NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Erenumab for preventing migraine [ID1188]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Novartis ACD comments
   - Migraine Trust
   - Association of British Neurologists
   - British Association for the Study of Headache
   - Allergan and consultation response appendix

3. **Comments on the Appraisal Consultation Document received through the NICE website and via email**

4. **NICE request to clinical experts post consultation:**
   - NICE questions to the clinical experts post consultation
   - Clinical expert personal perspectives in response to NICE questions post consultation

New evidence in response to ACD (following first committee meeting)

5. **Company appendix of new evidence –** submitted by Novartis

6. **Evidence Review Group critique of company response** – prepared by Kleijnen Systematic Reviews Ltd

7. **Evidence Review Group critique – erratum**

8. **Evidence Review Group critique – addendum**

9. **Company factual accuracy check Evidence Review Group report**

10. **Evidence Review Group critique – addendum post factual accuracy check**

New evidence following second committee meeting

11. **Company additional evidence submission –** submitted by Novartis

12. **Evidence Review Group critique of the company additional evidence submission -** prepared by Kleijnen Systematic Reviews Ltd

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Erenumab for preventing migraine

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Novartis	Novartis is disappointed by the draft recommendation of NICE to not recommend erenumab for routine use on the NHS. If this decision remains unchanged patients will be denied access to the first licensed treatment specifically designed to prevent migraine in adults. We are pleased that the Appraisal Committee has recognised the clinical effectiveness of erenumab and that a significant unmet treatment need exists for people living with migraine in the UK. However, we disagree with the Appraisal Committee's view that erenumab is not a cost-effective use of NHS resources. We hope that our response below addresses any outstanding questions and concerns. Key elements of our response are as follows:- • The proposed patient population has been re-focussed to cover the spectrum of patients with ≥10 monthly headache days (MHDs), encompassing the arbitrary definitions of chronic migraine (CM) and high frequency episodic migraine (HFEM), i.e. those with the highest unmet medical need who are typically treated by headache specialists [see point 2] • The proposed dose for consideration is the 140 mg dose only [see point 2] [redacted] • Novartis disagrees with the Appraisal Committee's preferences on key inputs/assumptions included in the health economic modelling, including the Committee's preferences for: o Inclusion of treatment effect waning [see point 3] o Non-acceptance of treatment benefit from the indirect comparison of erenumab vs. botulinum toxin [see point 4] o Consideration of a 4th oral comparator [see point 5] o Inclusion of additional service costs [see point 6] • Revised cost-effectiveness analysis is submitted to reflect this response framework [see point 2 & Appendix Document]	Comments noted. Please find detailed responses to the individual comments in the relevant sections of this table below. Some detailed responses relate to the updated cost-effectiveness analysis and longer-term clinical evidence submitted by the company after the second committee meeting (not reproduced in this document - please see the committee papers for full details of the evidence). This evidence was considered at the third committee meeting (see FAD sections 3.9, 3.12, 3.14, 3.15, 3.21, 3.22, 3.25 and 3.26).

Consultee	Comment [sic]	Response
	Please note that information highlighted in turquoise and yellow in this response and the appendix document should be treated as strictly confidential.	
Novartis	**Novartis provides updated cost-effectiveness results as part of this response** In addition to this appraisal consultation document (ACD) response, Novartis provides an Appendix entitled ***'Additional Cost-Effectiveness Analyses'***. Further to the agreement obtained from NICE, this document provides a revised Novartis base case analysis and scenario analyses based on the issues raised in points 3 and 4 of this response. Please note that this ACD response should only be read in conjunction with the Appendix document entitled ***'Additional Cost-Effectiveness Analyses'*** and should not be considered in isolation. The analyses presented in the Appendix focus only on patients with chronic migraine (CM) and high frequency episodic migraine (HFEM), the latter being those with 10-14 monthly headache days. This represents a re-focusing of the proposed population for erenumab that takes account of the Appraisal Committee's considerations to date and reflects a patient cohort with the highest unmet need who are treated by headache specialists, for whom erenumab is particularly appropriate. As indicated in NICE's ACD and as outlined in our submission, patients with HFEM face a similar burden to those with CM and, in clinical practice, are likely to benefit from treatment to a similar extent as patients with CM. The analyses presented in the Appendix consider erenumab 140 mg versus botulinum toxin in patients with CM, and versus best supportive care in patients with HFEM. This reflects the Appraisal Committee's interpretation of the clinical evidence for the two doses of erenumab, with erenumab 140 mg considered to provide the greatest benefit to patients. As discussed in point 7, we request that the Committee only considers the 140 mg dose in its decision making [redacted]	Comments noted. At the second committee meeting, the committee considered Novartis' ACD response document in conjunction with the additional cost-effectiveness analyses in its decision making. This included consideration of the company's revised base-case and scenario analyses. At the third committee meeting, the committee considered Novartis' additional comments and cost-effectiveness analyses in its decision making. Please see the Final Appraisal Document (FAD) for a summary of all the committee considerations and decisions. The committee recognised the burden on quality of life experienced by people with HFEM and chronic migraine to be similar. However, the committee noted that the definition of HFEM was uncertain with no consensus amongst clinical experts. It was also noted that the clinical effectiveness results for the HFEM population was highly uncertain. For these reasons the committee did not consider the HFEM group to be a distinct subgroup (see FAD section 3.8). The committee accepted the inclusion of only the 140 mg dose in its decision making (see FAD section 3.12). The company's revised commercial arrangement for erenumab was taken into account in the committee's decision-making (see FAD section 3.21).

Consultee	Comment [sic]	Response
Novartis	**<u>Conclusions regarding treatment waning do not adequately reflect the collective evidence supporting a lack of waning effect with long-term erenumab treatment</u>** The ACD states that "erenumab's long-term effectiveness compared with best supportive care was uncertain" and that the committee understood that "a constant treatment effect was implausible". The ACD indicates that the Committee therefore considered scenarios whereby the treatment effect waned over 5- and 10-year periods in their decision-making. Novartis does not believe that the conclusions of the ACD with respect to treatment waning adequately reflect the collective evidence on the long-term efficacy of erenumab, and also challenges the appropriateness of assuming a waning effect for monoclonal antibodies as considered in other NICE appraisals. ***Case precedent from previous NICE appraisals of biologics*** Novartis acknowledges the absence of data to support the maintenance of erenumab efficacy beyond the 52-week and 64-week timepoints. However, there is a notable precedent for similar cases where evidence for maintenance of long-term efficacy is lacking. A number of NICE appraisals of biologics in other chronic, non-progressive diseases characterised by periods of episodic worsening of condition, similar to migraine, have assumed there to be no waning effect following long-term treatment, as detailed below.[7-9] This assumption has been accepted by the respective appraisal committees in the noted absence of long-term follow-up data.[7-9] • Omalizumab for previously treated chronic spontaneous urticaria (TA339)[8] • Omalizumab for treating severe persistent allergic asthma (TA278)[9] • Mepolizumab for treating severe refractory eosinophilic asthma (TA431)[7] Contrary to the above examples, the ACD cites the possible waning of monoclonal antibodies in rheumatoid arthritis as an indication that outcomes following treatment with erenumab may not persist in the long term. However, rheumatoid arthritis is a progressive disease that gets worse over time, meaning that it would not be expected that the same treatment benefit could be maintained. Indeed, the waning effect which may be observed in rheumatoid arthritis is likely on account of disease worsening, rather than a loss of efficacy. Rheumatoid arthritis therefore does not	Comments noted. At the second committee meeting, the committee considered Novartis' ACD responses regarding treatment waning in conjunction with the additional cost-effectiveness analyses and scenario analysers in its decision making. At the third committee meeting, the committee considered Novartis' additional comments, additional long-term clinical data, and cost-effectiveness analyses (not reproduced in this document - please see the committee papers for full details of the evidence). The Committee considered the longer-term clinical data submitted by the company after the second meeting, regarding long-term treatment effectiveness of erenumab for episodic migraine from an open-label trial. It considered that this data was not directly applicable to the population being considered in the appraisal and did not provide long-term comparative effectiveness evidence (see FAD section 3.9). ***Clinical expert opinion*** The committee was aware of conflicting clinical expert opinion as to whether treatment resistance could occur with erenumab, The committee acknowledged a clinical expert confirmed that there was no reason to believe that patients treated with erenumab would experience a waning effect over time. However, it also noted that a clinical expert at consultation that the development of treatment resistance was possible (see FAD section 3.9). ***Long term data for erenumab***

Consultee	Comment [sic]	Response
	represent an appropriate analogue to migraine, which sees patients experiencing fluctuations in the severity of their condition in both the short- and long-term.[10-12]. Accordingly, Novartis does not consider this evidence to be relevant in informing assumptions regarding waning, and instead asks that NICE considers the precedent set by appraisals of other biologics in other non-progressive diseases, as detailed above. ***Clinical expert opinion*** Further, it should be noted that the topic of waning was discussed at the committee meeting on 6th December 2018, and a clinical expert confirmed that there was no reason to believe that patients treated with erenumab would experience a waning effect over time. This is not acknowledged in the ACD. Additionally, feedback from 3 headache specialists in England stated that there is no evidence to suggest a waning effect in patients who respond well to erenumab treatment. ***Long term data for erenumab*** Open-label extension studies in both chronic and episodic migraine provide evidence to support the long-term efficacy of erenumab. As discussed in the response to Clarification Question B9a), patients enrolled in Study 295 (chronic migraine) and STRIVE (episodic migraine) demonstrated continued reductions in monthly migraine days over a 52-week and 64-week follow-up period, respectively.[1, 2] These extension studies both included a large number of patients (*n=609 and n=845*, respectively), of which a high proportion completed the entire duration of follow-up (*n=451 [74.1%] and n=737 [87%],*respectively) *[italics denotes new data not provided in original submission]*. Whilst no data are available from longer-term follow-up, the results of these studies provide no indication of a waning in the treatment effect: in both studies, patients experienced numerical reductions in monthly migraine days from the end of the double-blind treatment phase to Week 52 or Week 64. In addition, safety data are available from an open-label study of erenumab in episodic migraine that enrolled 383 patients; a pre-planned interim analysis is reported for which all remaining patients had completed ≥3 years of treatment.[3] This safety update demonstrates that 61.3% of patients entering the open-label study remained on treatment at this follow-up, with exposure to erenumab for those remaining in the study ranging from 3.0 to 3.9 years. This interim safety update provides evidence of patients continuing to receive erenumab for more than 3 years, therefore providing support for ongoing clinical benefit with erenumab in the long-term.	The committee considered the open label extension studies in both chronic and episodic migraine to support the long-term efficacy of erenumab. The committee was aware that there was no evidence that comparative efficacy was maintained beyond the blinded phase of the trials. It also noted that the efficacy of erenumab in the open-label extension studies was from the full trial populations, with 13% to 26% of people lost to follow-up (see FAD section 3.9) The committee considered the longer-term clinical data provided by the company after the second committee meeting, regarding longer-term treatment effectiveness of erenumab for episodic migraine from an open-label study. It considered that this data was not directly applicable to the population being considered in the appraisal and did not provide long-term comparative effectiveness evidence (see FAD section 3.9). ***Erenumab mechanism of action*** The committee considered the longer-term clinical data provided submitted by the company after the second committee meeting, regarding longer-term treatment effectiveness of erenumab for episodic migraine from an open-label study. It agreed that the long-term clinical data from the extension study did show that low numbers of people withdrew from erenumab treatment because of a lack of efficacy and that to date there is no evidence of impact of anti-erenumab antibody body development on efficacy and safety. Based on the evidence available, the committee considered that on balance it was reasonable to assume that the treatment effect does not wane over time (See section 3.14).

