTY*	
	Placebo (n=54)	**Erenumab 70mg (n=49)**	**Erenumab 140mg (n=58)**	**Placebo (n=49)**	**Erenumab 70mg (n=56)**	**Placebo (n=124)**	**Erenumab 140mg (n=119)**
Change from baseline in MMDs							
Baseline, mean (SD)	8.12 (2.49)	8.89 (2.04)	8.68 (2.51)	[redacted]	[redacted]	9.3 (2.71)	9.3 (2.58)
Mean change at Week 12 (SE)**	−0.24 (0.76)	−1.56 (0.74)	−2.95 (0.73)	[redacted]	[redacted]	−0.15 (0.41)	−1.76 (0.44)

	STRIVE			ARISE		LIBERTY*	
	Placebo (n=54)	**Erenumab 70mg (n=49)**	**Erenumab 140mg (n=58)**	**Placebo (n=49)**	**Erenumab 70mg (n=56)**	**Placebo (n=124)**	**Erenumab 140mg (n=119)**
Difference versus placebo (95% CI)	NA	−1.32 (−2.64, 0.00)	−2.70 (−3.97, −1.44)	NA	[redacted]	NA	−1.61 (−2.70, −0.52)
p-value	NA	0.051	<0.001	NA	[redacted]	NA	0.004
≥50% responder rate (MMDs)							
n (%)	6 (11.1)	13 (26.5)	21 (36.2)	[redacted]	[redacted]	17 (13.7)	36 (30.3)
Odds ratio (95% CI)	NA	2.89 (1.00, 8.33)	4.54 (1.66, 12.39)	NA	[redacted]	NA	2.73 (1.43, 5.19)
p-value	NA	0.045	0.002	NA	[redacted]	NA	0.002

Source: CS Tables 21 and 36

*For LIBERTY, the population of patients for whom ≥2 prior prophylactic treatments have failed is the same as the whole study ITT population

**For STRIVE this is mean change to last three months of the double-blind treatment phase

CI = confidence interval; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error

Table 4.11: Key clinical effectiveness results for the subgroup of patients with HFEM for whom ≥3 prior prophylactic treatments have failed in STRIVE, ARISE and LIBERTY

	STRIVE			ARISE		LIBERTY	
	Placebo (n=19)	**Erenumab 70mg (n=16)**	**Erenumab 140mg (n=17)**	**Placebo (n=19)**	**Erenumab 70mg (n=16)**	**Placebo (n=72)**	**Erenumab 140mg (n=76)**
Change from baseline in MMDs							
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	NR (NR)	NR (NR)	[redacted]	[redacted]
Mean change at Week 12 (SE)*	NR (NR)	NR (NR)	NR (NR)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]

placebo (95% CI)							
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
≥50% responder rate (MMDs)							
n (%)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]
p-value	NA	[redacted]	[redacted]	NA	[redacted]	NA	[redacted]

Source: CS Section B.2.6.3
*Week 24 for STRIVE
CI = confidence interval; MMD = mean migraine days; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error

ERG comment:

The ERG notes that in studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks, and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed (MMD or MHD, ≥50% responder rates, monthly severity of migraine pain, monthly acute migraine-specific treatment days, monthly cumulative hours of migraine. The ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed.

Results were similar for the expanded subgroup of patients for whom ≥2 prior prophylactic treatments had failed. The ERG notes that numbers of study participants were very small for the subgroup of patients with HFEM, for whom ≥3 prior prophylactic treatments have failed. The ERG also notes that, for the STRIVE trial, there is an inconsistency between the effect estimate for 140mg erenumab versus placebo in patients with HFEM for whom ≥3 prior prophylactic treatments have failed reported in the summary of key results box on page 60 of the CS (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]) and that reported in the main text (Section B.2.6.3 of the CS) and in Table 4.11 of this report (difference in change from baseline to week 24 in MMD : [redacted] days [95% CI: [redacted]).

The CS does not include any long-term (beyond 24 weeks) data on the effectiveness of erenumab compared to placebo in people with episodic migraine. The open-label extension of a phase II study (NCT01952574),[43] described in Appendix L of the CS,[38] provides some information about the longer term maintenance of the effects, relative to baseline, of erenumab (70mg, Q4W). At Week 64, patients achieved a mean reduction of 5.0 (SD: 4.2) MMDs from a baseline of 8.5 MMDs (SD: 2.6), with 65% of patients achieving a reduction of ≥50% in MMDs from baseline.[43] The double-blind phase of this study was not included in the clinical effectiveness section of the CS.

4.4.4 Health-related quality of life data for included erenumab studies

The erenumab studies included in the CS used a variety of instruments to assess the impact of erenumab treatment on health-related quality of life: Study 295, HIT-6, MSQ 2.1, MIDAS and PROMIS; STRIVE, HIT-6, MSQ 2.1, MIDAS and MPFID; ARISE, HIT-6, MSQ 2.1 and MPFID; LIBERTY, HIT-6, EQ-5D-5L and WPAI. All health-related quality of life results were for the full study populations; no health-related quality of life data were provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Economic modelling used utility values which were derived by mapping patient-level MSQ 2.1 data from Study 295, STRIVE and ARISE onto EQ-5D-3L (CS, Section B.3.4.1).[1] This approach is discussed in detail in Section 5.2.8 of this report.

4.4.5 Adverse events data for included erenumab studies

This section considers the information about AEs provided in the CS. Adverse events data reported in the CS were for erenumab studies only and for the whole study population. As the population of interest in this submission is patients for whom ≥3 prior prophylactic treatments have failed, the company was asked to provide AEs for this subgroup. The company's response to points of clarification included a summary of AEs, by grade, for this population (see Table 4.12). Table 4.13 shows the equivalent data for the whole trial safety analysis set of Study 295, STRIVE, ARISE and LIBERTY. Full details of individual AEs occurring in ≥2% of patients, AEs leading to discontinuation and SAEs in the safety analysis set of Study 295, STRIVE, ARISE and LIBERTY are provided in the CS (Tables 44 to 46).[1] However, these data are not available for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. For the whole trial safety populations, the most commonly observed AEs (of any grade) were consistent across all four studies (nasopharyngitis, nausea, fatigue, upper respiratory tract infection and arthralgia), and the most frequently reported adverse drug reactions for the 70mg and 140mg doses were injection site reactions (5.6% and 4.5%), constipation (1.3% and 3.2%), muscle spasms (0.7% and 2.0%) and pruritus (1.0% and 1.8%).[1]

The CS did not include any AE data for the PREEMPT study or any other AE data for botulinum toxin. Summary AE data for botulinum toxin, taken from Dodick et al. 2010,[49] are provided in Table 4.14. The most frequent treatment-related adverse events were neck pain (6.7%), muscle weakness (5.5%), eyelid ptosis (3.3%) and injection-site pain (3.2%).[49] No AE data are available for botulinum toxin the subgroup of patients for whom ≥3 prior prophylactic treatments have failed.

ERG comment:

The ERG agrees with the company's statement that: "Across all four trials, the vast majority of AEs experienced by patients in the erenumab treatment arms were of mild or moderate severity and very low numbers of patients experienced any SAEs."[1] This statement appears to be applicable to both the whole trial safety populations and to the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. However, given the small sample size it is not possible to draw firm conclusions regarding adverse events for patients for whom ≥3 prior prophylactic treatments have failed.

The rate of SAEs for botulinum toxin (4.8%) appears higher than that observed for the whole trial safety populations in the erenumab studies (see Table 4.13).

Table 4.12: Treatment-emergent AEs in patients for whom ≥3 prior prophylactic treatments have failed in Study 295, STRIVE, ARISE and LIBERTY (safety analysis set)

Total no. of patients (%)	Study 295			STRIVE			ARISE		LIBERTY	
	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Erenumab 140mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 70mg (n=[redacted])	Placebo (n=[redacted])	Erenumab 140mg (n=[redacted])
With AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With Grade ≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With AEs leading to discontinuation of investigational product	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 6, Response to clarification[22]
AE: adverse event; SAE: serious adverse event

Table 4.13: Treatment-emergent AEs in the safety analysis set of Study 295, STRIVE, ARISE and LIBERTY

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

Source: Table 43, CS[1]

a: Number of subjects reporting at least one occurrence of a treatment-emergent adverse event

b: Number of subjects with non-missing values.

c: Grading categories determined using Common Toxicity Criteria for Adverse Events version 4.03.

AE: adverse event; SAE: serious adverse event

Table 4.14: Summary of overall AEs reported in the 24-week double blind phase for the PREEMPT program (PREEMPT-1 and PREEMPT-2)

Total no. of patients (%)	**OnabotulinumtoxinA 150 to 195 U (n = 687)**	**Placebo (n = 692)**
With AEs	429 (62.4)	358 (51.7)
With treatment-related AEs	202 (29.4)	88 (12.7)
With SAEs	33 (4.8)	16 (2.3)
With treatment-related SAEs	1 (0.1)	0 (0.0)
With AEs leading to discontinuation of investigational product	26 (3.8)	8 (1.2)
Deaths	0 (0.0)	0 (0.0)
Source: Dodick et al. 2010[49] AE: adverse event; SAE: serious adverse event		

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS (Section B.2.8.2) states that Study 295 and the pooled PREEMPT study were judged to be similar in terms of their study design and the patient baseline characteristics; details are provided in Appendix D of the CS.[38] The patient baseline characteristics, for both trials, are summarised in Table 4.15 and the results from each trial, used as inputs for the ITC, are provided in Table 4.16.

The CS (Section B.2.8.3) provides a full description of the uncertainties relevant to the ITC assumption of comparable patient populations, in summary:

- Baseline characteristics were not reported for the subgroup of patients for whom ≥3 prior prophylactic treatments had failed in PREEMPT. Because the baseline characteristics for the full trial populations in Study 295 and PREEMPT were similar, it was assumed that the subgroup populations were also similar.
- In both trials, patients were not stratified by previous prophylactic use when randomised. As a result, the analysis for the subgroup comparisons breaks randomisation and patient characteristics may therefore be imbalanced between treatment arms for measured and unmeasured variables.
- Least squares means were reported for each outcome, but the variables adjusted for in PREEMPT are not reported.
- The outcomes were reported at different time points with Study 295 reporting outcomes at 12 weeks while PREEMPT reported outcomes at 24 weeks.

ERG comment:
The CS did not include any AE data for the PREEMPT study or any other AE data for botulinum toxin.

Appendix D (Section D.1.4) of the CS notes that:

"Data for both trials in the patient population for whom ≥3 prior prophylactic treatments have failed were only available for the change from baseline in mean monthly migraine days, change from baseline in mean monthly headache days and the percentage of patients with a 50% reduction in mean monthly headache days. Therefore, the ITC was performed on these three efficacy outcomes. There were no safety, tolerability or quality of life outcomes reported in the subgroup who did not respond to ≥3 previous prophylactic treatments for either study."

Appendix D (Section D.1.4) of the CS notes that:

"There was a difference in the study duration, 12 weeks for Study 295 versus 24 weeks for PREEMPT. This difference in timepoint is likely to have an impact when comparing efficacy outcomes at the primary endpoint, as data from PREEMPT show that botulinum toxin was more effective compared to placebo at 24 weeks compared to 12 weeks [1] Any comparisons between erenumab and botulinum toxin using primary endpoint data would therefore be likely to favour botulinum toxin." The ERG notes that the study cited does not report a comparison of the effectiveness of botulinum toxin at 24 weeks compared to 12 weeks. Graphical representations of change in MMD and MHD over time indicate a significant treatment effect, for botulinum toxin versus placebo, from week four onwards; it is not clear whether the difference in follow-up time, 12 weeks for Study 295 versus 24 weeks for PREEMPT, for the primary endpoint comparison would be likely to favour botulinum toxin.

Table 4.15: Summary of the participants' baseline characteristics for studies used in the ITC

Study	Treatment	Age, years, mean (SD)	Gender, % female	Race, % white	Migraine days/month, mean (SD)	Headache days/month, mean (SD)	Acute medication days/month, mean (SD)	≥1 prior prophylaxis treatments, %
PREEMPT*	Botulinum toxin 155U –195U	41.1 (10.4)	87.6	89.7	19.1 (3.99)	19.9 (3.68)	14.6 (6.4)	61.8
	Placebo	41.5 (10.7)	85.2	90.5	18.9 (4.05)	19.8 (3.68)	14.9 (6.4)	65.2
Study 295 (NCT02066415) full trial population	Erenumab 70mg	41.4 (11.3)	86.9	92.1	17.85 (4.39)	20.49 (3.82)	8.76 (7.16)	72.3
	Erenumab 140mg	42.9 (11.1)	84.2	96.8	17.78 (4.72)	20.73 (3.83)	9.66 (7.02)	71.6
	Placebo	42.1 (11.3)	79.0	93.7	18.22 (4.73)	21.12 (3.93)	9.46 (7.58)	76.2
Study 295 (NCT02066415) ≥3 prior treatment failures subgroup**	Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100
	Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100

Source: Table 16, Appendix D of the CS

*Baseline characteristics for the subgroups of patients for whom ≥3 prior prophylactic treatments have failed were not available for PREEMPT.

** Baseline characteristics are for the subgroups of patients for whom ≥3 prior protocol-defined treatment categories have failed; for example, prior non-responders to a beta-blocker, a tricyclic antidepressant and topiramate

SD: standard deviation

Table 4.16: Summary of study results used in the ITC

Study	Treatment	Population	CfB mean monthly migraine days, mean (SE)	CfB mean monthly headache days, mean (SE)	Patients with a 50% reduction in mean monthly headache days, n/N (%)
PREEMPT	Botulinum toxin 155U –195U	Full trial population, 24 weeks	–8.2 (–8.69, –7.70)[a]	–8.4 (–8.90, –7.92)[a]	NR (47.1)
	Botulinum toxin 155U –195U	Full trial population, 12 weeks	–7.09 (0.13)	–7.15 (0.26)	339/688 (49.3)
	Botulinum toxin 155U –195U	≥3 previous prophylaxis treatments, 24 weeks	–7.1[b] (NR)	–7.4[b] (NR)	76/189 (40)
	Placebo	Full trial population, 24 weeks	–6.2 (–6.69, –5.68)[a]	–6.6 (–7.07, –6.08)[a]	NR (35.1)
	Placebo	Full trial population, 12 weeks	–5.59 (0.23)	–5.97 (0.23)	NR
	Placebo	≥3 previous prophylaxis treatments, 24 weeks	–4.3[b] (NR)	–4.7[b] (NR)	51/207 (25)
Study 295 (NCT02066415)	Erenumab 70mg	Full trial population, 12 weeks	–6.63 (0.45)	–6.43 (0.45)	[redacted]
	Erenumab 70mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Erenumab 140mg	Full trial population, 12 weeks	–6.53 (0.50)	–6.96 (0.52)	[redacted]
	Erenumab 140mg	≥3 previous prophylaxis treatments, 12 weeks[c]	[redacted]	[redacted]	[redacted]
	Placebo	Full trial population, 12 weeks	–4.24 (0.38)	[redacted]	[redacted]
	Placebo	≥3 previous prophylaxis treatments, 12 weeks	[redacted]	[redacted]	[redacted]

Source: Table 17, Appendix D of the CS and Response to clarification, question A17

[a]95% confidence intervals are reported instead of standard error; [b]Means reported for these outcomes are least-squares means, not absolute means. [c]Note that the ITC utilised data from patients who had failed on ≥3 prior prophylactic treatments irrespective of category, in order to most accurately reflect the decision problem

CfB: change from baseline; NR: not reported; SE: standard error

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The indirect comparison (ITC) compared erenumab 70mg and 140mg with botulinum toxin for the optimised population (≥3 previous prophylactic treatments had failed) using data from Study 295 and PREEMPT. As the two studies reported outcomes at different timepoints (12 weeks for Study 295 and 24 weeks for PREEMPT) three different analyses were performed.

1. Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison
2. Full trial population primary endpoint comparison (12 weeks for erenumab and 24 weeks for botulinum toxin
3. Full trial population, 12 weeks for both treatments

The ITC used the recommended statistical analysis method, the Bucher method[35] and the analyses performed were appropriate. Apart from the differences in the timepoints, the CS judged the two studies to be similar for most baseline characteristics and the baseline values of the outcomes included in the ITC. "It was therefore determined that there was no risk of bias due to the imbalances". The conclusions from the supporting ITC analyses using full trial data for the primary endpoint and 12 weeks were similar to those from the subgroup for whom ≥ 3 prior prophylactic treatments have failed, and none of the analyses found any statistically significant differences between erenumab 70mg or 140mg and botulinum toxin for ≥ 50% response, or change from baseline in mean monthly migraine days or mean headache days.

The ERG does not have any concerns about the methods or results of the ITC analyses. A summary of the results of the ITC analyses is provided in Table 4.17.

Table 4.17: ITC results for erenumab versus botulinum toxin

Group	Treatment 1	Treatment 2	Point estimate: Treatment 1 vs Treatment 2 (95% CI)[a]
≥50% responder rate (monthly headache days)			
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 140mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
≥50% responder rate (defined in terms of monthly migraine for erenumab and monthly headache days for botulinum toxin)			
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70mg (12 weeks), n=188	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=189	[redacted]

Group	Treatment 1	Treatment 2	Point estimate: Treatment 1 vs Treatment 2 (95% CI)[a]
Full trial population, primary endpoint comparison	Erenumab 140mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140mg (12 weeks), n=187	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Mean monthly migraine days			
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=231	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70mg (12 weeks), n=178	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70mg (12 weeks), n=178	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=231	[redacted]
Full trial population, primary endpoint comparison	Erenumab 140mg (12 weeks), n=182	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140mg (12 weeks), n=182	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]
Mean monthly headache days			
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 70mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=231	[redacted]
Full trial population, primary endpoint comparison	Erenumab 70mg (12 weeks), n=178	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 70mg (12 weeks), n=178	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]

Group	Treatment 1	Treatment 2	Point estimate: Treatment 1 vs Treatment 2 (95% CI)[a]
Subgroup for whom ≥3 prior prophylactic treatments have failed, primary endpoint comparison	Erenumab 140mg (12 weeks), n=[redacted]	Botulinum toxin 155 U–195 U (24 weeks), n=231	[redacted]
Full trial population, primary endpoint comparison	Erenumab 140mg (12 weeks), n=182	Botulinum toxin 155 U–195 U (24 weeks), n=688	[redacted]
Full trial population, 12-week comparison	Erenumab 140mg (12 weeks), n=182	Botulinum toxin 155 U–195 U (12 weeks), n=688	[redacted]

Source: Tables 38 to 41 (CS Section B.2.8.2) and Tables 19 to 22 (CS Appendix D)

[a]A negative point estimate indicates that the comparison favours treatment A, n is number of patients at Week 12 of the trials

CI = confidence interval; NA = not applicable

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The NICE scope describes the clinical effectiveness of erenumab, within its marketing authorisation, for the prophylaxis of migraine. Erenumab has received marketing authorisation from the EMA for the prophylaxis of migraine in adults who have at least four migraine days per month when initiating treatment with erenumab. The submission focuses on a subgroup of adult patients, those with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed, who are considered likely to reflect the expected use of erenumab in the NHS. However, it does not fully reflect the final scope, and does not represent the whole population for which erenumab has received marketing authorisation from the EMA. The evidence for erenumab in the submission population (adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed) is based on *post-hoc* subgroup analyses of data from four RCTs involving approximately 20% of the total studied population. Regarding the extent to which the erenumab studies are representative of the UK population with migraine, both males and non-white populations appear to be under represented in the erenumab studies, both with respect to the whole study population and to the subgroup relevant to this submission. There is also a lack of evidence about the effectiveness of erenumab in older patients; all studies excluded patients over 65 years of age.

Given the definitions of chronic (≥15 headache days per month, of which ≥8 were migraine days) and episodic (≥4 and <15 migraine days per month with <15 headache days per month) migraine used in the included studies, there is a population group (≥15 headache days per month, of which between four and seven are migraine) who are not covered by either definition and hence are not represented in any of the included studies; no effectiveness evidence is presented for this population.

The description of comparators in the NICE scope is: "Established clinical management for migraine prophylaxis without erenumab, including Botulinum toxin type A for chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies." The company included BSC as a comparator for all populations considered and Botulinum toxin as a comparator for chronic migraine population only, in-line with NICE guidance (TA260).[21]) These comparators are appropriate for the population addressed in the company submission (adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed). However, any consideration of the broader population specified in the final scope would require the inclusion of oral prophylactic treatment(s) as comparator(s). For the main comparator, BSC, the company considered the placebo arms of the erenumab trials to be representative of BSC; this assumption is supported by the details of on-study treatments acute migraine episodes, which were provided in the company's response to points for clarification submitted by the ERG.

There is a lack of long-term (beyond 24 weeks) data on the effectiveness of erenumab in people with chronic or episodic migraine, for either the subgroup of adults with ≥4 migraine days per month for whom ≥3 prior prophylactic treatments have failed or the wider population covered by the marketing authorisation. Furthermore, three of the four erenumab studies had a double-blind phase of just 12 weeks, which may not be considered adequate, given that the primary outcome measure was mean monthly migraine days.

Studies evaluated different doses of erenumab; Study 295 and STRIVE evaluated 70mg and 140mg Q4W, ARISE evaluated 70mg Q4W, and LIBERTY evaluated 140mg Q4W. In Study 295 (chronic migraine) the optimised population (≥3 prior prophylactic treatments have failed) had better outcomes

in the erenumab 70mg and 140mg groups than in the placebo group. More specifically, at week 12 patients experienced approximately two and a half fewer migraine days whilst taking erenumab 70mg and four fewer whilst taking erenumab 140mg than on placebo. In total, 34.8% of patients taking 70mg of erenumab and 38.5% of patients taking 140mg erenumab achieved a ≥50% reduction in MMDs from baseline, compared to 15.3% of patients on placebo. In studies of episodic migraine (STRIVE, ARISE and LIBERTY) the optimised population (≥3 prior prophylactic treatments have failed) patients treated with erenumab had generally better outcomes than those on placebo. More specifically, at week 12 in the LIBERTY, trial patients on 140mg erenumab experienced approximately [redacted] than those on placebo and, at week 24 in the STRIVE trial, on 140mg erenumab experienced approximately [redacted] than those on placebo. In the LIBERTY trial, [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 12 weeks, and in the STRIVE trial [redacted] of patients taking 140mg of erenumab and [redacted] of patients on placebo achieved a ≥50% reduction in MMDs from baseline to 24 weeks. However, no trial found a statistically significant treatment effect for 70mg erenumab in patients for whom ≥3 prior prophylactic treatments have failed on any of the outcomes assessed.

The erenumab studies included in the CS used a variety of instruments to assess the impact of erenumab treatment on health-related quality of life: Study 295, HIT-6, MSQ 2.1, MIDAS and PROMIS; STRIVE, HIT-6, MSQ 2.1, MIDAS and MPFID; ARISE, HIT-6, MSQ 2.1 and MPFID; LIBERTY, HIT-6, EQ-5D-5L and WPAI. All health-related quality of life results were for the full study populations; no health-related quality of life data were provided for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Economic modelling used utility values which were derived by mapping patient-level MSQ 2.1 data from Study 295, STRIVE and ARISE onto EQ-5D-3L.

The rates of SAEs in the erenumab treatment arms were generally low, across all four studies. No adverse events data were provided for the active comparator, botulinum toxin, but data from the PREEMPT trials indicated that botulinum toxin may be associated with a higher rate of SAEs than erenumab.

No direct head-to-head comparisons of erenumab versus botulinum toxin were identified, therefore an indirect treatment comparison (ITC) was used to generate relative effectiveness estimates for erenumab versus botulinum toxin, in patients with chronic migraine. The ERG does not have any concerns about the methods or results of the ITC analyses.

Overall, although the evidence for erenumab is based on international RCTs investigating patient-relevant outcomes, there is uncertainty about the effectiveness of the lower (70mg Q4W) dose for the subgroup of patients for whom ≥3 prior prophylactic treatments have failed, particularly for those patients with episodic migraine. There is also a lack of data for male patients, those over 65 years of age and for non-white populations. The long-term effectiveness of erenumab (beyond 24 weeks) is unknown.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

A combined SLR was performed with the objective to identify and select relevant literature on 1) Economic evaluations of pharmacological interventions for the treatment of chronic or episodic migraine (CS Appendix G[38]); 2) Health state utility values for chronic or episodic migraine patients (CS Appendix H[38]); and 3) Cost and resource use data for chronic or episodic migraine patients (CS Appendix I[38]). The initial search was performed in July 2017 and updated in January 2018. In response to clarification, the cost effectiveness searches were updated again in September 2018.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

A SLR was conducted to identify economic evidence to support the development of a cost effectiveness model for erenumab for the treatment of chronic or episodic migraine. The search strategies applied included terms to identify utility values as well as economic evaluations, resource use and costs. Searches were originally carried out in July 2017 and subsequently updated in January and September 2018. The following databases were searched: Medline, including Medline Daily, In-Process and Epub Ahead of Print, Embase, HTA Database, NHS Economic Evaluation Database (NHS-EED) and EconLit. The host provider for each database was listed, the date span of the databases and the date the searching was conducted was provided. In addition to electronic database searches, manual searches of major migraine and neurological congresses held over the past three years (2015-2018) were undertaken. High-quality abstracts from congresses before 2015 were expected to have been published in full-text so searches earlier than 2015 were not needed. Supplementary searches were also carried out in NICE, Scottish Medicine Consortium (SMC), All Wales Medicines Strategy Group (AWMSG), National Centre for Pharmacoeconomics (NCPE), Cost-effectiveness Analysis (CEA) Registry, University of Sheffield Health Utilities Database (ScHARRHUD), EQ-5D Publications Database and EconPapers at Research Papers in Economics (RePEc). Embase and Medline searches used recognised study design filters from SIGN for economic studies with some added extra terms to increase sensitivity. To identify health state utility studies, search terms were based on those proposed in the NICE Decision Support Unit's (DSU) Technical Support Document 9.[30] Reference lists of relevant SLRs, meta-analyses, HTA submissions and economic evaluations were also checked. The searches met the requirements detailed in the NICE guide to the methods of technology appraisal.[50]

ERG comment:

- A wide range of resources to identify published and unpublished literature were searched and searches were well-reported and reproducible.
- The database searches were clearly structured (population and study design), using a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation.

5.1.2 Inclusion/exclusion criteria used in the study selection

Inclusion and exclusion criteria for cost effectiveness studies, utilities, and costs and resource use studies are presented in Table 5.1.

Table 5.1: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with chronic or episodic migraine	Articles reporting populations without chronic or episodic migraine patients, and articles reporting populations with ≥50% children
Intervention	Prophylactic pharmacological interventions, see CS Appendix G [38]	• Non-pharmacological interventions • Acute treatments • Herbal remedies • Several prophylactic treatments, see CS Appendix G[38]
Comparator	Any comparator	None
Outcomes(s) 1 (Published economic evaluations)	Outcomes of relevant study designs, including: • Costs • Life years gained (LYG) • Quality-adjusted life years (QALYs) • Incremental costs and QALYs • Incremental cost effectiveness ratios (ICERs)	Studies not reporting relevant outcomes
Outcomes(s) 2 (Utility studies)	Original health state utility data, for example those measured using: • EQ-5D • SF-6D • HUI3 • Time trade-off • Standard gamble	
Outcomes(s) 3 (Cost/resource use studies)	Original costs or resource use data relevant to a cost-utility analysis from the perspective of the UK NHS and personal and social services (PSS) (or social work in Scotland) or the Health Service Executive in Ireland	
Study design 1 (Cost effectiveness analysis studies)	Original economic evaluations considering both the costs and benefits of alternative interventions: • Cost effectiveness • Cost utility	• Publications without original data • Comments • Letters • Editorials

PICOS	Inclusion criteria	Exclusion criteria
	• Cost benefit • Cost minimisation • Cost consequence • SLRs of economic reviews (for reference list search)	• Non-systematic/narrative reviews • Articles not in the English language • Studies not in human subjects Studies not conducted from a UK or Irish perspective (applicable to cost effectiveness studies and cost and resources use studies)
Study design 2 (Utility studies)	• Primary research publications on any study design • HTAs, or SLRs of relevant primary publications (for reference list search)	
Study design 3 (Cost/resource use studies)	• Primary research publications on any study design • HTAs, or SLRs of relevant primary publications (for reference list search)	

Source: CS Appendix Tables 35-37[38]
Abbreviations: EQ-5D: EuroQol 5-Dimensions; HTA: Health Technology Assessment; HUI3: Health Utilities Index; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHS: National Health Service; PSS: Personal and Social Services; QALYs: quality-adjusted life years; SF-6D: Short-Form Six-Dimension; SLR: systematic literature review; UK: United Kingdom

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. However, the ERG is concerned about the potential language bias arising from restricting searches to English language only; this is not in line with current best practice.

5.1.3 Included/excluded studies in the cost effectiveness review

The initial SLR related to cost effectiveness evidence identified 3,410 publications which met the inclusion criteria, 3,410 titles/abstracts and 205 full texts were reviewed. Six additional publications were found through handsearching of conference proceedings and websites. The 2018 update of the SLR resulted in additional six publications, the updated hand search resulted in one additional article. Hence, a total of six unique economic evaluations, and 19 unique cost/resource use studies were identified. Twenty-two unique utility studies were identified of which 13 reported EQ-5D utility values (see Appendix G of the CS Figure 5 for the PRISMA diagram).[38] The included cost effectiveness studies were summarised and critically appraised using the checklist of Drummond et al. (1996),[51] in Tables 40 and 41 of the CS Appendix.[38] Summaries of utility studies, and cost and resource use studies included were presented in Tables 42 and in Appendices G, H and I of the CS.[38]

ERG comment: The rationale for excluding cost effectiveness studies after full paper reviewing is considered appropriate given the defined inclusion and exclusion criteria. Nine publications identified in the SLR were not fully extracted because they did not report EQ-5D data and were thus not in line with the NICE reference case (Table 43 of the CS Appendix H[38]). Considering the potential limitations of the EQ-5D in migraine patients and the scarcity of utility data in migraine patients with ≥3 prior prophylactic treatment failures, as outlined in Section 5.2.8, the ERG is concerned that relevant HRQoL

studies may have been excluded. Furthermore, for utility studies, and cost and resource studies, the reasons for exclusion of articles and a quality assessment of included articles were not presented.