Consultee	Comment [sic]	Response
	These studies did not contain a control arm, as this may have raised ethical challenges, which poses challenges to evaluating comparative efficacy of erenumab in the long-term. As such, the ACD states that there is "no evidence that comparative efficacy was maintained". However, a comparative benefit of erenumab versus placebo was observed at the end of the double-blind treatment phase and, as discussed above, the absolute efficacy of erenumab was maintained and even improved up to 52 or 64 weeks. Therefore, for the comparative efficacy of erenumab versus placebo not to be maintained requires an assumption that any patients who had continued on with placebo would have experienced greater improvements over the period from the end of the double-blind treatment phase to week 52 or 64 than were observed for erenumab. Even if patients had continued to receive placebo and maintained their observed benefit at the end of the double-blind treatment phase, comparative efficacy would still have been maintained. Therefore, it is implausible that comparative efficacy of erenumab is not maintained up to at least 52 weeks (chronic migraine) and 64 weeks (episodic migraine). ***Erenumab mechanism of action*** Erenumab's novel formulation and mechanism of action are expected to minimise the likelihood of waning, which has been supported by pharmacokinetic studies. Erenumab is a fully human IgG2 monoclonal antibody that acts as a potent and selective calcitonin gene-related peptide receptor antagonist. These properties mean that it is not expected to be associated with neutralising antibodies; IgG2 antibodies generally have little to no activation of the immune system, and erenumab targets the calcitonin gene-related peptide receptor directly, meaning that it does not require activation of the immune system.[4, 5] Accordingly, pharmacokinetic studies demonstrate that anti-erenumab antibodies have a low occurrence rate, are mostly transient in nature, and do not impact upon the efficacy of erenumab. In an analysis of 1,388 patients across four phase II/III clinical trials of erenumab (including Study 295 and STRIVE), anti-erenumab antibodies occurred in only *6.3% (56/884)* of patients treated with erenumab 70 mg, and *2.6% (13/504)* of patients treated with erenumab 140 mg, with over 50% of these patients reverting to an antibody-free status with continued treatment. Specifically, the incidence of neutralising antibodies in these patients was very low *([redacted] patients treated with erenumab 70 mg and [redacted] patients treated with erenumab 140 mg) [italics indicates new data not provided in original submission]*. Furthermore, long-term treatment with erenumab was not shown to be associated with an increased incidence of anti-erenumab antibodies compared to those observed during the double-blind treatment phases of the clinical trials.[6] Importantly, patients found to have anti-erenumab antibodies did not experience a loss of efficacy: the mean change in monthly	***Expected use of erenumab in UK clinical practice impacts waning considerations*** The application of a negative stopping rule using a 30% reduction in monthly migraine days was accepted by the committee (see FAD section 3.16). ***Treatment waning in the cost effectiveness analysis*** The committee considered the treatment waning scenarios provided by Novartis in response to ACD consultation and after the second committee meeting. It also considered the ERG's critique of these analyses. The committee considered that on balance it was reasonable to assume that the treatment effect does not wane over time and therefore did not consider treatment waning scenarios in its decision making. It agreed that the most plausible ICERs for erenumab compared with botulinum toxin type A and compared with best supportive care were from the company's base case ICERs using only the 2.38% for all-cause discontinuation rate. (see FAD sections 3.14, 3.15 and 3.21).

Consultee	Comment [sic]	Response
	migraine days from baseline to month 6 for patients without anti-erenumab antibodies was *−3.5 (0.2) and −3.8 (0.2)* for patients treated with erenumab 70 mg and 140 mg, respectively, compared to *−3.2 (0.9) and −5.2 (0.9)* for patients with anti-erenumab antibodies *[italics indicates new data not provided in original submission]*.[6] Therefore, the evidence available to date supports a low occurrence of anti-erenumab antibodies and provides no indication that the formation of anti-erenumab antibodies will lead to a waning effect in the long term. An assumption of no treatment waning has been accepted in appraisals of biologics in other chronic, non-progressive diseases (including omalizumab for previously treated chronic spontaneous urticaria and mepolizumab for severe refractory eosinophilic asthma) on the basis of results from pharmacokinetic studies that have similarly demonstrated that antibodies are typically transient and do not impact upon efficacy.[7, 8] ***Expected use of erenumab in UK clinical practice impacts waning considerations*** Another important consideration – not acknowledged in the ACD – is that it is expected in clinical practice that patients will not be maintained on erenumab treatment in the long-term. This aligns with the summary of product characteristics for erenumab, which states that "consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment", and that "evaluation of the need to continue treatment is recommended regularly thereafter".[13] Accordingly, it is anticipated that patients will discontinue erenumab if they no longer continue to experience a clinically meaningful response to treatment (i.e. negative discontinuation). This is reflected in the cost-effectiveness model presented by Novartis through the modelling of discontinuation on non-response at the assessment time point, and also a further 2.38% annual discontinuation rate in the long-term that reflects patients withdrawing from erenumab, including for reasons of loss of efficacy. The cost-effectiveness analysis therefore already accounts for the potential for loss of efficacy in a small number of patients in the long-term, and appropriately addresses this by modelling – in line with the summary of product characteristics as quoted above – that these patients terminate treatment with erenumab and thereby lose both the benefits of erenumab treatment but also the costs. This approach follows the precedent set by the appraisal for ocrelizumab in relapsing multiple sclerosis, whereby an annual treatment discontinuation rate was accepted as a means to account for the potential for treatment waning in the absence of evidence for a waning effect after four years.[14] Furthermore, continued	

Consultee	Comment [sic]	Response
	stakeholder feedback and UK advisory boards have indicated that, in the UK, clinicians would expect to also apply a positive stopping rule to the use of erenumab. Under such practice, patients who are continuing to benefit from erenumab would not continue to receive erenumab indefinitely, but would undergo "positive discontinuation". Newly published guidelines from the European Headache Foundation support this, citing an expert opinion-level recommendation that anti-CGRP monoclonal antibodies be stopped after 6-12 months of treatment. The expectation is that some patients will need to return to treatment. Incorporation of a positive stopping rule was presented as a scenario analysis in the company submission (scenario 6; further information re-presented in appendix document). In the context of application of a positive stopping rule in UK clinical practice, waning is no longer a relevant consideration as patients would not be expected to receive continuous erenumab treatment in the long-term. In summary, it is inappropriate to include the impact of treatment waning in the cost-effectiveness analysis, as patients will only continue to receive erenumab and incur erenumab treatment costs if they continue to respond to (i.e. benefit from) treatment, and this is currently reflected in the cost-effectiveness analysis. ***Conclusions*** In conclusion, Novartis believes that the combined evidence available from long-term follow up and pharmacokinetic studies of erenumab support the assumption that there is no waning effect with long-term treatment with erenumab. This assumption is also supported by the acceptance of an absence of a waning effect in the appraisals for biologics in other chronic non-progressive diseases, which have had a similar duration of long-term follow-up data and similar supporting data from pharmacokinetic studies.[7-9] Novartis does not believe that treatment waning is applicable. However, in response to clarification questions Novartis provided a scenario analysis exploring long-term effectiveness by reducing linearly over time the health state costs and health state utilities for erenumab and botulinum toxin, to reflect the health state costs and health state utilities associated with BSC non-responders. In this scenario, treatment waning was applied from 12 weeks. However, with more time to reflect on this issue, and given that Novartis has provided longer-term data which shows that treatment benefit of erenumab is maintained over 1 year in open-label studies (52/64 weeks; see ACD response document point 3), applying treatment waning from 12 weeks does not, in hindsight, accurately reflect the available evidence base. Therefore, we have provided alternative waning scenarios applying the treatment waning	

Consultee	Comment [sic]	Response
	beginning from year 5, to further explore alternative treatment waning assumptions. This is in line with appraisals in the progressive disease multiple sclerosis where waning was applied after 5 years treatment. In the context of the discussion above, Novartis does not believe a treatment waning effect should be applied however it considers that if a waning effect is incorporated to explore any remaining uncertainty, then anything less than a 5 year treatment effect followed by 10 years of waning would be inappropriate based on the clinical evidence and HTA case precedent. An updated scenario analysis, which incorporates this waning scenario is presented in the Appendix document. **Novartis request:** We request that the Committee reconsiders the assumptions regarding waning in light of the long-term clinical data for erenumab, the body of evidence from pharmacokinetic studies, the precedent set by previous NICE appraisals of biologics in non-progressive indications, and the fact that (i) the model discontinuation rate already accounts for the potential of some loss of efficacy and (ii) waning is not relevant as a consideration if patients are not expected to receive continuous erenumab treatment in the long-term. **References not reproduced here, please see company response to ACD**	
Novartis	**Results of the indirect treatment comparison between erenumab and botulinum toxin should be used in evaluating the cost-effectiveness of erenumab in the chronic migraine population** The Committee requested the results of "a scenario in the economic modelling in which erenumab and botulinum toxin type A are considered to have similar effectiveness". The results of cost-effectiveness analyses in which erenumab and botulinum toxin are considered to have equal efficacy are provided in the Appendix. It must be noted that this is an extreme scenario analysis and these results represent an unrealistic and highly conservative estimate of the incremental cost-effectiveness of erenumab versus botulinum toxin. They are presented solely to illustrate the sensitivity of changes to the odds ratio assumption. Whilst Novartis acknowledges the limitations of the indirect treatment comparison presented in Section B.2.8.2 of the company submission, erenumab was associated with a numerical benefit versus botulinum toxin for all outcomes assessed, meaning that these results are suggestive of a clinical benefit of erenumab versus botulinum toxin, and that cost-effectiveness	Comments noted. ***Comparative effectiveness of erenumab and botulinum toxin type A*** The committee noted that there was no direct evidence comparing erenumab with botulinum toxin type A. The committee considered the results from the indirect treatment comparison provided by the company. However it had a number of concerns about the analysis (the common comparator, different outcomes at different time points were reported in the included studies, baseline characteristics of people in the PREMPT trial, long-term variability in symptom frequency and severity associated with chronic migraine not adequately captured by the short duration of the indirect treatment comparison), the lack of statistically significant results and the wide confidence intervals.