5.1.4 Conclusions of the cost effectiveness review

The CS and CS appendices provided an overview of the included cost effectiveness, health-related quality of life, and resource use and costs studies. None of the identified economic evaluations assessed the cost effectiveness of erenumab. No specific conclusion has been formulated for the HRQoL studies included in the review. Studies identified on costs and resource use did not report results by MMD frequency, therefore resource use was mainly informed by the 2017 and 2018 National Health and Wellness Surveys.[52, 53]

5.2 Summary and critique of company's submitted economic evaluation by the ERG

The company developed a de novo model. Relevant parameters are described in Table 5.2. A checklist comparing the model to the NICE reference checklist is given in Table 5.3.

Table 5.2: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Combined decision tree and state transition model	To represent the assessment period (decision tree) and the long-term post-assessment period (state transition model)	Section B.3.2.2
States and events	Decision tree endpoints: responder, non-responder state transition model health states: on treatment, discontinuation, death.		Section B.3.2.2
Comparators	BSC Botulinum toxin (chronic migraine population only).	There are no treatment options for episodic migraine patients (for whom ≥3 prior prophylactic treatments have failed). Thus, BSC is the most relevant comparator. Botulinum toxin has been recommended in patients classified as having chronic migraine (for whom ≥3 prior prophylactic treatments have failed). However, due to limited availability of botulinum toxin (as it must be administered by a trained specialist), BSC is also a relevant comparator for chronic migraine patients.	Section B.3.2.3
Population	Migraine patients for whom ≥3 prior prophylactic treatments have failed. This population consisted of episodic migraine patients (with <15 MHDs and	The population is a subpopulation of the population as defined in the	Section B.3.2.1

	Approach	Source/Justification	Signpost (location in CS)
	≥4 to <15 MMDs) and chronic migraine patients (with ≥15 MHDs and ≥8 MMDs).	NICE scope and the licence for erenumab.	
Treatment effectiveness	Treatment effectiveness was estimated based on the estimated response, MMD frequency and treatment discontinuation.	Treatment effectiveness was informed from the subgroup of patients for whom ≥3 prior prophylactic treatments have failed in Study 295, STRIVE, ARISE and LIBERTY.	Section B.3.3
Adverse events	Adverse events were accounted for through treatment discontinuation, but the impact on costs and HRQoL was not explicitly modelled.	The company justified this approach based on expert advice from UK clinicians stating that adverse events associated with migraine prophylaxis are usually non-severe.	Section B.3.3.7
Health related QoL	Treatment independent utility values were estimated based on mapped MSQ data from Study 295, STRIVE, and ARISE for each MMD frequency. Treatment dependent health state utility values were estimated based on the MMD frequency distributions of each treatment.	The EQ-5D-5L data from LIBERTY were not used. The company states that the advantage of the MSQ over the EQ-5D is its recall period of four weeks, which makes it more likely to capture the impact of experiencing migraine than the EQ-5D.	Section B.3.4
Resource utilisation and costs	The cost categories included in the model were treatment costs and costs of disease management	Unit prices stemmed from the manufacturer, the British National Formulary (BNF) 2017, the National Health Service (NHS) Tariff 2017 and the Personal Social Services Research Unit (PSSRU) 2017. Resource use was mainly retrieved from the pivotal trials as well as the National Health and Wellness survey of 2017 and 2018.	Section B.3.5
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case.	Table 60
Subgroups	Patients with HFEM for whom ≥3 prior prophylactic treatments have failed (HFEM was defined as 8–14 MHDs).	The HFEM population is a recognised subgroup of episodic migraine patients who are considered to have a clinical burden similar to patients classified as having chronic migraine. However, unlike chronic migraine patients, patients with HFEM	Section B.3.2.1

	Approach	Source/Justification	Signpost (location in CS)
		at this line of therapy are unable to access botulinum toxin in line with its NICE recommendation. The subgroup of HFEM patients therefore face a particularly high unmet need.	
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses.		Section B.3.8

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	The company defines a narrower population (i.e. patients for whom ≥3 prior prophylactic treatments have failed).
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Yes	
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	No	Time horizon was restricted to ten years
Synthesis of evidence in outcomes	Systematic review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	No	Mapped utilities (from MSQ) were used in the base-case instead of EQ-5D-5L utilities.

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	No	Mapped utilities were used.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Partly	Important parameters were excluded from the sensitivity analyses

NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review

5.2.2 Model structure

The company developed a decision-tree plus state transition model (named Markov model by the company) in Microsoft Excel (Figure 5.1). The decision tree represented the assessment period and the state transition model represented the post-assessment period. The costs and QALYs associated with the health states are calculated as a function of the MMD frequency distributions.

Assessment period

A 12-weeks assessment period was modelled for erenumab and BSC, justified by the company as the length of time deemed clinically appropriate to observe a change in MMDs. The assessment period was 24 weeks for botulinum toxin (chronic migraine population only), which is consistent with previous TA260 and NICE guidance.[21]

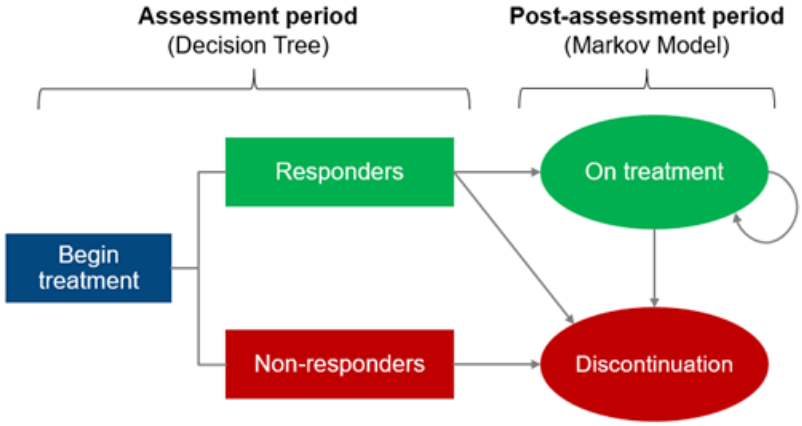
Response was assessed at the end of the assessment period and was defined as a ≥50% reduction from baseline MMD. Patients who discontinued treatment due to adverse events during the assessment period entered the 'discontinuation' health state in the state transition model and were assumed to rebound to the baseline MMDs distribution.

Post-assessment period

The state transition model consisted of three health states: on treatment, discontinuation and death. At the assessment time point, non-responders entered the discontinuation health state, discontinued prophylactic treatment and were assumed to receive only BSC (i.e. acute and background disease management). Non-responders maintained their non-responder MMD as measured at the assessment time point for the remainder of the model time horizon. From the assessment time point onwards (i.e. either 12 or 24 weeks), the post-assessment costs and utilities (depending on the MMD frequency distribution) were applied. Responders entered the on-treatment health state and were assumed to

remain on erenumab or the comparator treatment and hence maintain the responder MMD until treatment discontinuation.

Figure 5.1: Decision-tree plus state transition model (death not shown)



Source: Based on Figure 19 of the CS.[1]

ERG comment: The main concerns of the ERG relate to: a) the failure to fully capture natural progression of disease in the model; b) the 50% response threshold used to define response; c) the positive treatment discontinuation scenario (i.e. re-evaluating responders for continuation of treatment whereby positive discontinued patients maintain the responder MMD); d) the use of a discontinuation risk from 24 weeks onwards (as opposed to immediately following assessment) and; e) differential onset of responder/non-responder specific costs and utilities.

a) Based on the AMPP study (US), patients with migraine may over the course of one-year experience persistence of disease (84%), clinical remission (10%), partial remission (3%), and progression (3%).[54] This natural progression of migraine was not fully captured in the model. This was justified by the company by stating that it would require added complexity in the model, and noting the scarcity of natural progression evidence.[22] In clarification response, the company assumed that, when included in the model, the sum of temporary progressions and remissions would not lead to drastically different results. To illustrate this, the company explored three scenarios with: 1) decrease of respondent health state utility over time (to simulate progression in both arms; 2) the doubling of long-term discontinuation (to reflect remission) and; 3) a variation of scenario 6 (positive discontinuation scenario in the original CS) with an increased proportion of positive discontinuation (alternative scenario to reflect remission on erenumab). The estimated incremental cost-effectiveness ratios (ICERs) in these scenario analyses were lower than the ICER estimated for the company base-case. The ERG considers the company's justification for not modelling natural progression of migraine reasonable, wishes to point out that considerable uncertainty may arise from it (given that the impact and direction of this simplification is not fully known).

b) Based on expert opinion, the company defined a 50% reduction in MMDs as the criterion to determine treatment response. According to NICE TA260 on botulinum toxin in chronic migraine, treatment should be stopped in people whose condition is not adequately responding to treatment; defined as less than a 30% reduction in MHD after two treatment cycles.[21] The committee concluded that a 30% response rate was the most clinically relevant and reasonable negative (due to no response) stopping rule on which to base its decision. Given that the majority of the modelled population were patients with chronic migraine, the ERG considers the responder criterion defined

in TA260 clinically relevant, and presents a scenario analysis using a 30% reduction in MMD as response threshold.

c) According to NICE TA260 on botulinum toxin in chronic migraine, treatment should also be stopped in people whose condition has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.[21] To reflect the potential impact of this, the ERG adopted the positive discontinuation scenario (CS scenario 6) as a scenario analysis. This scenario assumed that continuously after a maximum of 64.5 weeks all patients on treatment discontinue treatment for a re-evaluation period of 12 weeks. In total, 20% of the re-evaluated patients experience positive treatment discontinuation i.e. they stop treatment and thus do not incur the cost of treatment, but continue to receive the benefit of treatment (i.e. the same MMD frequency distribution as responders that are on treatment). The ERG could not identify any evidence to support these assumptions, hence this scenario should be interpreted with caution.

d) The company included a long-term discontinuation probability to model all cause discontinuation in the post-assessment period. This probability was applied from week 24 onwards for erenumab and BSC, and from week 36 onwards for botulinum toxin. However, this should have been applied directly after the response assessment (i.e. 12 weeks for erenumab and BSC and 24 weeks for botulinum toxin). This was adjusted in the ERG base-case.

e) The timing of assessment of response was modelled dependent on the treatment arm, either after 12 weeks (erenumab and BSC) or after 24 weeks (botulinum toxin), whereby baseline utilities and costs were applied in the pre-assessment period and response-specific utilities and costs were applied in the post-assessment period. The ERG is concerned this approach is not reflective of the utility and cost benefits of response that are likely to manifest prior to this assessment point, especially regarding treatment with botulinum toxin where response-specific utilities and costs are only applied after 24 weeks. Hence, to explore the impact of this assumption the ERG applied the post-assessment costs and utility for botulinum toxin at 12 weeks in a scenario.

5.2.3 Population

Erenumab, as per the marketing authorisation, is indicated for the treatment of all patients with migraine who experience ≥4 MMDs (i.e. the licensed indication is not defined in terms of episodic or chronic migraine). In the final scope, issued by NICE, the population was defined as "all people with migraine". However, the company assessed the cost effectiveness of erenumab in adults with migraine with ≥4 MMDs for whom ≥3 prior prophylactic treatments have failed. Within this subgroup, three populations were considered, hereafter referred to as:

- Whole population base-case (patients with ≥4 MMDs)
- Episodic migraine population (patients with <15 MHDs and ≥4 to <15 MMDs)
- Chronic migraine population (patients with ≥15 MHDs and ≥8 MMDs)

In the model, patients had an average age of 42 years and 85% of the population was assumed to be female (based on the average from the pivotal trials, i.e. Study 295 for chronic migraine and ARISE, STRIVE and LIBERTY for episodic migraine). The whole population was based on a weighted average of chronic and episodic migraine (66% and 34% respectively; based on market research from the UK).

In addition, the HFEM (8-14 MHDs) subgroup was considered using subgroup specific clinical effectiveness data (e.g. proportion of responders, MMD frequency distributions). According to the company, this subgroup is considered to have a clinical burden similar to patients with chronic migraine. However, HFEM patients are not able to access botulinum toxin (NICE recommendation), and

therefore, this subgroup faces a particularly high unmet need. Finally, exploratory analyses modelled the population in whom ≥2 prophylactic treatments have failed and who are unable to receive further prophylactic treatment.

ERG comment: The main concerns of the ERG relate to: a) lacking evidence for patients with ≥15 MHDs and ≥4 to <8 MMDs; b) proportions of episodic and chronic migraine patients and; c) HFEM subgroup definition.

a) The ERG notes an inconsistency between the population of the main trials (Study 295, STRIVE, ARISE and LIBERTY) and the overall population as described in the model as well as the licensed indication. Patients with ≥15 MHDs and ≥4 to <8 MMDs were not included in either the trials on chronic migraine or the trials on episodic migraine (see also Sections 4.2.1 and 5.2.6). However, these patients are included in the definition of the whole population (migraine patients with ≥4 MMDs). The company assumed that data from chronic and episodic patients are transferable to this patient group.[22] As no justification was provided for this assumption and the characteristics of the excluded population are unknown, the ERG finds this assumption not well-founded and considers the evidence for the cost effectiveness of erenumab in patients with ≥15 MHDs and ≥4 to <8 MMDs to be lacking.
b) In the company base-case, it was assumed that chronic and episodic migraine patients make up the base-case population at a ratio of 66% and 34%. The company justified this assumption using their 2018 market research.[1] In response to clarification question B5, the company provided evidence from the BECOME trial and the literature supporting their assumption.[22] The ERG believes that the ratio of 66% and 34% is reasonable but that it is more informative to consider the chronic and episodic populations separately. This is in line with the pivotal trials and does not imply that all patients with ≥4 MMDs are covered (including the population with ≥15 MHDs and ≥4 to <8 MMD).
c) Throughout the CS, two definitions of HFEM were used (8-14 MHDs or 8-14 MMDs).[1] In response to clarification question B3, the company stated that in the LIBERTY trial, HFEM was defined as 8-14 MMDs, but in the economic mode, HFEM was defined as 8-14 MHDs.[22] This latter definition is more in line with definitions used in the literature, but assumes that data from patients with 8-14 MMDs can be used to inform outcomes in patients with 8-14 MHDs. Given that MMDs and MHDs are separate outcomes, this assumption may be invalid. The potential bias caused by this assumption is unclear. Additionally, other HFEM definitions can be found in the literature (e.g. 10-14 MHDs). To assess the impact of the definition used for the HFEM subgroup, the ERG presents a scenario using a 10-14 MHDs definition for HFEM.

5.2.4 Interventions and comparators

As per the licensed posology, the recommended dose for erenumab (self-administered subcutaneously) is 70mg Q4W. However, some patients may benefit from the higher 140mg Q4W dosage (given as two injections of 70mg). The company therefore assumed in their base-case that 50% of patients started treatment on erenumab 140mg and the remaining 50% started on erenumab 70mg. Erenumab was modelled to be used in combination with BSC.

BSC was defined as continued treatment with acute medication and healthcare resource use as a function of the MMD frequency being experienced. The company stated that the placebo arms in Study 295, STRIVE, ARISE and LIBERTY can be considered as reasonably representative of BSC in UK clinical practice, because patients were prescribed any treatments necessary to provide adequate supportive care in these trials.

Botulinum toxin was modelled as a comparator for patients having chronic migraine for whom ≥3 prior prophylactic treatments have failed, in line with its recommended use.

ERG comment: The main concern of the ERG relates to the use of the blended dose.

The base-case presented by the company used a blended dose of erenumab 70mg and erenumab 140mg for the intervention arm, assuming a dose mix of 50% and 50%, respectively.[1] The recommended and licensed dose of erenumab is 70mg, for which the results were presented in CS Appendix Z.2.[38] The use of the blended dose and the 50%/50% distribution were not appropriately justified. The employment of a blended dose is illogical because the purpose of the model is to estimate the cost effectiveness per patient of one mutually exclusive treatment compared to another: no patient will receive the blended dose. Put another way, the cost effectiveness analysis aims to inform a decision as to which single treatment to provide to a patient, which, if it is erenumab, can only be either one dose or the other. Although, in their clarification response letter, the company mentioned that "numerically superior clinical outcomes were observed for patients treated with erenumab 140mg compared to erenumab 70mg in the subgroup of patients for whom ≥3 prior treatments have failed", it did not specify which subgroup of patients would be most suitable for the 140mg dose of erenumab or how these patients should be identified.[22] Therefore, the ERG included erenumab 70mg and erenumab 140mg separately in its base-case analysis (instead of the blended dose).

ERG comment: The ERG questioned the use of placebo arms as a proxy for BSC in the UK. In their clarification response, the company elaborated that continued treatment with acute medication is the only treatment available in patients with ≥3 prophylactic treatment failures.[22] The company stated that "Patients in the placebo arms of Study 295, STRIVE, ARISE and LIBERTY were prescribed any treatments deemed necessary to provide adequate supportive care for the duration of the studies",[22] and provided information to show that the medications used were reflective of NICE guideline CG150 recommendations.[11] The ERG considers the evidence supportive of the assumption that BSC is adequately reflected by the studies' placebo arms (see also Section 3.3).

5.2.5 Perspective, time horizon and discounting

The analysis took an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was 12 weeks with a 10-year time horizon, and a half-cycle correction was applied.

ERG comment: In their base-case, the company used a 10-year time horizon for the cost effectiveness analysis of erenumab versus BSC and botulinum toxin, which is not in accordance with the NICE reference case. In scenario analysis 9 of the CS, this time horizon was extended to 15 years, causing the ICER of erenumab versus botulinum toxin to increase, and the ICER of erenumab versus BSC to decrease.[1] To adhere to the NICE reference case, the ERG extended the time horizon to a lifetime time horizon in their ERG base-case analysis. The ERG also noted that the company converted between weekly and annual results by using the factor 52, because the preferred method is to divide by 52.18 (365.25 divided by 7), the ERG amended this in their base-case.

5.2.6 Treatment effectiveness and extrapolation

Clinical parameters were mainly derived from the subgroup of patients for whom ≥3 prior treatments had failed in the pivotal trials: Study 295 for chronic migraine (i.e. patients with ≥15 MHDs and ≥8 MMDs) and ARISE, STRIVE and LIBERTY for episodic migraine (i.e. patients with <15 MHDs and ≥4 to <15 MMDs). The whole base-case population consisted of a weighted average of chronic and episodic migraine (66% and 34% respectively).

Response assessment (decision tree period)

In the model, response was defined as a ≥50% reduction from baseline MMD. This was implemented at week 12 for erenumab and BSC, and at week 24 for botulinum toxin. For botulinum toxin the proportion of responders was estimated using odds ratios of [redacted] and [redacted] versus erenumab 70mg and 140mg respectively. These odds ratios were obtained from an indirect comparison of erenumab (response based on MMD) versus botulinum toxin (response based on MHD), see Table 5.4 and CS Tables 40 and 41.[1]

Table 5.4: Proportion of responders (at 12- or 24-weeks response assessment)

Treatment	Chronic migraine	Episodic migraine
Erenumab 70mg (12 weeks)	[redacted]	[redacted]
Erenumab 140mg (12 weeks)	[redacted]	[redacted]
BSC (12 weeks)	[redacted]	[redacted]
Botulinum toxin (24 weeks)	[redacted]	NA

Source: Based on Table 52 of the CS[1]
Abbreviations: BSC = best supportive care; NA = not applicable

Treatment discontinuation for responders

All non-responders were assumed to discontinue treatment at the response assessment (continuing to receive BSC). At the response assessment, responders could discontinue treatment due to adverse events (see Table 5.5). Finally, after the response assessment, a 'long-term' treatment discontinuation probability of 2.38% per cycle was applied for responders (i.e. 9.9% annually).

Table 5.5: Proportion of responders discontinuing due to adverse events (at response assessment)

Treatment	Chronic migraine	Episodic migraine
Erenumab 70mg (12 weeks)	0.00%	[redacted]
Erenumab 140mg (12 weeks)	1.06%	[redacted]
BSC (12 weeks)	0.71%	[redacted]
Botulinum toxin (24 weeks)	3.40%	NA

Source: Based on Table 53 of the CS[1]
Abbreviations: BSC = best supportive care; NA = not applicable

Monthly migraine days frequency distributions

The MMD frequency distributions were incorporated in the economic model assuming a normal distribution with a range truncated between 0-28 migraine days per month. Table 5.6 provides an overview of the mean and standard deviations used to estimate the truncated normal distributions. The MMD frequency distributions were not available for botulinum toxin, hence the company assumed the same MMD frequency distributions for botulinum toxin as for erenumab.

The baseline MMD frequency distributions were used until the response assessment. Afterwards, treatment- and response-dependent MMD frequency distributions were used for the remainder of the time horizon. It should be noted that the company assumed that where discontinuation occurred for any other reason than non-response (either due to adverse events or due to long-term discontinuation), patients would return to their baseline MMD frequency distribution (i.e. not the MMD frequency distribution for non-responders).

Table 5.6: MMD frequency distributions used in the economic model

	Treatment	Chronic migraine	Episodic migraine
		Mean (standard deviation)	Mean (standard deviation)
Baseline	Treatment independent	[redacted]	[redacted]
Responders 12 weeks	Erenumab 70mg	[redacted]	[redacted]
	Erenumab 140mg	[redacted]	[redacted]
	BSC	[redacted]	[redacted]
Non-responders 12 weeks	Erenumab 70mg	[redacted]	[redacted]
	Erenumab 140mg	[redacted]	[redacted]
	BSC	[redacted]	[redacted]

Source: Based on Table 88 of the CS Appendices[38]
Abbreviations: BSC = best supportive care

Mortality

No excess mortality was assumed. Hence, general population mortality was included in the model based on the Office of National Statistics (ONS) National Life Tables in England and Wales (2014-2016).

Extrapolation of treatment effectiveness

The treatment effectiveness was extrapolated by assuming that the transition probabilities (i.e. probability of treatment discontinuation) as well as the MMD frequency distributions are constant over time. The company justified the extrapolation of treatment effectiveness by referring to two (non-comparative) open-label extension studies: NCT01952574[43, 55] (considering erenumab 70mg in episodic migraine patients) and the open-label extension of Study 295[47] (considering erenumab 70mg and 140mg in chronic migraine patients). It was stated (based on NCT01952574[43, 55]) that "At Week 64, patients achieved a mean reduction of 5.0 (SD: 4.2) MMDs from a baseline of 8.8 MMDs (SD: 2.6), with 65% of patients achieving a reduction of ≥50% in MMDs from baseline". Moreover, based on the open-label extension of Study 295 (NCT20130255[47]) it was stated that "the mean (95% CI) change from Study 295 baseline in MMDs was [redacted] days at Week 24 and [redacted] days at Week 52 for the [redacted] patients who received either erenumab 70mg, erenumab 140mg or a combination of erenumab 70mg followed by erenumab 140mg over the course of the OLE"

ERG comment: The main concerns of the ERG relate to: a) the extrapolation of treatment effectiveness up to 52/64 weeks; b) the extrapolation of treatment effectiveness beyond the open-label extension studies; c) the floor and ceiling effects related to the truncated normal distributions assumed for the MMD frequency distributions; d) inconsistency between the company submission and the economic model regarding MMD frequency distributions; e) difference in definition of response for erenumab and botulinum toxin; f) assumptions related to the MMD distribution after treatment discontinuation and; g) the method used to combine data from STRIVE, ARISE and LIBERTY.

a) In response to clarification question B9a, the company argued that whilst the open-label extension studies "did not contain a control arm as this may have raised ethical challenges, these results support the assumption that the reduction in MMDs in patients treated with erenumab 70mg and 140mg is maintained at 64 weeks". The ERG believes this is reasonable to assume up to 64 weeks. However, it is unclear this is similar for the comparative effectiveness of erenumab versus placebo (i.e. BSC). Particularly, given that based on Figure 7 in the clarification response, the change from

baseline MMD seemed to have plateaued at the end of the initial trial period for erenumab (weeks 8-12) while for placebo this was still decreasing.

b) Considering the extrapolation beyond the open-label extension studies (after 52 weeks for chronic migraine and after 64 weeks for episodic migraine) up to 10 years (model time horizon), the company argued, in response to clarification question B9b, that "Whilst no data are available from longer-term follow-up of patients treated with erenumab, the results of these [open-label extension] studies provide no indication of a waning in the treatment effect: in both studies, patients experienced numerical reductions in MMDs from the end of the double-blind treatment phase to Week 52 or Week 64". However, the ERG believes that, given the absence of evidence related to the long-term effectiveness, it is uncertain whether there is a treatment waning effect. In response to clarification question B9d, the company explored an alternative scenario for the long-term effectiveness by reducing the health state costs and health state utilities for erenumab and botulinum toxin linearly over time, to eventually reflect the health state costs and health state utilities associated with BSC non-responders. This scenario indicated that a treatment waning effect could substantially increase the estimated ICERs. The scenario presented by the company assumed a treatment waning period of 10 years: decreasing this period would be likely to further increase the estimated ICERs. This scenario, as well as a similar scenario with a five-year waning period is adopted by the ERG.

c) For the implementation of the MMD frequency distributions in the model, the company assumed normal distributions with a range truncated between 0-28 migraine days per month. This restricted range resulted in floor and ceiling effects (see for instance CS Figure 24), which the company acknowledged may introduce bias (response to clarification question B12c). Although the company argues that this bias is conservative this is not completely convincing to the ERG given that no evidence was provided to support this.

d) The MMD frequency distributions were summarised in Table 88 of the CS Appendix S.[38] However, additional MMD distributions to those described in the CS were used for the episodic migraine. Specifically, 24-week MMD distributions were added for responders. Given that the rationale for only using 24-week MMD distributions for responders with episodic migraine was lacking, this inconsistency was adjusted in the ERG base-case to be in line with the CS description as well as with the chronic migraine population.

e) For the indirect comparison the different timings of response for erenumab (based on 12 weeks MMD) and botulinum toxin (based on 24 weeks MHD) were (implicitly) assumed to have no effect on the size of the response. This may have biased the estimated cost and effects of botulinum toxin. However, the direction and magnitude of this bias is unclear to the ERG (see Sections 4.3 and 4.4 for more details).

f) The company assumed that the nature of treatment discontinuation determines whether patients either return to the baseline MMD distribution (discontinuation due to adverse events or long-term discontinuation) or maintain the non-responder MMD as measured at week 12 (discontinuation due to non-response at week 12). In response to clarification question B10 the company argued that response status reveals heterogeneity within the patient population of interest and thus it was assumed that a different propensity to respond to treatment also means a different disease status when coming off treatment. The company argued that those who respond to treatment would hence have experienced a 'better' natural improvement in MMDs compared to non-responders. The ERG believes that this argumentation is inconsistent with the modelling approach adopted by the company, given that in chronic migraine non-responders actually have a [redacted] MMD frequency than the baseline MMD frequency and in episodic migraine [redacted]. (see Table 5.6). Therefore, the ERG assumed that all treatment discontinuers would have the week 12 non-responder MMD frequency.

g) In response to clarification question B11, the company indicated that the patient-level data from STRIVE, ARISE and LIBERTY were combined without adjustment or weighting. This assumes that there is no trial-level effect and that the trials sample from the same patient population with the same MMD frequency at baseline. It is unclear to the ERG to what extent this latter assumption is reasonable or may induce bias. Moreover, this assumption might result in discrepancies with the data presented in chapter 4.

5.2.7 Adverse events

Adverse events were accounted for in terms of treatment discontinuation, but the impact on costs and HRQoL was not explicitly modelled. The company justified this approach based on expert advice from UK clinicians, stating that adverse events associated with migraine prophylaxis are usually non-severe (serious adverse events occurred in 1%-3% in Study 295, ARISE, STRIVE and LIBERTY).

ERG comment: The main concerns of the ERG relate to not explicitly modelling the impact of adverse events on costs and HRQoL. When considering the population for whom ≥3 prior prophylactic treatments have failed (instead of the whole trial population), the proportion of serious adverse events may be [redacted]. According to the company's response to clarification question A9, the serious adverse events may be as high as [redacted] and [redacted] for erenumab 70mg and 140mg respectively. However, given the small sample size it is not possible to draw firm conclusions regarding adverse events for patients for whom ≥3 prior prophylactic treatments have failed.

5.2.8 Health-related quality of life

For the company base-case analysis, treatment independent utility values for each MMD frequency were estimated based on Study 295, STRIVE, and ARISE. Utility values were estimated based on the MMD frequency distributions.

Health-related quality of life data identified in the review

According to the CS, the SLR identified 25 publications meeting the inclusion criteria. Of these, 16 publications reported EQ-5D utility values. None of these studies reported EQ-5D values by MMD frequency, or by migraine subpopulation.[1] Hence, none of the studies identified in the SLR were used in the company base-case analysis.