Consultee	Comment [sic]	Response
	results assuming equal efficacy as presented in the Appendix should be interpreted as highly conservative. Limits of statistical significance are arbitrary, and as stated in Claxton *et al*., "decisions should be based only on the mean net benefits irrespective of whether differences are statistically significant", with failure to do so by "accepting the arbitrary rules of inference" imposing costs in terms of resources or health benefits foregone.[15] This is supported by the precedent for considering results of indirect treatment comparisons despite lack of statistical significance, such as the appraisal for ocrelizumab in relapsing-remitting multiple sclerosis in which the Committee accepted a cost-effectiveness model informed by the results of a network meta-analysis in which the differences between treatments were not statistically significant.[14] Furthermore, while the benefits of erenumab in 5 RCTs were consistent across the full spectrum of migraine (EM and CM), 7 randomised studies of botulinum toxin versus placebo failed to show a significant benefit for patients in EM. In addition, outside of direct efficacy benefits as evaluated by any indirect comparison, erenumab is also associated with further benefits versus botulinum toxin. This notably includes the reduced burden of administration and benefits to service capacity. As discussed in the company submission (Section B.1.2.2), botulinum toxin requires frequent intramuscular injections, which place a high burden on patients, clinicians and healthcare resources.[16] In contrast, erenumab is self-administered subcutaneously, providing a treatment option that is significantly easier for patients, and less burdensome on the NHS than botulinum toxin. As discussed in Document B of the company submission, Section B.3.4.4, and Appendix U.2, the results of a time trade-off study have indicated that the administration of botulinum toxin results in a considerable utility decrement relative to erenumab; this was not acknowledged or discussed by the Committee during the Committee meeting or in the ACD. The scenario which incorporated the disutility associated with the mode of administration of erenumab and botulinum toxin is presented again in the Appendix. A further benefit of erenumab versus botulinum toxin is the earlier timepoint for assessment of response (3 months with erenumab versus 6 months with botulinum toxin). This allows non-responders to be identified after a shorter time period with erenumab, meaning that ineffective treatment can be discontinued earlier in these patients. In light of the evidence which suggests there is some clinical benefit of erenumab versus botulinum toxin, Novartis also present results in the Appendix whereby the difference between the two treatments represents a midpoint between the odds ratio	The committee concluded that there was a high degree of uncertainty as to whether erenumab is more clinically effective than botulinum toxin type A (see FAD section 3.10). It also considered the different odds ratios presented by the company and concluded that the mid-point odds ratio was not methodologically justified. Because of the uncertainty in the results of the indirect treatment comparison, the committee considered it appropriate to consider both the indirect treatment comparison odds ratio and a scenario in which erenumab and botulinum toxin type A are thought to have similar effectiveness (see FAD section 3.13). ***Benefits to service capacity*** The committee noted that all the relevant costs for implementing erenumab in clinical practice were captured in the model (see FAD section 3,20). ***Utility decrement to botulinum toxin type A*** The committee did not agree that a utility decrement should be applied to botulinum toxin type A (see FAD section 3.19).

Consultee	Comment [sic]	Response
	of the ITC (Section B.2.8.2 of the company submission), and an odds ratio of 1 (an assumption of equal efficacy, as per the Committee-requested scenario analysis). **Novartis request:** We request that the results of the extreme scenario in which erenumab and botulinum toxin are modelled to have equal efficacy are considered as highly conservative and unlikely to reflect clinical reality, and viewed in the context that they do not capture all benefits of erenumab over botulinum toxin, as outlined below:  • Erenumab offers a reduced burden of administration compared to botulinum toxin and this has been confirmed by headache specialists. Erenumab is therefore significantly easier for patients and will reduce the burden of treatment for clinicians. This is captured as a resource use in the cost-effectiveness analysis • Erenumab will alleviate the substantial burden imposed by botulinum toxin on patients, which is a benefit not captured in the cost-effectiveness analysis Erenumab offers the potential to provide access to treatment for a patient population with a high unmet need, given the reduced administration requirements compared to botulinum toxin. **References not reproduced here, please see company response to ACD**	
Novartis	**<u>Inclusion of a fourth oral preventive treatment as a comparator to erenumab is not reflective of clinical practice and is inconsistent with NICE's previous view on the migraine treatment pathway</u>** The ACD states that "a fourth oral preventive treatment would also be a relevant comparator for erenumab". It is suggested that "botulinum toxin type A or another oral preventive treatment [are] the relevant comparators in chronic migraine, and that another oral preventive treatment or best supportive care [are] the relevant comparators in episodic migraine".	Comments noted. The committee noted that evidence from clinical experts suggested that some patients may receive a fourth oral prophylactic agent but with little expectation of achieving a clinically meaningful benefit. The committee concluded that botulinum toxin type A or best supportive care were the relevant comparators in chronic migraine. But it considered that most people would receive botulinum toxin A rather than best

Consultee	Comment [sic]	Response
	Novartis does not believe that a fourth oral prophylactic accurately reflects the treatment pathway of patients with migraine in the UK managed by headache specialists, and hence is not a relevant comparator to erenumab under its expected positioning. Relevant comparators in the Novartis submission were based on combined consideration of clinical guidelines, feedback from UK neurologists and the precedent set by botulinum toxin in chronic migraine, which together indicate that a fourth oral prophylactic does not represent an appropriate comparator for this appraisal.[16] As per the positive recommendation resulting from the NICE appraisal for botulinum toxin in the treatment for chronic migraine (TA260), botulinum toxin is recommended in patients with chronic migraine for whom ≥3 prophylactic treatments have failed. Botulinum toxin is therefore a direct comparator for patients with chronic migraine for whom ≥3 prophylactic treatments have failed.[16] In the appraisal for botulinum toxin, "standard management", comprising rescue medications such as analgesics, was accepted as the single relevant comparator in the population of patients with chronic migraine for whom ≥3 prophylactic treatments have failed. As TA260 is the only previous NICE appraisal in this disease area, this establishes the precedent that there are no further prophylactic treatment options available for chronic migraine patients for whom ≥3 prior prophylactic treatments have failed at the time of this appraisal.[16] To consider a fourth oral prophylactic as a relevant comparator for the chronic migraine population is therefore to imply that there has been a change in the treatment pathway since the appraisal of botulinum toxin as part of TA260 in 2012. Consideration of the relevant comparator in the botulinum toxin appraisal was informed by the 2012 NICE clinical guideline for the diagnosis and management of headaches in over 12's (CG150). This guideline has not been updated since the publication of the guidance for botulinum toxin in chronic migraine; therefore, CG150 continues to be the relevant guideline for assessing current clinical practice. It should be further noted that this guideline does not distinguish between chronic and episodic migraine, and therefore provides the appropriate reference guideline for considering both the chronic migraine population and the high frequency episodic migraine population; with the exception of the recommendation of botulinum toxin for chronic migraine patients as per TA260, the treatment pathway for patients with chronic and high frequency episodic migraine is the same in current clinical practice.[16, 17]. CG150 provides clear recommendations for use of oral prophylactic	supportive care after trying 3 oral preventive treatments (see FAD section 3.4).

Consultee	Comment [sic]	Response
	treatment, and states that topiramate, propranolol and amitriptyline should be considered as treatment options.[17] This guideline does not recommend any other therapies as options for the prophylactic treatment of migraine, and therefore clearly establishes that these three oral prophylactics are the only recommended current treatments in both the episodic and chronic migraine pathway, supporting that there are no further recommended oral prophylactics for patients in whom ≥3 prophylactic treatments have failed. Feedback from headache expert neurologists collected in 2017 has stated that clinical practice has been largely unchanged for several years, confirming the ongoing relevance of CG150 and hence the relevance of the precedent set by the appraisal for botulinum toxin in terms of comparators, which can be considered relevant both for the chronic migraine setting and the high frequency episodic migraine setting.[18] This is supported by the most recent surveillance update for CG150, conducted in 2016, which sought to identify clinical and cost-effectiveness evidence for other prophylactic treatments in chronic and episodic migraine, including antidepressants, beta blockers and calcium channel blockers.[19] As discussed in the company submission, Document B, Section B.1.1.2, the current options for the prophylactic treatment for migraine (topiramate, propranolol and amitriptyline) have been in use for many years, and there has been little research into the safety and efficacy of these treatments since the publication of the original guidelines in 2012. The authors of this surveillance update concluded that new evidence was unlikely to change guideline recommendations, confirming the continued relevance of topiramate, propranolol and amitriptyline alone as the key prophylactic therapies for patients with migraine.[19] In the context of the lack of evidence for efficacy and safety of these treatments, use of a fourth oral prophylactic treatment would be poor practice from a patient quality of life perspective, requiring headache specialists in practice to prescribe ineffective interventions, unsupported by evidence, that may be associated with considerable side effects. Importantly, no oral prophylactic therapies have been licensed for the treatment of patients with migraine as a fourth oral prophylactic, and there is no high-quality clinical evidence to support the efficacy of a potential fourth-line prophylactic treatment. As such, it would be inappropriate and methodologically impossible to conduct a robust indirect treatment comparison to consider the cost-effectiveness of erenumab versus a fourth oral prophylactic therapy for the population of patients for whom ≥3 prophylactic treatments have failed.	

Consultee	Comment [sic]	Response
	In summary, there has been no change in the treatment pathway for episodic migraine or chronic migraine since the appraisal of botulinum toxin, as supported by expert headache neurologist feedback and the surveillance update to CG150. Furthermore, there is no robust evidence to support the safety and efficacy of a fourth oral prophylactic treatment in patients with migraine. As such, botulinum toxin is the relevant comparator in the chronic migraine population as per the NICE appraisal TA260, and best supportive care, defined by continued treatment with acute medication and healthcare resource use in line with the monthly migraine days experienced, is the relevant treatment comparator to erenumab for high frequency episodic migraine patients for whom ≥3 prophylactic treatments have failed.[16] **Novartis request:** We request that the Committee accepts botulinum toxin as the relevant comparator for erenumab in the population of patients with chronic migraine for whom ≥3 prophylactic treatments have failed, and best supportive care as the relevant comparator for erenumab in the population of patients with high frequency episodic migraine for whom ≥3 prophylactic treatments have failed, based on NICE HTA precedent and the NICE Clinical Guideline. **References not reproduced here, please see company response to ACD**	
Novartis	**<u>Inclusion of additional service set-up in the cost-effectiveness analysis is inappropriate and not reflective of the service implications related to the introduction of erenumab</u>** The ACD states that "additional resources would likely be needed, and that the cost of setting up these additional services should be accounted for in the economic model". This refers to an anticipated requirement for initiation and additional monitoring within secondary care specialist headache clinics with the use of erenumab. Erenumab is expected to be <u>initiated</u> by headache specialists experienced in the diagnosis and management of migraine in the NHS, in accordance with the summary of product characteristics which states that "treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine". However, subsequent to this initiation, erenumab can be self-administered (as per the summary of product characteristics); it is anticipated that ultimately subsequent administration of erenumab and follow-up will therefore not require specialist services and that ongoing treatment with erenumab will therefore place a much	Comments noted. The committee heard from clinical experts that erenumab is unlikely to have an impact on resource use in specialist services. The committee was satisfied that all relevant treatment costs were included in the model (see FAD section 3.20).

Consultee	Comment [sic]	Response
	lower burden on specialist services compared to botulinum toxin. Furthermore, as a self-administered treatment, erenumab directly supports the NHS's long-term focus on promoting patient self-care and self-management, as set out in the most recent NHS Long Term Plan in 2019.[20] Insight from headache specialist with experience in setting up headache specialist service was missing from the Committee discussions. There is the possibility that whilst clinicians gain experience in the use of erenumab there may be a requirement for specialist follow-up beyond the initiation of treatment for patients being treated with erenumab; however, such follow-up would involve a straightforward evaluation of a patients' response to erenumab, and it is likely that such follow-up could take place through telephone or video conference, or via a nurse. Furthermore, it is important to note that the patient population considered in the revised cost-effectiveness analyses (patients with chronic and high frequency episodic migraine for whom ≥3 prior prophylactic treatments have failed) are likely to be managed within headache specialist services already. In addition, the reduction of migraine days in responders to erenumab within these patient populations would be likely to result in a reduced number of unscheduled physician visits and emergency room visits (see Table 58 of the company submission for data supporting resource use associated with migraine frequency). This would contribute towards alleviating the burden of migraine on the healthcare system. Therefore, the introduction of erenumab is not anticipated to lead to a substantial increase in the requirement for specialist headache services or the need to establish a specialist service where none currently exists and may help alleviate pressure on existing services over time. As discussed in the company submission (Section B.1.2.2), treatment with botulinum toxin, which has been recommended for the treatment of patients with chronic migraine for whom ≥3 prophylactic treatments have failed, involves intramuscular injections to between 31 and 39 sites in the head and the back of the neck every 12 weeks, which must be performed by a trained specialist.[16] Treatment with botulinum toxin therefore requires in excess of four appointments with specialist services per year, placing a substantial burden on headache services. Once clinical experience with erenumab has developed and specialist services are only required for patient initiation on erenumab, introduction of erenumab would therefore be expected to reduce the burden of migraine treatment compared to that of botulinum toxin by 3–4 specialist appointments per patient per year. This would have a considerable impact on the lives of patients currently receiving treatment with botulinum toxin, who may have to travel long distances to attend one of the few	

Consultee	Comment [sic]	Response
	clinics that currently administers this treatment. In freeing up space within clinics, this also has the potential to reduce the length of time patients currently have to wait to access life-changing treatment, as the high administrative burden means that waiting lists for botulinum toxin are lengthy. Accordingly, the introduction of erenumab would not only save resource for the NHS compared to the current use of botulinum toxin but would also bring potential benefits in terms of capacity pressure release. Furthermore, healthcare professionals must undertake lengthy training in how to initiate patients on botulinum toxin due to its administration requirements, which limits the capacity within clinics. This lengthy training is not required for specialists initiating patients on erenumab; with erenumab, any member of staff within headache clinics will be able to perform the initial training. The above considerations have been supported by feedback from advisory boards and a recent meeting with 3 healthcare professionals in England experienced in the management of migraine, who have stated that they do not believe that there would be any additional service set-up or maintenance costs associated with the use of erenumab, and that the use of this treatment would be less burdensome than botulinum toxin and would allow their services to run more efficiently. In summary, it is not anticipated that erenumab will increase the requirement for specialist headache services, as it is likely that the majority of patients with chronic and high frequency episodic migraine will already be managed within secondary services. Furthermore, the reduced administration requirements for erenumab versus botulinum toxin are expected to lead to substantial resource *savings*. The introduction of erenumab would also directly support the NHS's long-term focus on promoting self-care and management.[20] Finally, erenumab would bring substantial benefits to patients, who would have access to a treatment which is considerably less burdensome than botulinum toxin. This burden encompasses not only the treatment itself, which consists of a single, self-administered subcutaneous injection for erenumab versus multiple unpleasant injections to the head and neck for botulinum toxin, but also the time and financial burden resulting from the requirement for patients to travel to clinics – often covering long distances – for frequent treatment with botulinum toxin, which will not be necessary for erenumab. **Novartis request:** The cost of additional services is not relevant to this appraisal and should not be incorporated into the economic model.	

Consultee	Comment [sic]	Response
	References not reproduced here, please see company response to ACD	
Novartis	**<u>The ACD does not acknowledge the magnitude of the clinical benefit for patients who respond to erenumab</u>** Whilst Novartis is pleased the clinical benefit of erenumab has been recognised, it is important that the magnitude of the clinical benefit gained for responder patients is understood, as this was not discussed at the Committee meeting. The difference in monthly migraine days between responders and non-responders is provided in the response to Clarification Question B12 (response status defined on the basis of ≥50% reduction from baseline in MMDs, as per the response definition used of the cost-effectiveness analysis). In patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed, responders treated with erenumab 70 mg and 140 mg had [redacted] and [redacted] monthly migraine days at 12 weeks, compared to [redacted] and [redacted] days for non-responders, respectively. Similarly, a pooled analysis of STRIVE, ARISE and LIBERTY demonstrated that responders treated with erenumab 70 mg and 140 mg, respectively, had mean monthly migraine days at 12 weeks of [redacted] and [redacted] days, respectively, compared to [redacted] and [redacted] days for non-responders. This demonstrates the substantial benefit which can be attained by patients treated with erenumab who respond to treatment, which is masked when considering outcomes from clinical trials for the entire study population, including non-responders. In clinical practice, non-responders would discontinue treatment: as per the Summary of Product Characteristics for erenumab, “clinical studies have demonstrated that the majority of patients responding to therapy showed clinical benefit within 3 months” and therefore “consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment”. Patients who continued treatment would be those who have responded to therapy within 3 months, and would therefore be expected to experience important clinical benefits; a one-day reduction in monthly migraine days is considered to be the minimally important difference, a value which is far exceeded by responders to erenumab.[24] **Novartis request:** We request that the ACD includes a statement that acknowledges the substantial clinical benefit of treatment with erenumab for patients who do respond to treatment.	Comments noted. The committee recognised that the 140 mg dose of erenumab is clinically effective for chronic migraine compared with best supportive care (see FAD section 3.6).

Consultee	Comment [sic]	Response
	References not reproduced here, please see company response to ACD	
Novartis	**<u>The ACD does not take into account the strength of the clinical evidence for erenumab in the chronic migraine population</u>** The ACD states that "given the uncertainty in the clinical evidence and utility values, an acceptable ICER would be around £20,000 per QALY gained". Novartis does not believe this statement is an accurate reflection of the clinical evidence in the population of patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed. Clinical evidence for erenumab in this subgroup is provided by Study 295, which was a large, high-quality, randomised, double-blind, placebo-controlled trial of erenumab in 667 patients with chronic migraine. As discussed in the company submission, Document B, Section B.2.6.1, erenumab demonstrated statistically significant benefits versus placebo in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Patients treated with erenumab 140 mg achieved statistically significant reductions in mean monthly migraine days from baseline to Week 12 compared to placebo (difference: −4.09 [95% confidence interval: −5.84, −2.33; p<0.001]). In total, 38.5% of patients in the erenumab 140 mg arm achieved a ≥50% reduction in monthly migraine days from baseline, compared to 15.3% of patients in the placebo arm, which corresponded to an odds ratio of 3.48 (95% CI: 1.64, 7.39; p=0.001). Patients treated with erenumab 140 mg also achieved significantly superior outcomes versus placebo for several other outcomes, including the change in the monthly severity of migraine pain, and change in monthly headache days, highlighting the consistency of the observed benefit. Accordingly, we believe that the statement claiming that there is uncertainty over the clinical evidence for erenumab provides a misleading interpretation of the data supporting the efficacy of erenumab in the population of patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed. **Novartis request:** We request that the Committee interprets the cost-effectiveness results presented in the Appendix document with reference to the strength of the clinical evidence in the population of patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed. On this basis, in chronic migraine, we believe that a cost-effectiveness threshold of greater than £20,000 per QALY is appropriate.	Comments noted. The committee recognised that the 140 mg dose of erenumab is clinically effective for chronic migraine compared with best supportive care (see FAD section 3.6). The committee was aware that the ICERs were highly sensitive to the assumption for the effectiveness of erenumab compared with botulinum toxin type A. When the odds ratio from the indirect treatment comparison was used, best supportive care and erenumab 'extendedly dominated' botulinum toxin type A, (that is,botulinum toxin type A was less effective and had a higher ICER than erenumab), leaving the relevant comparison between best supportive care and erenumab. The ICER for erenumab compared with best supportive care was below £30,000 per QALY gained. When an odds ratio of 1 (assuming equal effectiveness) was used, the ICER for erenumab compared with botulinum toxin type A was substantially above £30,000 per QALY gained. The committee considered both ICERs plausible. However, it considered the ICER based on the odds ratio from the indirect treatment comparison was more uncertain. The committee considered the substantial impact on the ICER when assuming equal effectiveness between erenumab and botulinum toxin type A and noted the ICER was substantially above the £20,000 to £30,000 per QALY gained range usually considered a cost-effective use of NHS resources (See FAD sections 3.22 and 3.26)