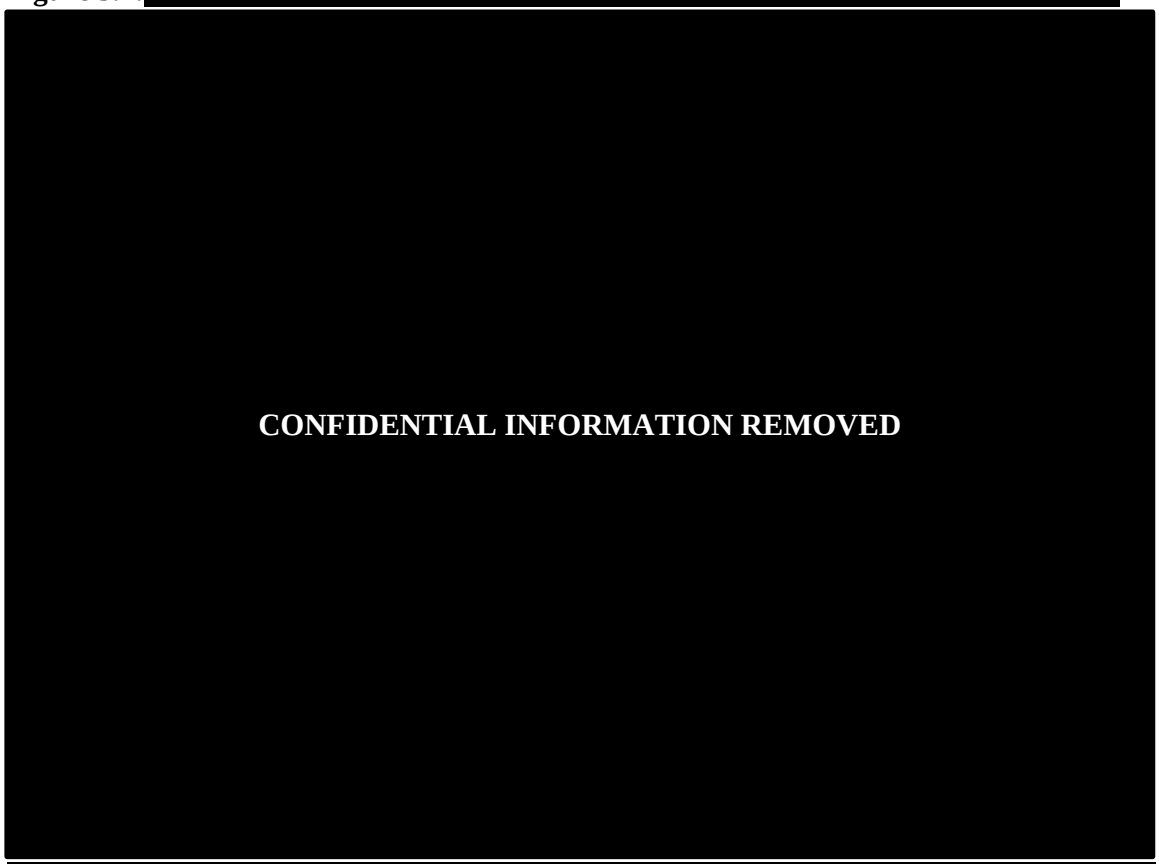
Health state utility values

The company stated that the advantage of the MSQ over the EQ-5D is its recall period of four weeks, which makes it more likely to capture the impact of experiencing migraine on quality of life than the EQ-5D-5L, which were collected in LIBERTY. For the base-case analysis, the company therefore mapped MSQ v2.1 utility data collected in Study 295, STRIVE, and ARISE trials to EQ-5D-3L utility values using the mapping algorithm described by Gillard et al. 2012.[56] MSQ data were not collected in LIBERTY.

The mapped MSQ utility values were used and multilevel models fitted to estimate disutility values associated with each MMD frequency. These multilevel models were fitted to all three studies combined for the whole migraine population analysis; and separately to Study 295 data and the pooled STRIVE and ARISE data for the indication specific (chronic and episodic migraine) analyses. The resulting estimated disutility values were re-converted into utility values by subtracting the disutilities from 1. Figure 5.2 provides an overview of the estimated utility values for each MMD frequency for the different populations. Health state utility values were obtained by multiplying the proportion of patients

in each MMD frequency by the utility values associated with each MMD frequency. A summary of all health state utility values used in the cost effectiveness analysis is provided in Table 5.7.

Figure 5.2:



EQ-5D-5L data were collected during the LIBERTY trial but were (according to the company) not deemed suitable to inform the cost effectiveness analysis, because the utility elicitation took place on appointment days and asked the patients to rate their health at that moment. The company argued that most of the patients experiencing a migraine were likely to postpone their appointment and thus unlikely to experience a migraine during appointment days. Hence, utility values collected during LIBERTY do not represent the impact of experiencing migraine on quality of life. The utility values elicited in LIBERTY were used in a scenario analysis for the episodic migraine population (using the cross-walk from EQ-5D-5L to EQ-5D-3L[57]).

Based on expert opinion, disutilities associated with AEs and modes of administration were not included in the base-case analysis (see Section 5.2.7). A scenario analysis explored the influence of incorporating disutilities associated with mode of administration on the results. These disutilities were obtained from an unpublished vignette-based study including mostly general population respondents and some patients with migraine.[58]

Table 5.7: Health state utility values (conditional on MMD distributions; see Section 5.2.6)

	Treatment	Whole population	Chronic migraine	Episodic migraine
Baseline[a]	Treatment independent	0.577	0.466	0.688
Responders	Erenumab 70mg	0.743	0.735	0.769
	Erenumab 140mg	0.762	0.752	0.784
	BSC	0.746	0.731	0.770
Non-responders	Erenumab 70mg	0.601	0.491	0.695
	Erenumab 140mg	0.603	0.512	0.686
	BSC	0.592	0.495	0.685
On treatment (post-assessment period)[b]	Erenumab 70mg	0.741	0.735	0.760
	Erenumab 140mg	0.761	0.752	0.779
	BSC	0.741	0.731	0.756

[a] AE-related and long-term negative discontinuation have the same utility value as baseline

[b] See critique in 5.2.6 (ERG comment point d) regarding the addition of this time point for responders with episodic migraine only.

ERG comment: The main concerns of the ERG relate to a) the population in which the utility values were elicited, b) a lack of detail concerning the modelling of MMD specific disutilities, c) the exclusion of HRQoL impact of AEs, d) the use of EQ-5D data collected in LIBERTY, and e) the use of HIT-6 data mapped to EQ-5D.

a) Whilst treatment effectiveness was based on the population with ≥3 prior prophylactic treatments, utility values in the model were informed by the full trial population, as the company clarified in response to clarification question B14.b.[22] According to the company, using the population with ≥3 prior prophylactic treatments, the number of patients available in the analysis would be significantly reduced, particularly for STRIVE and ARISE. The ERG is concerned about this inconsistency in the evidence used. It is noteworthy that cost estimates were also derived from the full trial population. In response to clarification question B14.b, the company implemented a scenario using utility values estimated from the population with ≥3 prior prophylactic treatments, but only for the episodic and chronic migraine populations combined instead of for the indication-specific populations, due to small sample sizes. As the company indicated, the utility estimates estimated in the population with ≥3 prior prophylactic treatments reflect a greater increase in disutility associated with each MMD frequency, which improves the cost effectiveness of erenumab. This was supported by a decreased ICER for the blended dose of erenumab compared with placebo in the whole migraine population. Since the company only provided utility values estimated from the population with ≥3 prior prophylactic treatments for the episodic and chronic migraine populations combined (i.e. not indication-specific), the ERG maintains the company's base-case analysis using the full trial population in the ERG base-case. This ensures consistency in the derivation of utilities and resource use, but results in inconsistencies between utility and effectiveness estimates. Therefore, the ERG implemented the utility values estimated from the population with ≥3 prior prophylactic treatments in a scenario analysis.
b) The ERG is concerned about the lack of detail provided in the CS concerning the modelling of MMD frequency specific disutilities, in particular with regards to the pooling of studies, the handling of missing data and model selection. It should be acknowledged that the company provided most of the requested information in response to the clarification letter and most of the ERG's concerns have been addressed. One issue regarding missing data remains unresolved: the ERG notes that the number of missing observations in STRIVE (16.2%) was significantly larger than in Study 295 (3.9%) and ARISE (2.5%). It is not clear why this was the case and whether this may introduce any bias in the analyses. With regards to model selection, the ERG has further concerns. The linear model was chosen even though the company showed, in response to clarification question B14.a, that the cubic model made a better statistical fit. However, the ERG acknowledges that these models were very similar in terms of their statistical fit and agrees that the choice of linear model is likely to be appropriate. The alternative models, however, were not (correctly) implemented in the company's model (e.g. not all covariates were included), so any effect of this on the ICERs cannot be assessed by the ERG.
c) As was highlighted in Section 5.2.7, the ERG is concerned that HRQoL and costs associated with AEs are not reflected in the model (apart from causing treatment discontinuation). The ERG considers the impact of on-treatment AEs on HRQoL estimates to be relevant to this setting, in which patients will continuously receive prophylactic treatment with erenumab. In such a setting, even Grade 1/2 AEs may have an impact on patients' HRQoL. In response to clarification question B17, the company implemented a scenario including AEs. However, the ERG considers this to be potentially flawed, as the selection procedure for AEs was unclear, it assumed equal AE for erenumab 70mg and 140mg based on Study 295 only and the utility decrements relied on an unpublished vignette-based study[38] including mostly general population respondents and some

migraine patients, which is not in accordance with the NICE reference case.[50] It is further noteworthy that the company's results, presented in response to clarification question B17.e, also include a utility decrement for mode of administration associated with botulinum toxin (based on the same vignette-based study).

d) The company's argument that EQ-5D values did not capture the impact of migraine on HRQoL because they were elicited mostly during migraine-free days (and hence preferred mapped utilities from MSQ data over EQ-5D utilities), is plausible. However, using EQ-5D utilities from LIBERTY had a large impact on the ICER (increased from £35,787 in the CS base-case to £68,080 per QALY gained in the company's scenario, see CS Table 87). Since using EQ-5D utilities is in line with the NICE reference case, the ERG considers the use of LIBERTY EQ-5D data as a scenario analysis.

e) The company used mapped utilities from MSQ data, whilst mapped utilities from HIT-6 data could also have been used. In response to clarification questions B16, the company provided scenarios using the mapping algorithm by Gillard et al (2012)[56] to map HIT-6 data to EQ-5D utilities. In these scenarios, ICERs in all populations and comparisons increased by at least £10,000 per QALY gained (Tables 72-79 of response to the clarification letter).[22] However, the company pointed out that the HIT-6 instrument measures the impact of headaches, rather than that of migraines, on HRQoL. The ERG found that utility values per MMD frequency ranged from [redacted] using the HIT-6 instrument whilst they ranged from [redacted] using the MSQ instrument (whole migraine population). The latter are more aligned with utility ranges considered in the previous TA260,[21] which is likely to be because these were also based on MSQ data. The ERG considers that MSQ is likely to be a better source than HIT-6 for mapped utility data in this population.

5.2.9 Resources and costs

The cost categories included in the model were treatment costs and costs of disease management. Treatment costs included drug costs, administration costs and initiation costs. Costs for disease management included visits to the emergency department, general practitioner, nurse practitioner and neurologist, hospitalisations, migraine-specific medication (assumed to be represented by triptan use) and other medication (assumed to be represented by analgesics).

Unit prices stemmed from the manufacturer, the British National Formulary (BNF) 2017,[59] the National Health Service (NHS) Tariff 2017[60] and the Personal Social Services Research Unit (PSSRU) 2017.[61]

Resource use and costs data identified in the review

According to the CS, the SLR identified 22 publications reporting UK relevant resource use and costs, corresponding to 19 unique studies.[1] The company did not use these studies to inform resource use as none of them reported costs or resource use by MMD frequency. Instead resource use data from their National Health and Wellness survey (NHWS) of 2017 and 2018 were used.[52, 53]

Treatment costs (with PAS)

An overview of treatment costs is provided in CS Table 48.[1] Erenumab is either delivered per 70mg (1 × 70mg pre-filled pen) or per 140mg (currently two packs of 1 × 70mg pre-filled pen). The prices of the 70mg dose and 140mg dose are £[redacted] and £[redacted] respectively. Erenumab was administered three times per model cycle (of 12 weeks), the treatment cost per cycle were thus £[redacted] and £[redacted] for 70mg and 140mg respectively. Administration costs do not apply but a one-off initiation cost of £40.04 was incorporated to reflect training of the patient on how to use the injection (assumed to be the cost of one working hour of a Band 5 hospital nurse, applied in the first cycle only).[61]

No treatment costs for BSC were incorporated (besides the health state costs described below) given that both erenumab and botulinum toxin are used in conjunction with BSC. Botulinum toxin for chronic migraine was used at a list price of £276.40 per 200 IU vial, corresponding to the Summary of Product Characteristics (SmPC) recommended dose of 155 to 195 units, applied once per cycle. Administration costs of £116.00 were applied (assumed to be the tariff "WF01A Follow Up Attendance - Single Professional (code 400)" in the non-mandatory prices worksheet).[60] This resulted in treatment cost per model cycle (of 12 weeks) of £392.40.

Health state costs

Acute and background disease management costs were applied to all patients. This was solely dependent on the number of MMDs, i.e. independent of treatment status (see CS Table 51[1] for resource use frequency and cost per cycle by MMD frequency). Each model health state was associated with a different MMD frequency distribution (see Section 5.2.6 for more details). By combining these MMD frequency distributions with the costs per MMD frequency, average costs were calculated per health state.

The following components were included in the health state costs: emergency department (A&E) visits, hospitalisations, general practitioner visits, nurse practitioner visits, neurologist visits. Resource use by MMD frequency was informed by the NHWS 2017[52] and unit prices were taken from the NHS Tariff 2017[60] and the PSSRU 2017,[61] see CS Table 57.[1]

Migraine-specific medication use and other medication use per MMD frequency were also included. The company assumed migraine-specific medication could be represented by triptan use and other medication use could be represented by use of analgesics. The proportions of medications used were informed by the NHWS 2018,[53] unit prices and doses per migraine drug day/other medication day were taken from the BNF 2017.[59] A regression model based on pooled clinical data from Study 295, ARISE, LIBERTY and STRIVE informed the number of migraine drug days/other medication days per cycle by MMD frequency. Health state costs based on MMD distribution and MMD frequency-dependent healthcare utilisation are shown in Table 5.8.

Table 5.8: Health state costs per cycle (of 12 weeks)

Health state	Erenumab 70mg	Botulinum toxin[d]	Erenumab 140mg	Botulinum toxin[e]	BSC
Total population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Episodic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic population					
Baseline[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	Erenumab 70mg	Botulinum toxin[d]	Erenumab 140mg	Botulinum toxin[e]	BSC
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment post-assessment[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Model sheet 'Costs'[1]
Abbreviations: BSC: Best supportive care
[a] Patients with adverse event-related or long-term discontinuation in the post-assessment period are assumed to have baseline health state costs
[b] Referring to non-responders in the assessment period and patients off treatment in the post-assessment period due to initial non-response
[c] See critique in 5.2.6 (ERG comments point d) regarding the addition of this time point for responders with episodic migraine only.
[d] When compared to erenumab 70mg
[e] When compared to erenumab 140mg

Adverse event related costs

As described in Section 5.2.7., costs and resource use related to adverse events were not explicitly included in the cost effectiveness analysis.