Consultee	Comment [sic]	Response
Novartis	**Technical correction to the description of the indirect treatment comparison** Section 3.9 of the ACD refers to the output of the indirect treatment comparison as a hazard ratio. The relative effectiveness statistic produced by the indirect treatment comparison is an odds ratio, not a hazard ratio. The wording should therefore be adapted accordingly for technical correctness.	Comment noted. This has now been corrected in the FAD (see FAD section 3.13).
Association of British Neurologists Advisory Group on headache and pain	**Has all of the relevant evidence been taken into account?** Yes, all currently available peer reviewed trials have been included in the analysis	Comment noted. No action required.
Association of British Neurologists Advisory Group on headache and pain	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, however: A. There is no currently available phase 3 trial evidence for chronic migraine B. The trials do not completely reflect the expected patient cohort who may receive erenumab in the UK: i) 2 of the published phase 3 trials of episodic migraine ('ARISE' and 'STRIVE') excluded those who had no therapeutic response to more than 2 classes of migraine preventative treatment, only the smaller phase 3 trial 'LIBERTY' included patients who had previously failed 2-4 preventative treatments, whereas in practice we expect eligibility criteria for erenumab to be in line with Botulinum toxin therapy ie failure of at least 3 previous migraine preventative drugs ii) patients were excluded from the phase 3 trials if they had co-morbid psychiatric disease, whereas in real life the frequency of depression and anxiety is high in chronic migraine populations and should not be basis for exclusion • C. The duration of treatment and waning effect of utility over time is uncertain. The general standard of care with migraine preventative treatments is that if migraine is well controlled on a given preventative agent for 6-12 months then treatment is re-evaluated and often withdrawn usually without immediate return to former state. If a patient requires longer term use we would certainly advocate re-evaluation of need for treatment at least every 18 months. The cost-effectiveness model presented assumes that longer term treatment would	Comments noted. ***Comments A and B*** The committee recognised that the trial data did not fully represent the relevant population who may be eligible for erenumab treatment (see FAD section 3.5). The committee noted the uncertainty in the evidence regarding the long-term effectiveness of erenumab (see FAD section 3.9). ***Comment C*** The committee agreed that the long-term clinical data from the extension study did show that low numbers of people withdrew from erenumab treatment because of a lack of efficacy and that to date there is no evidence of impact of anti-erenumab antibody body development on efficacy and safety. Based on the evidence available, the committee considered that on balance it was reasonable to assume that the treatment effect does not wane over time. The Committee therefore did not consider treatment waning scenarios in its decision making and agreed that the most plausible ICERs for erenumab compared with botulinum toxin type A and compared with best supportive care

Consultee	Comment [sic]	Response
	be the standard of care. However, we are aware that there are no long-term studies supporting continued benefit after cessation of successful treatment • D. We agree that it is appropriate to consider the 70mg and 140mg dose separately, not as a 'blended' dose	were from the company's base case ICERs using only the 2.38% for all-cause discontinuation rate. (see FAD sections 3.14,3.15 and 3.21). ***Comment D*** The committee accepted the company's decision to only include the 140 mg dose in the cost-effectiveness model (see FAD section 3.12).
Association of British Neurologists Advisory Group on headache and pain	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Whilst the committee recommendations may reflect the mean response of the patient population to erenumab, the data support the concept that there is a cohort of patients who have an exceptional response with, in some cases, a 75-100% reduction in mean monthly migraine days and a significantly improved quality of life. It may be appropriate to evaluate this group of responders separately and consider a 2-3 month clinical trial of erenumab appropriate to determine the level of response.	Comment noted. The committee considered the evidence in relation to the relevant subgroup and concluded that the 140 mg dose of erenumab is clinically effective for chronic migraine compared with best supportive care (see FAD section 3.6). However, when considering the committee's preferred assumptions, erenumab was not cost-effective for chronic migraine (see FAD sections 3.21 and 3.22).
British Association for the Study of Headache	**Has all of the relevant evidence been taken into account?** Yes	Comment noted. No action required.
British Association for the Study of Headache	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** BASH would like to make the following comments: 1. The Phase III trials STRIVE, ARISE and LIBERTY are for episodic migraine. The trial 295 for chronic migraine is Phase IIb. There are no published phase III studies in chronic migraine. 2. Whilst the reduction of monthly migraine days is the standard outcome measure for clinical trials in migraine, the 50% (and where available 75% and 100% responder rates) are a truer reflection of the efficacy of treatments in everyday clinical practice. 3. The 50% responder rate for Erenumab in Chronic Migraine Study (295) is 38.5% (140 mg) and 34.8% (70mg) compared to placebo 15.3%. The	Comments noted. ***Comment 1*** The committee recognised the uncertainty in the trial data (see FAD sections 3.4 and 3.5). ***Comment 2*** The committee concluded that a clinically meaningful response was a 30% reduction (for chronic migraine) or a 50% reduction (for episodic migraine) in migraine frequency (see FAD section 3.3). ***Comment 3***

Consultee	Comment [sic]	Response
	comparable figures for OnabotulinumtoxinA are 48% versus 36%. The therapeutic gain versus placebo, especially at the higher 140 mg dose, is therefore very significantly greater than for onabotulinumtoxinA. Moreover, patients receiving onabotulinumtoxinA are required to attend the out-patient clinics in secondary or tertiary care centres up to 5 times a year, and are given 31 injections by the treating physician/specialist nurse. 4. There is no direct comparison for onabotulinumtoxinA and Erenumab, however, direct comparison for any new treatment is rarely available. The best comparator for new therapy is best supportive care. Hence for the purpose of recommendation the committee should consider Erenumab in the standard manner that was used when considering the cost effectiveness of onabotulinumtoxinA, i.e. versus best supportive care. 5. There has been no significant change in standard clinical practice with regard to the use of oral preventive medication since the publication of NICE guidance on the management of headaches (CG 150), and on the use of onabotulinumtoxinA (TA 260), both of which are based on the accepted clinical practice that after three failures with oral preventives, patients are unlikely to respond to further oral treatment, and should be offered alternative effective treatments at that point. It is not appropriate to consider use of a 4th oral agent as a comparator due to the side effect profile and poor tolerability of oral preventives beyond the two first line agents of beta-blockers and amitriptyline. 6. The decision to use new treatments such as onabotulinumtoxinA after failure of three treatments is not evidence based. In PREEMPT trial a third of patients never received prophylaxis and others had failed one or two treatment, yet recommendations were to recommend following failure of three treatments. Such recommendations were based on economic modelling rather than clinical trial evidence as the cost of the new treatments is very high. 7. ARISE and STRIVE excluded those who had no therapeutic response to more than 2 classes of migraine preventive treatment, but it is standard practice in randomised control trials to exclude very refractory populations, and the decision to recommend in refractory population is need-based, not evidence-based. To consider that Erenumab is given to those that have	The committee considered the evidence from the indirect treatment comparison. The committee had a number of concerns about the analysis, including the use of placebo as the common comparator. Given the concern over the analysis, the lack of statistically significant results, and the wide confidence intervals, the committee concluded that there was a high degree of uncertainty as to whether erenumab is more clinically effective than botulinum toxin type A for chronic migraine (see FAD section 3.10). ***Comment 4*** Section 6.22 of NICE's Guide to the methods of technology appraisal 2013 states that When selecting the most appropriate comparator(s), the Committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator As botulinum toxin type A has been recommended by NICE and is now part of established clinical practice, the committee considered it as an appropriate comparator for chronic migraine. The committee concluded that best supportive care was the most appropriate comparator in episodic migraine and that that botulinum toxin type A or best supportive care were the relevant comparators in chronic migraine. But it considered that most people would receive botulinum toxin A rather than best supportive care after trying 3 oral preventive treatments (see FAD section 3.4)

Consultee	Comment [sic]	Response
	failed three treatments is not unreasonable, as a high cost treatment will thereby only be made available to a small refractory patient population. 8. Medication overuse is not seen in patients with episodic migraine as they are more likely to be suffering from chronic migraine. Patients with Chronic Migraine and medication overuse were not excluded from the trial (295). 9. We agree that there is lack of data confirming long term effectiveness, although this applies to any new high cost drug. Real life data remains the only source of such information and that can only be available once a recommendation is made to treat a limited refractory population, based on cost effectiveness. 10. We feel the committee will have to make reasonable assumption for duration of treatment in chronic migraine based on the data with existing prophylactic agents. We suggest the treatment should be stopped if there is no response at three months (negative stopping rule). Most prophylactic agents are required for 6-18 months, with only a small proportion of patients continuing treatment for longer duration. Duration of treatment of two years would be reasonable for modelling purposes, and the treatment could be stopped earlier if the patient is successfully converted to a low frequency episodic migraine (positive stopping rule). 11. We agree that there are no long term studies on any agent for continuing benefit, nor there is any data for relapse after cessation of successful treatment.	***Comment 5*** The committee recognised that an insufficient response to at least 3 oral preventative treatments represents usual NHS practice before a more specialist treatment is considered (see FAD section 3.3). The committee noted that evidence from clinical experts suggested that some patients may receive a fourth oral prophylactic agent but with little expectation of achieving a clinically meaningful benefit (see FAD section 3.4). ***Comment 6*** The committee was aware that there was long-term evidence to suggest that the adherence, efficacy and safety of botulinum toxin type A is sustained or improved over a 5-year period. It also was aware that botulinum toxin type A improved quality of life compared with best supportive care (see FAD sections 3.13 and 3.18). ***Comment 7*** The committee recognised that an insufficient response to at least 3 oral preventative treatments represents usual NHS practice before a more specialist treatment is considered (see FAD section 3.3). ***Comment 8*** Comment noted. No action required. ***Comment 9*** The committee was aware that there was long-term evidence to suggest that the adherence, efficacy and safety of botulinum toxin type A is sustained or

Consultee	Comment [sic]	Response
		improved over a 5-year period. It also was aware that botulinum toxin type A improved quality of life compared with best supportive care (see FAD sections 3.13 and 3.18). In response to consultation and after the second committee meeting, Novartis provided additional clinical data on the long-term treatment effectiveness of erenumab. Long term follow up data showed that the effectiveness of erenumab was maintained while on treatment up to month 57 for episodic migraine and for up to 52 weeks for chronic migraine, however there was no evidence of comparative effectiveness beyond 12 weeks. The committee therefore concluded that it was unclear whether erenumab works in the long term because there was no evidence that comparative efficacy was maintained beyond 12 weeks (24 weeks for the STRIVE trial) (see FAD section 3.9). ***Comment 10*** The application of a negative stopping rule using a 30% reduction in monthly migraine days was accepted by the committee (see FAD section 3.16) ***Comment 11*** Please see response to comment 9 above
British Association for the Study of Headache	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The draft recommendation will deprive a potentially effective treatment to a highly disabled population with chronic migraine who have failed three first line treatments (or four, including onabotulinumtoxinA or have not been able to tolerate some or all of these treatments. A 3 month trial of Erenumab in such patients would be highly appropriate before considering more invasive and expensive treatment options such	Comment noted. The committee recognised that migraine significantly affects health-related quality of life and that well-tolerated treatments are needed (see FAD sections 3.1 and 3.2).

Consultee	Comment [sic]	Response
	as intravenous dihydroergotamine, occipital nerve stimulation or even some of the non-invasive neuromodulation therapies that have limited NICE recommendations without mandatory funding.	
The Migraine Trust	The costs for erenumab would be expected to be cheaper as the doses are self administered and no cost for a health professional to inject 31 sites as in Botox	Comment noted. The committee considered costs from an NHS resource use perspective and concluded that all relevant costs for implementing erenumab in practice had been captured in the model (see FAD section 3.20).
The Migraine Trust	Self administration of the treatment allows the patient a sense of control. This feeling of control should not be underestimated as to how important this is to the patient.	Comment noted. The committee noted that self-self-administration is important as it gives the patient a sense of control (see FAD section 3.20)
The Migraine Trust	The Migraine Trust understands that nothing works for everybody, but we are aware that people on the trials of this drug saw real benefits. The side effect profile is good and many people were able to resume living and working normally as opposed to being on sick leave and unable to take part in family life.	Comment noted. The committee noted that erenumab is generally well tolerated in the populations studied (see FAD section 3.11).
The Migraine Trust	The cost to society of people unable to work is huge. Access to a treatment that works for them benefits everybody. For these reasons the provisional recommendations are not sound.	Comment noted. The committee considered costs from an NHS resource use perspective and concluded that all relevant costs for implementing erenumab in practice had been captured in the model (see FAD section 3.20).
The Migraine Trust	The preliminary recommendations discriminate against women. Three times more women than men experience migraine. Migraine generally affects sufferers in their most productive years.	Comment noted. The committee recognised the potential equalities issues raised by clinical and patient comments during the consultation and concluded that there were no specific adjustments required to the NICE methods in this circumstance (see FAD section 3.24).
The Migraine Trust	In some circumstances chronic migraine can be classed as a disability. To deny people the chance to contribute more to society is simply unfair.	Comment noted. The committee recognised the potential equalities issues raised by clinical and patient comments during the consultation and concluded that there were no specific adjustments required to the NICE methods in this circumstance (see FAD section 3.24).

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
The Migraine Trust (Dr S Afridi)	There is an unmet need for better treatments for patients with treatment resistant migraine. There is evidence that erenumab can be effective in some patients who have not had a good response or cannot tolerate (3 or more) preventatives. Tolerability is a major problem amongst migraineurs and in the literature and in our limited experience using it in the FOC scheme erenumab is well tolerated. I cannot comment on long term tolerabilty	Comments noted. The committee recognised that migraine significantly affects health-related quality of life and that well-tolerated treatments are needed (see FAD sections 3.1 and 3.2). The committee noted that erenumab is generally well tolerated in the populations studied (see FAD section 3.11).
The Migraine Trust (Dr S Afridi)	With regards to set up costs, after the first/ second injection they can self-administer. Botox requires a 3 monthly hospital attendance (time off work etc) and a trained clinician to administer.	Comment noted. The committee considered costs from an NHS resource use perspective and concluded that all relevant costs for implementing erenumab in practice had been captured in the model (see FAD section 3.20).

Comments received from commentators

Commentator	Comment [sic]	Response
Allergan	Allergan welcomes the opportunity to respond to the Appraisal Consultation Document for erenumab for migraine. In this response, we will focus specifically on chronic migraine, for which our product BOTOX® (onabotulinumtoxinA) is licensed and recommended by NICE, and is therefore a comparator in this appraisal. (On a point of terminology, we will refer here to onabotulinumtoxinA rather than botulinum toxin A, which is NICE's preferred usage, but a generic term that is not specific to BOTOX®. It should be understood that all references to data in what follows are specifically for onabotulinumtoxinA [i.e. BOTOX®], and that it is the only botulinum toxin product licensed for the treatment of chronic migraine.) <u>Allergan Response – Key Points</u> • Allergan concurs with the Committee's assessment that the long-term effectiveness of erenumab is uncertain. In contrast, the long-term effectiveness of onabotulinumtoxinA has been demonstrated extensively in both clinical trials and real-world settings.	Comments noted. Please find detailed responses to the individual comments in the relevant sections of this table below. Some detailed responses relate to the updated cost-effectiveness analysis and longer-term clinical evidence submitted by the company after the second committee meeting (not reproduced in this document -please see the committee papers for full details of the evidence). This evidence was considered at the third committee meeting (see FAD sections 3.9, 3.12, 3.14, 3.15, 3.21, 3.22, 3.25 and 3.26).

Commentator	Comment [sic]	Response
	• Allergan concurs with the Committee's assessment that there is no robust evidence that erenumab is more clinically effective than onabotulinumtoxinA. • We agree with the Committee's assessment that erenumab is unlikely to be cost effective compared to onabotulinumtoxinA for chronic migraine patients who have failed at least three prior preventive treatments. We note that this is consistent with the view reached in other international health technology assessments of erenumab, including a recent review by the Institute for Clinical and Economic Research (ICER) in the United States. • Allergan believes that the economic evidence provided to the Committee underestimates the degree of uncertainty regarding the cost-effectiveness of erenumab compared to onabotulinumtoxinA, and that the range of the cost per QALY gained is likely to be substantially higher than the estimates in the Appraisal Consultation Document.	
Allergan	We believe that it would be of most assistance to the Committee if we concentrate this response on the substantial body of evidence that exists to support both the long-term effectiveness and safety of onabotulinumtoxinA for chronic migraine. We note that, while it was argued during the Appraisal Committee meeting that there is a significant unmet need for erenumab, and that this argument in part rests upon what are supposed to be difficulties for patients getting access to onabotulinumtoxinA, this argument has not been endorsed in these terms in the ACD. Allergan agrees with the Committee that effective and well-tolerated treatment options are needed and, as our response below shows, onabotulinumtoxinA meets these criteria so far as chronic migraine is concerned. We further acknowledge that onabotulinumtoxinA must be administered by properly trained practitioners who either are, or who operate under the supervision of, a neurologist or headache specialist. There are, however, a large number of centres across the UK where onabotulinumtoxinA is administered for chronic migraine and service capacity continues to expand. Allergan is also working with the NHS to increase capacity and access for patients, recently concluding, for example, two Joint Working Agreements, one at the Salford Royal Hospital and the other at University Hospital Birmingham, both with this intent.	Comments noted. The committee acknowledged that there was long-term evidence to suggest that the adherence, efficacy and safety of botulinum toxin type A is sustained or improved over a 5-year period. It also acknowledged that botulinum toxin type A improved quality of life compared with best supportive care (see FAD sections 3.13 and 3.18).

Commentator	Comment [sic]	Response
	The studies summarised in this response comprise a total of over 5,600 patients (including over 1,200 from the UK) treated with onabotulinumtoxinA with up to five years of patient exposure. They show that the clinical efficacy of onabotulinumtoxinA is sustained or improved in patients over an extended period of treatment, as well as that the product is generally safe and well-tolerated. Additionally, HRQoL (measured by HIT-6 [Headache Impact Test], MSQ [Migraine-Specific Quality-of-Life questionnaire] and EQ-5D [EuroQol five-dimensional questionnaire]) and work productivity were improved following onabotulinumtoxinA treatment in clinical trials and observational studies.[1–8] The evidence for the long-term effectiveness and safety of onabotulinumtoxinA in chronic migraine comes principally (though not exclusively) from the following sources: • A prospective analysis of a total of over 650 CM patients treated by the Hull Migraine Clinic going back to 2010 and providing data for patients in some cases treated for as long as two years (n=508) and as long as five years (n=211).[8–11] • Two-year data from the prospective observational REPOSE study, involving over 600 patients in seven European countries, including 94 from the UK.[5,12] • Two-year data from the Phase IV long-term open label prospective COMPEL study, involving over 700 patients in the USA, Australia and Korea.[13] • Two-year data from a prospective observational study of 275 patients treated at the Sant Andrea Hospital in Italy between 2010 and 2015.[14,15] These data are in addition to those reported in the two pivotal randomised control trials for onabotulinumtoxinA in chronic migraine (PREEMPT 1 and PREEMPT 2) that together provide data for a further 1,384 patients up to 56 weeks.[16] The CM-PASS study further demonstrates the safety of onabotulinumtoxinA over 52 weeks, involving over 1100 patients, including 422 from the UK; no efficacy data were collected in this study.[17]	

Commentator	Comment [sic]	Response
	A summary of the key characteristics and findings from the trials and studies relevant to this response is set out in tabular form in the attached appendix. It may be helpful to refer the Committee to the recent ADIS drug evaluation[18] in which the long-term effectiveness and safety of onabotulinumtoxinA for the prevention of chronic migraine have been summarised. The studies covered in this review include the PREEMPT programme[16,19,20]; the CM-PASS study[17]; the multinational, open-label COMPEL trial (N=715, 108 weeks of follow up)[13]; the multinational, post-authorization REPOSE study (N=641, 2 years of follow up)[5]; as well as observational studies at the Hull Migraine Clinic,[8] Sant Andrea Hospital in Italy (N=275, 2 years of follow up),[14,15] and a multicentre study in Spain (N=725, 1 year of follow up).[21] The authors of the ADIS paper conclude that "the totality of evidence from clinical trials and real-world studies indicates that [onabotulinumtoxinA] is an effective and generally well-tolerated option for the prevention of CM that may be particularly useful for patients who have previously failed to respond to or are intolerant of commonly prescribed oral prophylactics."[18] Studies and analysis carried out at the Hull Migraine Clinic since 2010[8,9] provide the largest consolidated source of UK real-world evidence for the effect of onabotulinumtoxinA in CM prophylaxis, and results extend for up to five years of treatment. In this dataset, all patients had failed at least three prior preventive treatments, except for 14 patients who initiated treatment before the NICE guidance came into effect in 2012.[8] This makes the evidence from Hull particularly relevant to the decision problem in this appraisal. In the Hull studies, onabotulinumtoxinA treatment was stopped if there was no response after two consecutive cycles (response being defined as at least a 50% reduction in headache days, a 50% reduction in migraine days, or a 2-fold increase in the number of crystal clear [headache free] days to at least six crystal clear days per month).[8,9] Patients who met the initial criteria for response were also permitted to stop treatment if their condition converted to episodic migraine, defined as less than 10 headache days for three consecutive months (Hull modified positive stopping rule), and to recommence treatment if they relapsed to chronic migraine (more than 15 headache days for at least three consecutive months).	