ERG comment: The main concerns of the ERG relate to: a) the use of evidence from populations without ≥3 prior failures of prophylactic treatment, b) the merging of datasets related to migraine and other medication days, c) the inconsistency and representativeness of medication brands selected, d) assumptions related sumatriptan injections costs, e) patient grouping by MHDs for medication use per MMD and, f) the exclusion of the cost impact of AEs.

a) Due to the scarcity of data on patients with ≥3 prior failures of prophylactic treatment, all estimates of resource use and costs were obtained from patient populations not specified to have ≥3 prior failures of prophylactic treatment. The company provided no evidence that prior treatment failure does not impact the costs of migraine treatment.[22] Given that no evidence was provided, the ERG cannot rule out that the estimates presented are subject to bias.
b) The company pooled data on acute medication days and other headache medication days from Study 295, STRIVE and ARISE by merging datasets. This approach differs from the method used to pool QoL data (using a multi-level regression model) and assumes that there is no trial-level effect and that the trials sample from the same patient population with the same MMD frequency. It is unclear to the ERG to what extent these assumptions are reasonable or may induce bias.
c) To inform the prices of acute medication and other headache medication days, per medication item, a brand was selected to inform the price per medication dose. No specified criteria were used in the selection of the brand, causing inconsistency. It is unclear to what extent the brands chosen correspond with the brands predominantly used in UK clinical practice. The identified prices may therefore not be fully representative of the mix of brands used in UK clinical practice.
d) The company assumed sumatriptan injections (used in 18.4% of patients as headache medication,[22]) to have the same price as oral sumatriptan.[38] The justification for this assumption is unclear to the ERG. The ERG therefore amended the cost per triptan medication to reflect the costs of sumatriptan injections (instead of the costs of oral sumatriptan) in the ERG base-case analysis.
e) In their clarification response, the company amended a typographical error in Table 58 of the CS and clarified that patients were grouped by number of MHDs to estimate medication use by MMD.[22] The ERG considers the assumption of MHDs approximating MMDs to be questionable, given that

these are separate outcomes, and wishes to highlight that the estimates of resource utilisation may consequently be biased.

f) As was highlighted in Sections 5.2.7 and 5.2.8, the ERG is concerned that HRQoL and costs associated with AEs are not reflected in the model (apart from causing treatment discontinuation). The ERG cannot rule out that the exclusion of AE-related resource use and costs introduces bias in the cost effectiveness results.

5.2.10 Cost effectiveness results

The company presented their base-case results separately for the whole migraine, the chronic migraine population and the episodic migraine populations; and separately for the blended dose (50% of patients receiving erenumab 70mg and 50% erenumab 140mg), erenumab 140mg and erenumab 70mg (although the latter was only presented in Appendix Z.2). The deterministic base-case cost effectiveness results of erenumab (with PAS) compared with BSC for the blended dose amount to an ICER of £22,446 per QALY gained in the whole migraine population, to £18,893 per QALY gained in the chronic migraine population, and to £35,787 per QALY gained in the episodic migraine population. The results (including fully incremental results for the chronic migraine population, and the other doses) are shown in Tables 5.9-5.11.

Table 5.9: Company's deterministic base-case cost effectiveness results (blended dose)

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Fully incremental ICER (£/QALY)	ICER versus BSC
Company base-case whole migraine population						
BSC	[redacted]	[redacted]				
Erenumab 70mg/140mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£22,446
Company base-case chronic migraine population						
BSC	[redacted]	[redacted]			-	
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£15,953	£15,953
Erenumab 70mg/140mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,893	£17,212
Company base-case episodic migraine population						
BSC	[redacted]	[redacted]				
Erenumab 70mg/140mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£35,787

BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY =quality-adjusted life-year.
*Based on company's reported total costs and QALYs

Table 5.10: Company's deterministic base-case cost effectiveness results (erenumab 140mg)

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Fully incremental ICER (£/QALY)	ICER versus BSC
Company base-case whole migraine population						
BSC	[redacted]	[redacted]				
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£19,827
Company base-case chronic migraine population						
BSC	[redacted]	[redacted]			-	
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,601	£10,601
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,832	£13,340
Company base-case episodic migraine population						
BSC	[redacted]	[redacted]				
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£40,662

BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year.
*Based on company's reported total costs and QALYs

Table 5.11: Company's deterministic base-case cost effectiveness results (erenumab 70mg)

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Fully incremental ICER (£/QALY)	ICER versus BSC
Company base-case whole migraine population						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£26,803
Company base-case chronic migraine population						
BSC	[redacted]	[redacted]			-	
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£8,948	£8,948
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£20,339	£24,668
Company base-case episodic migraine population						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	-	£29,200

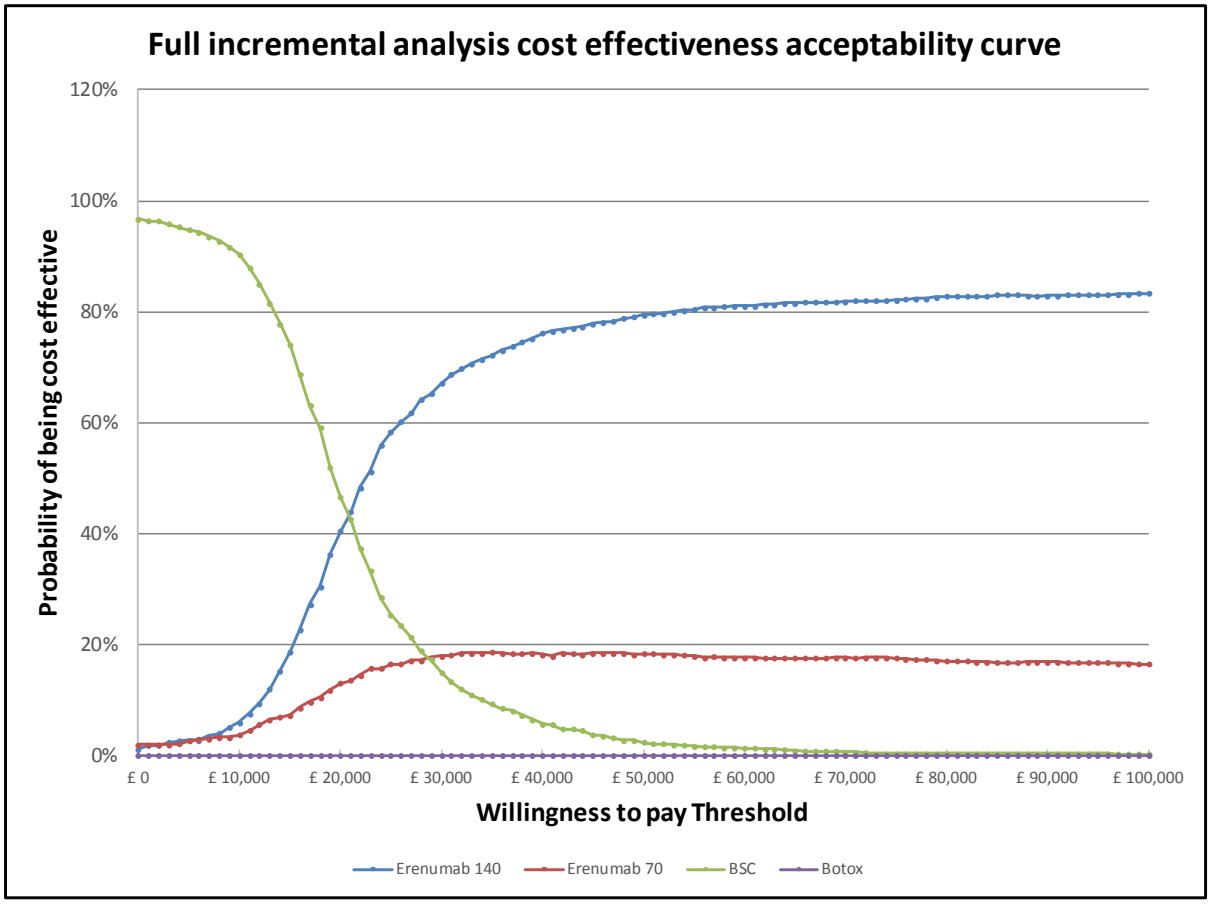
BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY= quality-adjusted life-year.
*Based on company's reported total costs and QALYs

The probabilistic sensitivity analysis (PSA) was run with 1,000 simulations and obtained largely similar results to the deterministic analysis. Results can be found in the CS Tables 72-77[1] and in Figures 30-33.

ERG comment: The main concerns of the ERG relate to: a) lack of presentation of incremental results for the erenumab 140mg and 70mg doses, and b) incomplete PSA.

a) The PSA did not enable simultaneous calculation of outcomes for more than two comparators and representation of multiple comparators in the cost effectiveness acceptability curve (CEAC). The company amended this in their model in response to clarification question B22.
b) The ERG was concerned that not all of the important parameters (treatment discontinuation) were included in the PSA. The company amended this omission in response to clarification question B22. The revised CEAC with all included comparators for the whole migraine population is presented in Figure 5.3.

Figure 5.3 Company's base-case CEAC in the whole migraine population



Source: CS model in response to clarification letter[22]

5.2.11 Sensitivity analyses

The company performed various sensitivity and scenario analyses. Parameter values were varied in one-way sensitivity analyses. For both the whole migraine as well as the episodic migraine population, and for the blended dose compared with BSC, the three most influential parameters included the non-responder MMD frequencies for BSC, erenumab 70mg and 140mg (CS Figures 34 and 40).[1] In the chronic migraine population, for the blended dose compared with botulinum toxin, the three most influential parameters (excluding the discount rate for costs) were the erenumab 140mg and 70mg treatment costs per cycle and the chronic migraine non-responder MMD frequency for erenumab 140mg

(CS Figure 36),[1] but many other parameters had a similar impact (mainly those related to the probabilities of response and the MMD frequencies). Full results were presented in Figures 34-41 of the CS.[1]

Scenario analyses indicated that alternative assumptions could significantly increase or decrease the ICERs in all populations. The most influential alternative scenarios in the comparison with BSC (apart from adopting a societal perspective) for the whole migraine population and blended dose were a) changing the non-responder MMD distribution following the assessment period to that of BSC non-responders (ICER increases), b) applying a 30% stopping rule instead of the 50% stopping rule (ICER increases), and c) changing the non-responder MMD distribution following the assessment period to baseline (ICER increases).

For the chronic population and blended dose compared with botulinum toxin, the most influential alternative scenarios were a) application of a utility decrement related to the method of administration for botulinum toxin (ICER decreases), b) applying periodical re-evaluation where a proportion of patients discontinues (ICER decreases), and c) changing the non-responder MMD distribution following the assessment period to the baseline MMD distribution (ICER decreases).

The impact of alternative scenarios was possibly largest in the episodic migraine population. For the blended dose compared with BSC (apart from adopting a societal perspective) the most influential alternative scenarios were a) applying a 30% stopping rule instead of the 50% stopping rule (ICER increases), b) changing the non-responder MMD distribution following the assessment period to that of BSC non-responders (ICER increases), and c) the use of (EQ-5D-5L) utility values from LIBERTY for episodic migraine patients (ICER increases). Full results were presented in Tables 81-88 of the CS.[1]

In additional to sensitivity and scenario analyses, the company also performed further subgroup analysis, in which the episodic migraine population was restricted to the HFEM population (8-14 MMDs) based on both the whole migraine population and the episodic migraine population base-cases. This resulted in a small decrease in the ICER (by approximately £200 per QALY gained) for the whole migraine population, and an increase in the ICER (by approximately £2,000 per QALY gained) for the episodic migraine population.

ERG comment: The ERG considered the sensitivity analyses to be appropriate. Some further scenario analyses requested by the ERG were provided in response to the clarification letter[22] and are described in the relevant sections of this report.

5.2.12 Model validation and face validity check

Face validity

Discussions with UK clinical experts and a UK health economics expert were held to assess the face validity of the model structure. Further input was sought at advisory boards.[1] It is, however, unclear whether data inputs were agreed on with, or results were presented to, experts.

Internal validity

Two independent health economics experts checked the model for internal validity.

Cross validity

No detailed cross validation was reported in the CS.

External validity

The company provided a comparison between clinical trial data for erenumab 70mg and 140mg versus placebo (Study 295, STRIVE, ARISE and LIBERTY) for mean change from baseline in MMDs, showing overall relatively similar results (see CS Table 93).[1]

Predictive validity

No predictive validation was reported.

ERG comment: The main concerns of the ERG relate to: a) lack of details on internal validation; b) lack of cross validation and; c) inability to reproduce the external validation.

a) The internal validation was not reported in detail. However, the ERG was able to independently rebuild the cohort analysis and recalculated the estimated QALYs for the company base-case, supporting its internal validity.
b) The ERG was concerned about the lack of a detailed cross validity exercise comparing the present model with that developed for botulinum toxin in TA260,[21] which was missing from the CS. The company provided a cross validation in response to clarification question B23 in Table 88,[22] however more detail may have been useful to assess the impact of differences in model structure, assumptions and inputs on results.
c) Although the company did provide external validation, the ERG was unable to reproduce these findings (i.e. the mean change from baseline MMD versus placebo as reported in CS Table 93).[1] As a result the validity of the external validation performed by the company can be questioned.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Table 5.12 summarises the main issues highlighted by the ERG in Section 5.2, and indicates the expected direction of bias introduced by these issues and whether these are examined in any analyses or incorporated in the ERG base-case.

Table 5.12: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Model structure (Section 5.2.2)			
Natural progression of the disease is not fully captured	+/-		Clarification response (partly)
Response was defined as a ≥50% reduction from baseline MMD	+	Scenario	CS scenario 7
Positive discontinuation (according to NICE TA260 treatment should also be stopped in people whose condition has changed from chronic to episodic migraine for 3 consecutive months)	-	Scenario	CS scenario 6
No discontinuation risk the first cycle after response assessment	+	Fixing error	
Botulinum toxin responders have response MMD frequencies (and the associated cost and HRQOL) only 24 weeks after starting treatment	+	Scenario	
Population, interventions and comparators, perspective and time horizon (Sections 5.2.3-5.2.5)			
Lacking evidence for patients with ≥15 MHDs and ≥4 to <8 MMDs	+/-		
Conversion between weekly and annual results	+	Fixing error	
Definition of HFEM subgroup	+	Scenario	Clarification response
Using blended dose for erenumab (instead of 70mg and 140mg separately)	+/-	Fixing violation	Clarification response
Time horizon limited to ten years (i.e. not lifetime time horizon)	+	Fixing violation	
Treatment effectiveness and extrapolation (Section 5.2.6)			
Extrapolation assuming a continued treatment effect (i.e. no waning of treatment effect)	+	Matter of judgement	Clarification response
Definitions of response for erenumab (based on 12 weeks MMD) and botulinum toxin (based on 24 weeks MHD) were (implicitly) assumed to be identical in the indirect treatment comparison	+/-		
Floor and ceiling effects of truncated normal distributions for MMD frequency	+/-		
Inconsistency regarding the use of 24-week MMD distributions for responders.	+	Fixing error	

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Assumption that the nature of treatment discontinuation determines whether patients rebound to the baseline MMD distribution or are assumed to maintain the non-responder MMD	-	Matter of judgement	Clarification response
Adverse events (Section 5.2.7)			
The impact of adverse event on HRQOL and costs is not explicitly modelled	+		Clarification response (partly)
Health-related quality of life (Section 5.2.8)			
HRQOL based on the whole trial population (not restricted to patients for whom ≥3 prior prophylactic treatments have failed)	-	Scenario	
Use of HIT-6 data to map EQ-5D utilities	+		Clarification response
Using mapped utilities instead of Euroqol-5D data from LIBERTY	+	Scenario	CS scenario 13
Resources and costs (Section 5.2.9)			
Resource use and costs are based on the whole trial population (not restricted to patients for whom ≥3 prior prophylactic treatments have failed)	+/-		
Oral triptan medication costs assumed for triptan injections	-	Fixing violations	
Method used for estimating resource use per MMD frequency (i.e. not using a multi-level approach, similar as for HRQOL)	+/-		
Cost effectiveness analyses (Sections 5.2.10 and 5.2.11)			
No incremental analyses (including erenumab 70mg and 140mg separately)	+/-	Fixing violations	Clarification response
Not all relevant parameters are included in the PSA	+/-	Fixing violations	Clarification response

Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.
ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; MJ = matters of judgement

Based on all considerations in Section 5.2 (summarised in Table 5.12), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments, made by the ERG, formed the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[62]):

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing errors

1. No discontinuation risk during the first cycle after response assessment (Section 5.2.2).
   The ERG corrected this error.
2. Conversion between weekly and annual results (Section 5.2.5).
   The ERG corrected this error.
3. Inconsistency between CS and economic model regarding the use of 24-week MMD frequency distributions (Section 5.2.6).
   The ERG corrected this error.