Commentator	Comment [sic]	Response
	The sustained benefit of onabotulinumtoxinA is clearly evident: • In a three-year analysis, a majority of patients (66%) demonstrated a response in at least one of the endpoints, i.e., at least a 50% reduction in headache days, a 50% reduction in migraine days, or a 2-fold increase in the number of crystal clear days to at least six crystal clear days per month.[8] The results of a more recent analysis of 687 patients treated over a seven-year period were generally consistent with the earlier results.[9] • In 294 patients with an initial response to onabotulinumtoxinA, 87.4% (n = 257) experienced a successful treatment response over two years of follow up, i.e., were either still on treatment or had successfully withdrawn treatment without relapse to chronic migraine.[10] • Over five years of follow up, 80.2% (n = 101) of initial responders (N = 126) experienced a successful treatment response, i.e., were either still on treatment or had successfully withdrawn treatment without relapse to chronic migraine.[11] • In all these analyses, the most common adverse events were consistent with the known safety profile for onabotulinumtoxinA.[8,9] OnabotulinumtoxinA was originally licensed on the basis of data from two phase III studies (PREEMPT 1[19] and PREEMPT 2[20]). In these pivotal studies, onabotulinumtoxinA was generally well tolerated and effective in producing statistically significant and clinically meaningful improvements in headache symptoms, acute headache pain medication usage, headache impact and health-related quality of life in adults with CM. Pooled analyses of the PREEMPT studies demonstrated that patients who received five treatment cycles of onabotulinumtoxinA experienced improvement in all efficacy endpoints between the end of the double-blind phase (week 24, two treatment cycles) and the end of the open-label phase (week 56, five treatment cycles), as well as statistically significantly greater reductions in headache days and migraine days from baseline to week 56 than patients who received three cycles of treatment during the open-label phase.[16] One third of patients in these trials had not responded to ≥ 3 prior oral preventive therapies.[22]	

Commentator	Comment [sic]	Response
	The findings from the PREEMPT programme have been both confirmed and extended by the results of a long-term phase IV study (COMPEL),[13] in which patients received up to nine treatment cycles over a period of 2 years, and by findings from several real-world clinical practice studies from Europe,[14,15,21,23–26] including the prospective multinational REPOSE[5] and CM-PASS[17] studies. Beyond confirming the PREEMPT programme findings, COMPEL assessed the impact of onabotulinumtoxinA on comorbid symptoms of anxiety, as measured by the Generalized Anxiety Disorder 7-item scale (GAD-7), and depression, as measured by the Patient Health Questionnaire (PHQ-9).[27] The presence of these comorbidities can exacerbate chronic migraine and increase migraine related burden in those already impacted; therefore, addressing and treating these common comorbidities is part of appropriate management for chronic migraine.[28–30] Findings demonstrated that onabotulinumtoxinA improved symptoms of depression and anxiety among those treated for chronic migraine. No new safety signals were identified in either COMPEL[13] or REPOSE,[5] while adverse events in the 52-week CM-PASS study (N=1160) were also consistent with the product label and the results of the PREEMPT trials.[17] In real-world studies conducted in clinical practice settings, adverse events were mild to moderate and transient,[14,15,21,23,24] and the most common types of adverse events were consistent with the known safety profile of onabotulinumtoxinA.[8,9,14,15,23–25]	
Allergan	In response to the question of whether the summaries of the clinical and cost effectiveness provide reasonable interpretations of the evidence, Allergan concurs with the Committee's assessment as follows: • The long-term effectiveness of erenumab is uncertain. In contrast, as described above, the long-term effectiveness of onabotulinumtoxinA has been demonstrated extensively in both clinical trials and real-world settings. • There is no robust evidence that erenumab is more clinically effective than onabotulinumtoxinA. • Due to the high uncertainty in the clinical evidence for the subgroup of interest and key model inputs, erenumab is unlikely to be cost effective compared to onabotulinumtoxinA for chronic migraine patients who have failed at least three prior preventive treatments.	Comments noted. The committee concluded that the long-term comparative effectiveness of erenumab is unknown (see FAD section 3.9) and that there is a high degree of uncertainty as to whether erenumab is more clinically effective than botulinum toxin type A (see FAD section 3.10) After the second committee meeting, Novartis provided an updated base case and scenario analyses for patients with chronic migraine only (not reproduced in this document -please see the committee papers for full details of the evidence). The committee was aware that the ICERs were highly sensitive to the assumption for the effectiveness of erenumab compared with botulinum toxin type A. When the odds ratio from

Commentator	Comment [sic]	Response
	We further note that the Committee's assessment is consistent with the view reached in other international health technology assessments of erenumab, including a recent review by the Institute for Clinical and Economic Research (ICER) in the United States. ICER's view in summary is that there is insufficient evidence to demonstrate a net health benefit for erenumab compared with onabotulinumtoxinA.[31] Its review omitted a comparison between the two products from the primary cost-effectiveness analysis due to lack of sufficient evidence to demonstrate a net health benefit for erenumab compared to onabotulinumtoxinA.	the indirect treatment comparison was used, best supportive care and erenumab 'extendedly dominated' botulinum toxin type A, (that is,botulinum toxin type A was less effective and had a higher ICER than erenumab), leaving the relevant comparison between best supportive care and erenumab. The ICER for erenumab compared with best supportive care was below £30,000 per QALY gained. When an odds ratio of 1 (assuming equal effectiveness) was used, the ICER for erenumab compared with botulinum toxin type A was substantially above £30,000 per QALY gained. The committee considered both ICERs plausible. However, it considered the ICER based on the odds ratio from the indirect treatment comparison was more uncertain. The committee considered the substantial impact on the ICER when assuming equal effectiveness between erenumab and botulinum toxin type A and noted the ICER was substantially above the £20,000 to £30,000 per QALY gained range usually considered a cost-effective use of NHS resources (See FAD sections 3.22 and 3.26) .
Allergan	We would also like to make a number of comments arising from our review of the manufacturer's economic model for this appraisal to which, as a commentator, we were granted temporary access, albeit in a heavily redacted form. Based on this review, Allergan concurs with the Committee's feedback on the modelling approach, assumptions and data inputs which are discussed in the ACD. We also agree that, due to lack of long-term effectiveness data for erenumab, modelling long term treatment effects required a range of assumptions that contributed to considerable uncertainty of the model results. However, due to the extensive redaction of the model that obscured several important input parameter values it was impossible to verify the reliability of how the economic evaluation of erenumab vs. comparators was performed.	Comments noted. The committee noted that all the relevant costs for implementing erenumab in clinical practice were captured in the model. The committee concluded that applying a mode of administration utility decrement to botulinum toxin type A is not appropriate (see FAD sections 3.19 and 3.20). The committee concluded that there is substantial uncertainty in the evidence for clinical and cost-effectiveness of erenumab in chronic migraine and that including plausible estimates of relative effectiveness compared with botulinum toxin type A results in ICERs much higher than what NICE normally considers a cost-effective use of NHS resources. Therefore, it could not recommend

Commentator	Comment [sic]	Response
	One key issue in the economic model is that in the scenario analyses that incorporate utility decrements for adverse events and method of administration, it is assumed that onabotulinumtoxinA patients have lower utility scores than placebo patients with equivalent monthly migraine days. This is contradicted by the evidence in the PREEMPT trials. These demonstrated that onabotulinumtoxinA patients had generally higher utility scores than placebo patients with equivalent monthly headache days.[32] The PREEMPT trials also demonstrated that onabotulinumtoxinA had a statistically significant effect on headache severity compared to placebo. In a pooled analysis of the intent-to-treat population, onabotulinumtoxinA patients experienced a significantly lower proportion of headache days rated as severe and a significantly higher proportion of headache days rated as mild than placebo patients.[33,34] In a subgroup analysis of patients who failed to achieve at least a 50% reduction in headache days, onabotulinumtoxinA patients were significantly more likely than placebo patients to achieve at least a 1-grade improvement in the HIT-6 questionnaire item "When you have headaches, how often is the pain severe?"[35] These assumptions regarding utility decrements are also inconsistent with the NICE guidance for onabotulinumtoxinA (TA260). The Committee took note of comments from consultees and commentators, and supportive data from a survey of chronic migraine patients in the UK, that onabotulinumtoxinA is associated with a range of benefits beyond the reduction in headache days. The Committee's preferred approach was to apply different utilities to onabotulinumtoxinA and placebo in the economic analysis, although there was considerable uncertainty regarding the degree to which differential utilities existed within each health state.[36] The US ICER review also incorporated a utility benefit for onabotulinumtoxinA into its economic analysis, based on the evidence of its beneficial effect on headache severity.[31,37] Finally, Allergan notes that the cost-effectiveness analyses of erenumab compared to onabotulinumtoxinA submitted by the manufacturer and the Evidence Review Group did not incorporate the evidence demonstrating the long-term effectiveness of onabotulinumtoxinA that has been published since the NICE guidance was issued in 2012 and which is summarised in this response. The scenarios explored in the economic analyses assumed that erenumab maintains higher effectiveness than onabotulinumtoxinA for anywhere from five years to a lifetime horizon, despite the absence of robust evidence demonstrating that erenumab is more clinically effective than onabotulinumtoxinA. Therefore, Allergan believes that the economic evidence provided to the Committee underestimates the degree of uncertainty regarding the	erenumab for use in the NHS for preventing migraine (see FAD sections 3.26 and 3.27).

Commentator	Comment [sic]	Response
	cost-effectiveness of erenumab compared to onabotulinumtoxinA, and that the range of the cost per QALY gained with erenumab is likely to be substantially higher than the estimates in the Appraisal Consultation Document.	

Summary of comments received from members of the public

Theme	Response
Do not agree with the ACD decision to not recommend erenumab	Comment noted. At the third committee meeting, the committee concluded that erenumab is not recommended, within its marketing authorisation, for preventing migraine in adults who have at least 4 migraine days per month (see FAD section 1 and the section 'Why the committee made these recommendations'). The guidance on erenumab will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators (see FAD section 5). Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations (See NICE's Guide to the Process of Technology Appraisals, section 6.2).
Migraine negatively impacts quality of life	Comment noted. The committee recognised the significant effect of migraine on health-related quality of life (see FAD section 3.1).
Become reliant on other people for help	Comment noted. The committee recognised the significant effect of migraine on health-related quality of life (see FAD section 3.1).
Migraine increases prevalence of psychiatric illness	Comment noted. The committee acknowledged the prevalence of psychiatric illness, however, also noted that the trials excluded significant comorbidities (see FAD sections 3.1 and 3.11).
Migraine affects employment	Comment noted. The committee recognised the significant effect of migraine on employment (see FAD section 3.1).
Affects all age groups and more women than men	Comment noted. The committee recognised the potential equalities issues raised by clinical and patient comments during the consultation and concluded that there were no specific adjustments required to the NICE methods in this circumstance (see FAD section 3.24).