Fixing violations

4. The use of the blended dose for erenumab (Section 5.2.4).
   The ERG considered erenumab 70mg and erenumab 140mg separately.
5. Time horizon limited to 10 years (Section 5.2.5).
   The ERG adopted a lifetime time horizon
6. Oral triptan medication costs were assumed for triptan injections (Section 5.2.9).
   The ERG used triptan injection costs for triptan injections.
7. Not all relevant parameters were included in the PSA (Section 5.2.10).
   The ERG included additional parameters in the PSA.

Matters of judgment

8. Extrapolation assuming a continued treatment effect (Section 5.2.6).
   The ERG adopted a five-year treatment waning effect.
9. Assumptions related to the MMD frequency distributions after treatment discontinuation (Section 5.2.6).
   The ERG assumed the non-responder MMD frequency distribution after treatment discontinuation (independent on the nature of discontinuation)

Tables 6.1 and 6.3 indicate how individual adjustments impact the results plus the combined effect of all of the abovementioned adjustments simultaneously, resulting in the deterministic ERG base-case. The 'fixing error' adjustments were combined and the other ERG analyses were also performed incorporating these 'fixing error' adjustments, given that the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues. The ERG adjustment to the PSA (adjustment 7) was not included separately in the breakdown since this adjustment does not affect the deterministic results. All analyses were presented using incremental analyses. As incremental analyses were not implemented for the blended dose, all analyses were performed considering erenumab 70mg and erenumab 140mg separately (i.e. conditional on adjustment 4).

5.3.1 ERG base-case results

The ERG base-case consisted of an ICER range reflecting the uncertainty surrounding the extrapolation of treatment effectiveness.

The ERG base-case (probabilistic) indicated that erenumab 70mg was dominated in the chronic migraine population. Erenumab 140mg was considered cost effective at willingness to pay thresholds higher than £16,905 and £38,622 per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period, respectively (Table 6.6). For these two assumptions, the probabilities of Erenumab 140mg being cost effective were 75% and 20%, respectively, at a willingness to pay threshold of £20,000 per QALY gained while this increased to 79% and 43%, respectively, at a willingness to pay threshold of £30,000 per QALY gained (Figures 5.4 and 5.5).

For the episodic migraine population, the probabilistic ERG base-case results indicated that erenumab 70mg would be cost effective at willingness to pay thresholds higher than £10,047 and £95,227 per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period respectively (Table 6.7). Erenumab 140mg was either dominated by erenumab 70mg (due to worse non-responder MMD frequencies for erenumab 140mg than for erenumab 70mg) or became cost effective at a willingness to pay threshold of £267,487 per QALY gained. When assuming a constant treatment effect over time, the probability of erenumab 70mg being cost effective was 60% and 64% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively. This decreased to 3% and 8%, respectively, when assuming treatment effect waning over a five-year period (Figures 5.6 and 5.7).

Figure 5.4: ERG base-case CEAC for the chronic migraine population (assuming constant treatment effectiveness)

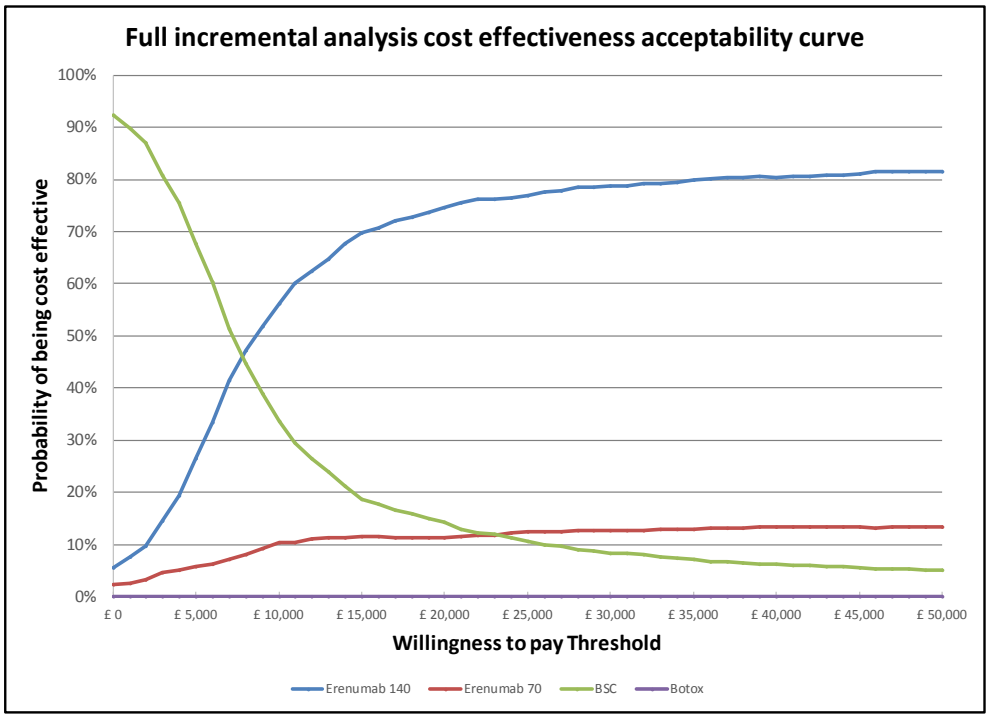


Figure 5.5: ERG base-case CEAC for the chronic migraine population (assuming treatment effect waning over five-year)

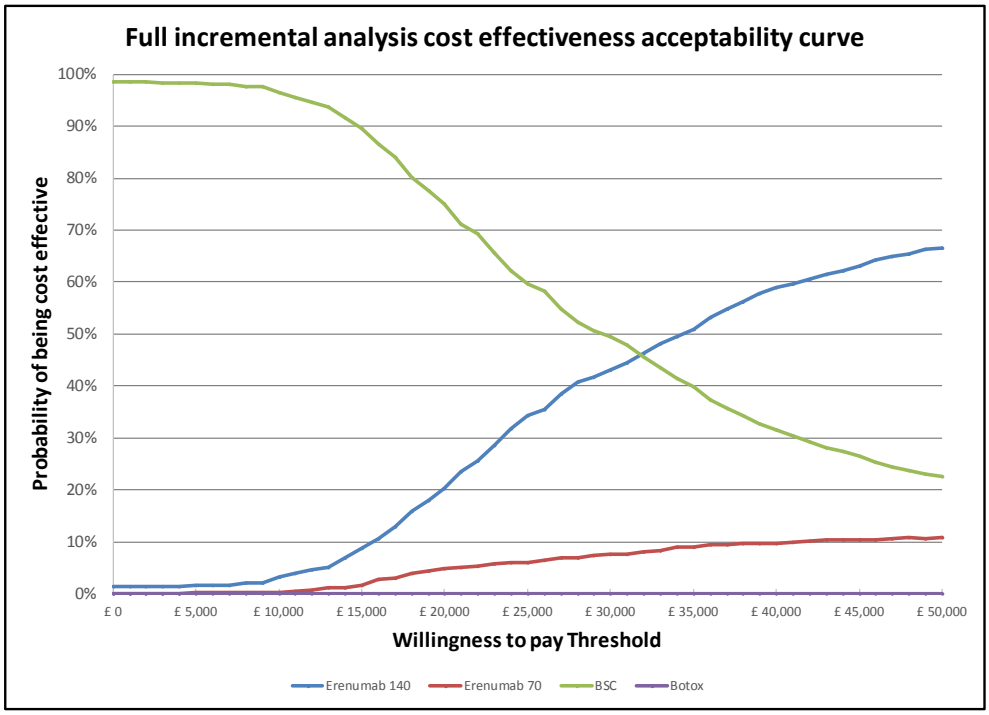


Figure 5.6: ERG base-case CEAC for the episodic migraine population (assuming constant treatment effectiveness)

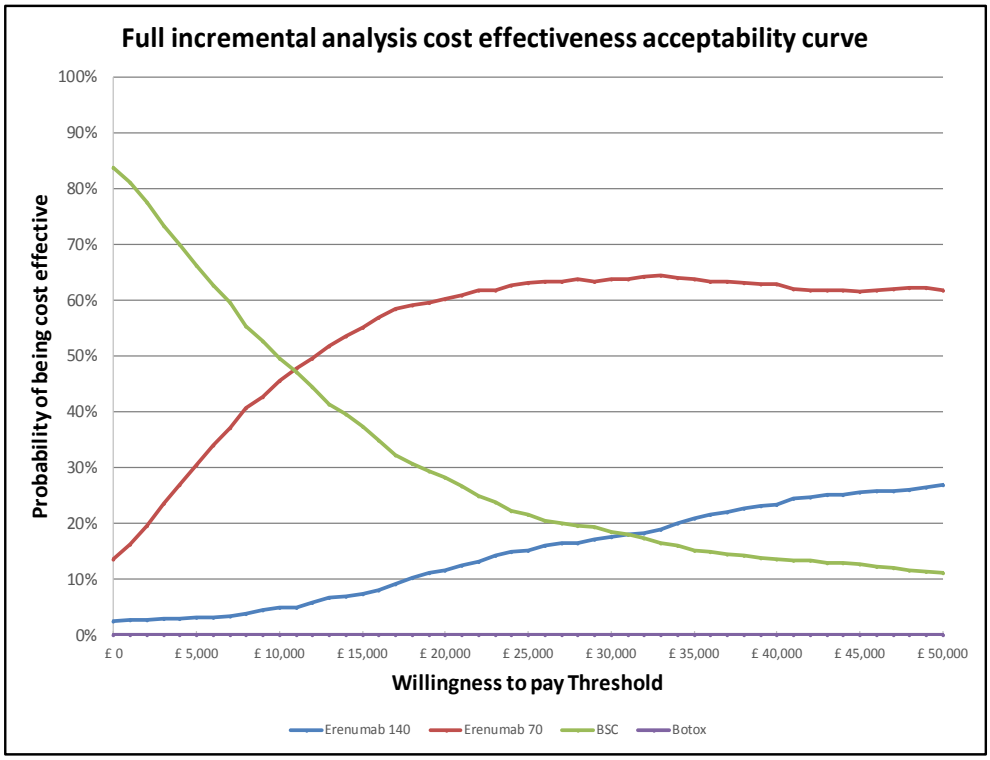
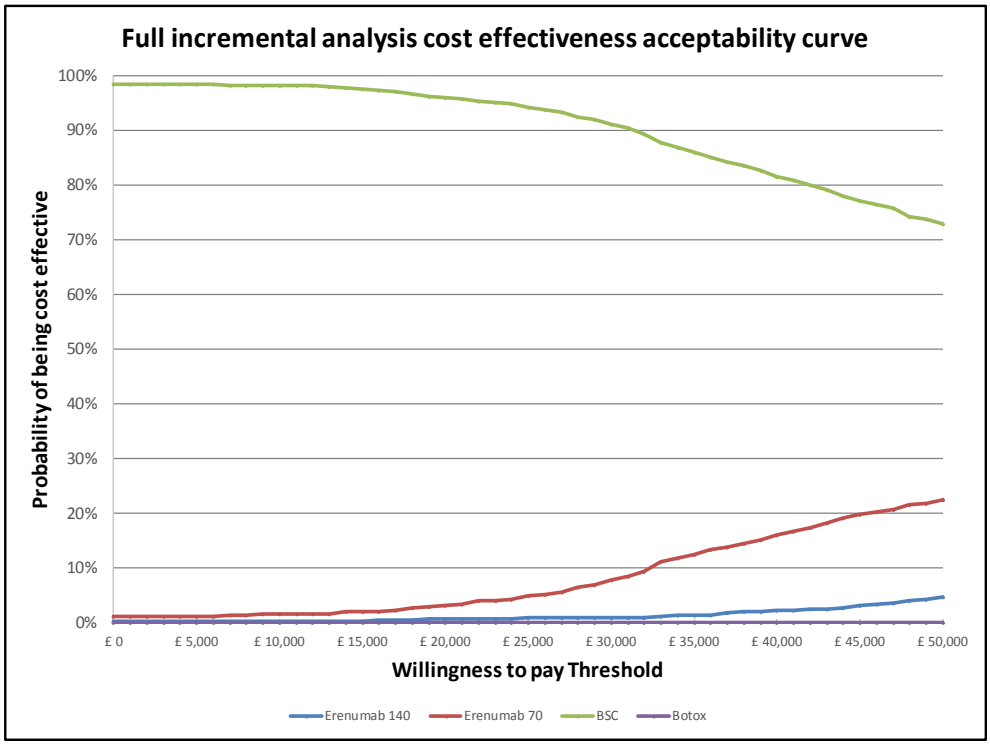


Figure 5.7: ERG base-case CEAC for the episodic migraine population (assuming treatment effect waning over five-year)



5.3.2 Additional exploratory analyses performed based on the ERG base-case

Additional deterministic exploratory scenario analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. The exploratory scenario analyses were performed conditional on the ERG base-case assuming constant treatment effectiveness and are listed below:

1. Assuming a response definition of ≥30% reduction from baseline MMD (Section 5.2.2)
2. Incorporating positive treatment discontinuation (Section 5.2.2)
3. Assuming that patients treated with botulinum toxin would have a response 12 weeks after starting treatment (Section 5.2.2)
4. Assuming a 10-year treatment waning period (Section 5.2.6)
5. Using HRQOL (mapped from MSQ) based on the patients for whom ≥3 prior prophylactic treatments have failed (Section 5.2.8)
6. Using EQ-5D utilities (LIBERTY) instead of mapped utilities (Section 5.2.8)

The results of the deterministic exploratory scenario analyses for the chronic and episodic populations are presented in Tables 6.2 and 6.4 respectively. These analyses indicate that the definition of response (i.e. either 30% or 50% reduction from baseline MMD), incorporating positive treatment discontinuation as well as the source of HRQoL data used might have a substantial impact on the estimated cost effectiveness. It should however be noted that the evidence used to support the positive treatment discontinuation scenario is considered to be weak by the ERG (see Section 5.2.2 for more details).

5.3.3 Subgroup analyses performed based on the ERG base-case

Subgroup analyses, conditional on the ERG base-case, were performed for the HFEM subgroup (8-14 MHD). An exploratory analysis was performed using an alternative (10-14 MHD) definition for HFEM.

Consistent with the ERG base-case results for the chronic and episodic populations, the estimated cost effectiveness for the HFEM subgroup depended on the assumptions related to the extrapolation of treatment effectiveness. The deterministic ERG base-case assuming constant treatment effectiveness over time indicated that erenumab 70mg was cost effective at willingness to pay thresholds higher than £10,781 per QALY gained (erenumab 140mg was dominated). When assuming treatment effect waning over a five-year period, erenumab 70mg only became cost effective at a willingness to pay threshold of £113,172 per QALY gained while this was £126,000 for erenumab 140mg.

5.4 Conclusions of the cost effectiveness section

Cost effectiveness searches in the CS and in the response to clarification were well documented and easily reproducible and were carried out in line with the NICE guide to the methods of technology appraisal. Searches were reported for a wide range of databases and additional searches of conference proceedings, grey literature sources and reference checking were also reported.

The company developed a de novo economic model. The model structure proposed by the company, however, does not fully capture natural progression of migraine. The ERG believes that the justification provided by the company, not to model natural progression of migraine, is reasonable. However, the impact of this simplification is not fully known and hence increases the uncertainty regarding the cost effectiveness results. The definition of response to treatment is another source of uncertainty. The company used a ≥50% reduction in baseline MMDs to define response, however, guidelines state that a ≥30% reduction can be clinically meaningful in patients with chronic migraine. Moreover, for NICE TA260 on botulinum toxin in chronic migraine[21] the committee stated that a 30% (MHD) response rate was the most clinically relevant and reasonable negative (due to no response) stopping rule on which to base its decision. The main uncertainty in this cost effectiveness assessment is the extrapolation of treatment effectiveness. Although the company provided data from open-label extension studies, these studies did not provide comparative effectiveness data and the follow-up of these studies was limited (52 weeks for chronic migraine and 64 weeks for episodic migraine). After this period there was no evidence to inform the extrapolation of treatment effectiveness. There was also a general lack of evidence for patients with ≥15 MHDs and ≥4 to 8 MMD as this population was not considered in the pivotal trials. Additionally, the ERG considers that the economic model and base-case analyses described in the CS only partly meet the NICE reference case. Deviations from the NICE reference case included the restricted time horizon of 10 years and the use of mapped utilities.

In the company base-case (probabilistic, simulation performed by the ERG) erenumab 140mg was cost effective in the chronic population at willingness to pay thresholds higher than £19,113 per QALY gained (erenumab 70mg was dominated). For the episodic population, the company base-case (probabilistic, simulation by the ERG) results indicated that erenumab 70mg was cost effective at willingness to pay thresholds higher than £27,125 per QALY gained. Erenumab 140mg became cost effective at willingness to pay thresholds higher than £83,170 per QALY gained.

The ERG has incorporated various adjustments to the company base-case. The ERG base-case consisted of an ICER range, reflecting the uncertainty surrounding the extrapolation of treatment effectiveness. The ERG base-case (probabilistic) indicated that erenumab 140mg was cost effective at willingness to pay thresholds higher than £16,905 and £38,622 per QALY gained when assuming a constant treatment effect over time and treatment effect waning over a five-year period respectively (erenumab 70mg was dominated). For the episodic population the probabilistic ERG base-case results indicated that erenumab 70mg would be cost effective at willingness to pay thresholds higher than £10,047 per QALY gained, when assuming a constant treatment effect over time (erenumab 140mg is dominated). When assuming treatment effect waning over a five-year period, this would be £95,227 per QALY gained for

erenumab 70mg (erenumab 140mg became cost effective at a willingness to pay threshold of £267,487 per QALY gained).

It should, however, be noted that the increased effectiveness (in terms of QALYs) of erenumab 70mg versus erenumab 140mg (when assuming constant treatment effectiveness), in the episodic migraine population, is inconsistent with the clinical effectiveness evidence presented in chapter 4 (Table 4.9). In Section 4.2.3, the ERG notes that the evidence presented in the CS does not appear to support the effectiveness of the 70mg dose of erenumab in patients with episodic migraine, for whom ≥3 prior prophylactic treatments have failed. Indeed, there is a numerically larger difference vs. placebo in change from baseline MMD for 140mg than for 70mg; only the former is statistically significant, and this only in the STRIVE trial. The favourable cost effectiveness of erenumab 70mg for the episodic population seems driven by the MMD frequency distribution for non-responders that is lower than for erenumab 140mg and BSC. It is questionable whether, given the above results for all patients, there would be an advantage for 70mg vs. 140mg for those patients who do not respond. It is also questionable whether extrapolating this benefit for non-responders (or any benefit in MMD frequency distribution for responders) is plausible given the changing response over time. This is to some extent mitigated in the treatment waning scenarios given benefits in terms of MMD frequency distributions are decreased over time.

In conclusion, the cost effectiveness of erenumab in the chronic and episodic migraine populations largely depends on the assumptions related to the extrapolation of treatment effectiveness. Based on willingness to pay thresholds of £20,000 and £30,000 per QALY gained, erenumab 140mg and erenumab 70mg may be cost effective for the chronic and episodic migraine populations respectively if a constant treatment effect over time is assumed. However, as mentioned above, the plausibility of this assumption may be questionable. The estimated ICERs for erenumab increased above these willingness to pay thresholds of £20,000 and £30,000 per QALY gained if a treatment effect waning with a five-year period is assumed. Finally, it is unclear whether these results can be extrapolated to the population with ≥15 MHDs and ≥4 to <8 MMDs as no cost effectiveness evidence is provided for this population.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Tables 6.1 and 6.3 show how individual changes impact the deterministic results plus the combined effect of all changes simultaneously for the chronic and episodic migraine populations, respectively. The deterministic exploratory scenario analyses for these populations are presented in Tables 6.2 and 6.4. These are all conditional on the ERG base-case assuming constant treatment effectiveness. Table 6.5 provides the deterministic results for the HFEM subgroup (described in Section 5.3.3). Finally, probabilistic analyses are provided for the chronic and episodic migraine populations in Tables 6.6 and 6.7, respectively. The submitted model files contain technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

6.1 Deterministic analyses undertaken by the ERG (all with PAS)

Table 6.1: Deterministic ERG base-case for the chronic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,609	£10,609
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£24,668
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,832	£13,340
Fixing errors						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,637	£10,637
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,045
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,001	£13,400
Fixing errors + lifetime time horizon						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£7,093	£7,093
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£36,599
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£27,070	£11,862
Fixing errors + applying triptan injections costs for triptan injections						
BSC	[redacted]	[redacted]				

Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£9,243	£9,243
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,605	£12,005
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£23,650
Fixing errors + assuming non-responder MMD frequency distribution after treatment discontinuation						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£9,546	£9,546
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£23,574
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,198	£12,048
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£3,813	£3,813
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,653	£7,067
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,842
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£26,536	£26,536
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£115,310
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£36,680	£30,896

Table 6.2: Deterministic scenario analyses for the chronic migraine population conditional on ERG base-case (assuming constant treatment effectiveness)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£3,813	£3,813
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,653	£7,067
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,842

ERG base-case + assuming a response definition of ≥30% reduction from baseline MMD						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£17,332	£17,332
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£61,033
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£18,876	£18,065
ERG base-case + positive discontinuation scenario						
Botulinum toxin	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£1,548	£1,548
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
ERG base-case + assuming response benefits 12 weeks after start treatment for botulinum toxin						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£2,915	£2,915
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,093	£7,067
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,842
ERG base-case + treatment effect waning over ten years						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£15,576	£15,576
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£58,192
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£26,368	£19,798
ERG base-case + MSQ mapped utilities based on patients for whom ≥3 prior prophylactic treatments have failed						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£4,144	£4,144
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,013	£7,681
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£28,087
ERG base-case + EQ-5D-5L utilities (cross-walk) from LIBERTY						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,689	£10,689

Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,880	£19,810
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£72,442

Table 6.3: Deterministic ERG base-case for the episodic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£29,200	£29,200
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£73,282	£40,662
Fixing errors						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£29,690	£29,690
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£74,869	£41,391
Fixing errors + lifetime time horizon						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£13,784	£13,784
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£36,534
Fixing errors + applying triptan injections costs for triptan injections						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£27,634	£27,634
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£72,838	£39,341
Fixing errors + assuming non-responder MMD frequency distribution after treatment discontinuation						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£28,127	£28,127
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£91,053	£41,721
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,207	£10,207
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£35,505

ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£95,010	£95,010
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£311,432	£143,520

Table 6.4: Deterministic scenario analyses for the episodic migraine population conditional on ERG base-case (assuming constant treatment effectiveness)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,207	£10,207
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£35,505
ERG base-case + assuming a response definition of ≥50% reduction from baseline MMD						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£91,042	£91,042
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
ERG base-case + positive discontinuation scenario						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£3,667	£3,667
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£17,778	£6,754
ERG base-case + treatment effect waning over ten years						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£74,372	£74,372
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£97,660	£84,310
ERG base-case + MSQ mapped utilities based on patients for whom ≥3 prior prophylactic treatments have failed						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£7,528	£7,528
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£26,187
ERG base-case + EQ-5D-5L utilities (cross-walk) from LIBERTY						
BSC	[redacted]	[redacted]				

Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,418	£19,418
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£67,542

Table 6.5: Deterministic ERG base-case and scenario analysis for the HFEM subgroup

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£37,331	£37,331
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£38,194	£37,749
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,781	£10,781
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£29,275
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£113,172	£113,172
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£126,000	£119,426
ERG base-case (assuming constant treatment effectiveness) with alternative HFEM definition (10-14 MHDs)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£13,555	£13,555
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£41,001

6.2 Probabilistic analyses undertaken by the ERG (all with PAS)

Table 6.6: Probabilistic ERG base-case for the chronic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case (PSA run by the ERG)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£10,075	£10,075
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£23,417
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£19,113	£14,181
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				

Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£3,695	£3,695
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£16,905	£6,804
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£25,912
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	£25,402	£25,402
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£115,654
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£38,622	£25,943

Table 6.7: Probabilistic ERG base-case for the episodic migraine population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
Company base-case (PSA run by the ERG)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£27,125	£27,125
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£83,170	£40,204
ERG base-case (assuming constant treatment effectiveness)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,047	£10,047
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated	£33,943
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 70mg	[redacted]	[redacted]	[redacted]	[redacted]	£95,227	£95,227
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	£267,487	£139,447

7. REFERENCES

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Appendix 1: Details of acute headache medication usage during the erenumab studies

Source: response to clarification question A5 – "Please provide a table with patient numbers showing all concomitant medication received in the 4 main trials (Study 295, STRIVE, ARISE and LIBERTY) in intervention and placebo groups, for the specified optimised population (≥3 failed prophylactic therapies), whole trial populations and exploratory analysis population (≥2 failed prophylactic therapies).

Study 295

The most common acute headache medications used during baseline or during the double-blind treatment phase were in the categories of triptan-based migraine medications ([redacted]%, [redacted]%, and [redacted]% of subjects in the placebo, erenumab 70mg, and erenumab 140mg arms, respectively) and non-opioid acute headache medications ([redacted]%, [redacted]%, and [redacted]%, respectively; see Table A2.1).

Table A1.1: Concomitant medication usage in Study 295

Population	Placebo	Erenumab 70mg	Erenumab 140mg
Full study population	**n=282**	**n=190**	**n=188**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

Patients for whom ≥2 prior treatments have failed	**n=141**	**n=92**	**n=92**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

STRIVE

The most frequent (>10%) acute headache medications used during baseline and during the double-blind treatment phase were in the categories of non-opioid acute headache medications ([redacted]%, [redacted]%, and [redacted]% of subjects in the placebo, erenumab 70mg, and erenumab 140mg arms, respectively) and triptan-based migraine medications ([redacted]%, [redacted]%, and [redacted]%, respectively; see Table A1.2).

Table A1.2: Concomitant medication usage in STRIVE

Population	**Placebo**	**Erenumab 70mg**	**Erenumab 140mg**
Full study population	**n=319**	**n=314**	**n=319**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]

Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]
Patients for whom ≥2 prior treatments have failed	**n=54**	**n=49**	**n=58**
Triptan-based migraine medications	[redacted]	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]	[redacted]

ARISE

The most common acute headache medications used during baseline and during the double-blind treatment phase were in the categories of non-opioid acute headache medications ([redacted]% and [redacted]% of subjects in the placebo and erenumab 70mg arms, respectively) and triptan-based migraine medications ([redacted]% and [redacted]%, respectively; see Table A1.3).

Table A1.3: Concomitant medication usage in ARISE

Population	Placebo	Erenumab 70mg
Full study population	**n=289**	**n=283**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]

Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥2 prior treatments have failed	**n=[redacted]**	**n=[redacted]**
Triptan-based migraine medications	[redacted]	[redacted]
Non-opioid acute headache medications	[redacted]	[redacted]
Ergotamine-based migraine medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]

LIBERTY

Approximately a third of the total safety analysis set ([redacted]%) received concomitant therapy (any ATC class) during the double-blind treatment phase and the proportion was similar between the erenumab 140mg ([redacted]%) and placebo (34.7%) groups. Please see Table 14.3-13 on page 267-276 of the CSR for further details. The majority of patients used acute headache medication during baseline and the double-blind treatment phase. Triptan/ergotamine-based migraine medications and analgesic acute headache medications were the most frequently used headache medications. A similar proportion of patients in the erenumab 140mg and placebo groups had taken triptans/ergotamines ([redacted]% vs [redacted]%, respectively) as well as analgesics ([redacted]% vs. [redacted]%, respectively). In addition, a small percentage of patients in both treatment groups had taken opioid-containing acute headache medications during baseline and the double-blind treatment phase ([redacted]% vs [redacted]%, respectively; see Table A1.4).

Table A1.4: Concomitant medication usage in LIBERTY

Population	Placebo	Erenumab 140mg
Full study population	**n=123**	**n=1118**
Triptan/Ergotamine-based migraine medications	[redacted]	[redacted]
Analgesics acute headache medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]
Patients for whom ≥3 prior treatments have failed	n=[redacted]	n=[redacted]
Triptan/Ergotamine-based migraine medications	[redacted]	[redacted]
Analgesics acute headache medications	[redacted]	[redacted]
Opioid-containing acute headache medications	[redacted]	[redacted]
Non-opioid butalbital containing medications	[redacted]	[redacted]
Opioid-containing butalbital containing medications	[redacted]	[redacted]