Theme	Response
Existing treatments have limited effect and more side effects	Comments noted. The committee recognised that well-tolerated treatment options are needed (see FAD section 3.2) and that erenumab is generally well tolerated in the populations studied (see FAD section 3.11).
Botox needs specialist services and more difficult to administer	Comments noted. The committee considered costs from an NHS resource use perspective and concluded that all relevant costs for implementing erenumab in practice had been captured in the model (see FAD section 3.20).
There is an unmet need for a well-tolerated drug	Comments noted. The committee recognised that well-tolerated treatment options are needed (see FAD section 3.2) and that erenumab is generally well tolerated in the populations studied (see FAD section 3.11).
Erenumab is shown to be effective with few side effects	Comment noted. The committee noted that erenumab is generally well tolerated in the populations studied (see FAD section 3.11).
Erenumab is specifically designed to treat migraine	Comment noted. The committee recognised that erenumab is a specialist treatment and that current oral treatment options for preventing migraine include drugs that are used to treat other conditions (see FAD section 3.2).
Potential to improve quality of social and work lives	Comment noted. The committee acknowledged that erenumab may improve monthly migraine days whilst on treatment, however, the long-term effectiveness is uncertain (see FAD section 3.9).
Erenumab may not be effective for everyone	Comment noted. The committee concluded that erenumab 140 mg is clinically effective in chronic and episodic migraine (see FAD sections 3.6 and 3.7) however it acknowledged that that the trials excluded the most refractory population with migraine who may benefit from the drug in clinical practice (see FAD section 3.5). The committee concluded that the clinical effectiveness results of erenumab for high frequency episodic migraine were highly uncertain and that this was not a distinct subgroup was not appropriate to consider further (see FAD section 3.8).
Can self-administer erenumab	Comments noted. The committee considered costs from an NHS resource use perspective and concluded that all relevant costs for implementing erenumab in practice had been captured in the model (see FAD section 3.20).
Erenumab is too expensive for private treatment	Comment noted. No action required.

Theme	Response
Cost effectiveness analyses should consider the effect on the economy	Comment noted. In accordance with the NICE guide to the methods of technology appraisals (sections 5.1.9 and 5.1.10) the committee considered only direct costs to the NHS and personal social services. The committee concluded that all relevant costs for implementing erenumab in practice had been captured in the model (see FAD section 3.20).
Erenumab trials should be extended to include selected participants	Comment noted. At the third committee meeting, the committee concluded that erenumab is not recommended, within its marketing authorisation, for preventing migraine in adults who have at least 4 migraine days per month (see FAD section 1and the section 'Why the committee made these recommendations'). The guidance on erenumab will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators (see FAD section 5). Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations (See NICE's Guide to the Process of Technology Appraisals, section 6.2).
Botox and 4th oral drugs are not relevant comparators	The committee was aware that the clinical experts suggested that some patients may receive a fourth oral prophylactic agent but with little expectation of achieving a clinically meaningful benefit. The committee concluded that botulinum toxin type A or best supportive care were the relevant comparators in chronic migraine. But it considered that most people would receive botulinum toxin A rather than best supportive care after trying 3 oral preventive treatments (see FAD section 3.4).
Erenumab could have broader benefits to the health care system	Comment noted. In accordance with the NICE guide to the methods of technology appraisals (sections 5.1.9 and 5.1.10) the committee considered only direct costs to the NHS and personal social services. The committee concluded that all relevant costs for implementing erenumab in practice had been captured in the model (see FAD section 3.20).

The following consultees/commentators indicated that they had no comments on the Appraisal Consultation Document:

Organisation for the Understanding of Cluster Headache

NICE National Institute for Health and Care Excellence

Erenumab for preventing migraine [ID1188]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 31 January 2019 **email:** TACommD@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

NICE National Institute for Health and Care Excellence

Erenumab for preventing migraine [ID1188]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 31 January 2019 **email:** TACommD@nice.org.uk/NICE DOCS

Name of commentator person completing form:	Victoria Hacking

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Novartis is disappointed by the draft recommendation of NICE to not recommend erenumab for routine use on the NHS. If this decision remains unchanged patients will be denied access to the first licensed treatment specifically designed to prevent migraine in adults. We are pleased that the Appraisal Committee has recognised the clinical effectiveness of erenumab and that a significant unmet treatment need exists for people living with migraine in the UK. However, we disagree with the Appraisal Committee's view that erenumab is not a cost-effective use of NHS resources. We hope that our response below addresses any outstanding questions and concerns. Key elements of our response are as follows:- • The proposed patient population has been re-focussed to cover the spectrum of patients with ≥10 monthly headache days (MHDs), encompassing the arbitrary definitions of chronic migraine (CM) and high frequency episodic migraine (HFEM), i.e. those with the highest unmet medical need who are typically treated by headache specialists [see point 2] • The proposed dose for consideration is the 140 mg dose only [see point 2] [redacted] • Novartis disagrees with the Appraisal Committee's preferences on key inputs/assumptions included in the health economic modelling, including the Committee's preferences for: o Inclusion of treatment effect waning [see point 3] o Non-acceptance of treatment benefit from the indirect comparison of erenumab vs. botulinum toxin [see point 4] o Consideration of a 4th oral comparator [see point 5] o Inclusion of additional service costs [see point 6] • Revised cost-effectiveness analysis is submitted to reflect this response framework [see point 2 & Appendix Document] Please note that information highlighted in turquoise and yellow in this response and the appendix document should be treated as strictly confidential.

Erenumab for preventing migraine [ID1188]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 31 January 2019 **email:** TACommD@nice.org.uk/NICE DOCS

2	**Novartis provides updated cost-effectiveness results as part of this response** In addition to this appraisal consultation document (ACD) response, Novartis provides an Appendix entitled ***'Additional Cost-Effectiveness Analyses'***. Further to the agreement obtained from NICE, this document provides a revised Novartis base case analysis and scenario analyses based on the issues raised in points 3 and 4 of this response. Please note that this ACD response should only be read in conjunction with the Appendix document entitled ***'Additional Cost-Effectiveness Analyses'*** and should not be considered in isolation. The analyses presented in the Appendix focus only on patients with chronic migraine (CM) and high frequency episodic migraine (HFEM), the latter being those with 10-14 monthly headache days. This represents a re-focusing of the proposed population for erenumab that takes account of the Appraisal Committee's considerations to date and reflects a patient cohort with the highest unmet need who are treated by headache specialists, for whom erenumab is particularly appropriate. As indicated in NICE's ACD and as outlined in our submission, patients with HFEM face a similar burden to those with CM and, in clinical practice, are likely to benefit from treatment to a similar extent as patients with CM. The analyses presented in the Appendix consider erenumab 140 mg versus botulinum toxin in patients with CM, and versus best supportive care in patients with HFEM. This reflects the Appraisal Committee's interpretation of the clinical evidence for the two doses of erenumab, with erenumab 140 mg considered to provide the greatest benefit to patients. As discussed in point 7, we request that the Committee only considers the 140 mg dose in its decision making. [redacted]
3	**Conclusions regarding treatment waning do not adequately reflect the collective evidence supporting a lack of waning effect with long-term erenumab treatment** The ACD states that "erenumab's long-term effectiveness compared with best supportive care was uncertain" and that the committee understood that "a constant treatment effect was implausible". The ACD indicates that the Committee therefore considered scenarios whereby the treatment effect waned over 5- and 10-year periods in their decision-making. Novartis does not believe that the conclusions of the ACD with respect to treatment waning adequately reflect the collective evidence on the long-term efficacy of erenumab, and also challenges the appropriateness of assuming a waning effect for monoclonal antibodies as considered in other NICE appraisals. ***Case precedent from previous NICE appraisals of biologics*** Novartis acknowledges the absence of data to support the maintenance of erenumab efficacy beyond the 52-week and 64-week timepoints. However, there is a notable precedent for similar cases where evidence for maintenance of long-term efficacy is lacking. A number of NICE appraisals of biologics in other chronic, non-progressive diseases characterised by periods of episodic worsening of condition, similar to migraine, have assumed there to be no waning effect following long-term treatment, as detailed below.[7-9] This assumption has been accepted by the respective appraisal committees in the noted absence of long-term follow-up data.[7-9] • Omalizumab for previously treated chronic spontaneous urticaria (TA339)[8] • Omalizumab for treating severe persistent allergic asthma (TA278)[9]

- Mepolizumab for treating severe refractory eosinophilic asthma (TA431)[7]

Contrary to the above examples, the ACD cites the possible waning of monoclonal antibodies in rheumatoid arthritis as an indication that outcomes following treatment with erenumab may not persist in the long term. However, rheumatoid arthritis is a progressive disease that gets worse over time, meaning that it would not be expected that the same treatment benefit could be maintained. Indeed, the waning effect which may be observed in rheumatoid arthritis is likely on account of disease worsening, rather than a loss of efficacy. Rheumatoid arthritis therefore does not represent an appropriate analogue to migraine, which sees patients experiencing fluctuations in the severity of their condition in both the short- and long-term.[10-12]. Accordingly, Novartis does not consider this evidence to be relevant in informing assumptions regarding waning, and instead asks that NICE considers the precedent set by appraisals of other biologics in other non-progressive diseases, as detailed above.

Clinical expert opinion

Further, it should be noted that the topic of waning was discussed at the committee meeting on 6th December 2018, and a clinical expert confirmed that there was no reason to believe that patients treated with erenumab would experience a waning effect over time. This is not acknowledged in the ACD. Additionally, feedback from 3 headache specialists in England stated that there is no evidence to suggest a waning effect in patients who respond well to erenumab treatment.

Long term data for erenumab

Open-label extension studies in both chronic and episodic migraine provide evidence to support the long-term efficacy of erenumab. As discussed in the response to Clarification Question B9a), patients enrolled in Study 295 (chronic migraine) and STRIVE (episodic migraine) demonstrated continued reductions in monthly migraine days over a 52-week and 64-week follow-up period, respectively.[1, 2] These extension studies both included a large number of patients (*n=609 and n=845*, respectively), of which a high proportion completed the entire duration of follow-up (*n=451 [74.1%] and n=737 [87%],*respectively) *[italics denotes new data not provided in original submission]*. Whilst no data are available from longer-term follow-up, the results of these studies provide no indication of a waning in the treatment effect: in both studies, patients experienced numerical reductions in monthly migraine days from the end of the double-blind treatment phase to Week 52 or Week 64. In addition, safety data are available from an open-label study of erenumab in episodic migraine that enrolled 383 patients; a pre-planned interim analysis is reported for which all remaining patients had completed ≥3 years of treatment.[3] This safety update demonstrates that 61.3% of patients entering the open-label study remained on treatment at this follow-up, with exposure to erenumab for those remaining in the study ranging from 3.0 to 3.9 years. This interim safety update provides evidence of patients continuing to receive erenumab for more than 3 years, therefore providing support for ongoing clinical benefit with erenumab in the long-term.

These studies did not contain a control arm, as this may have raised ethical challenges, which poses challenges to evaluating comparative efficacy of erenumab in the long-term. As such, the ACD states that there is “no evidence that comparative efficacy was maintained”. However, a comparative benefit of erenumab versus placebo was observed at the end of the double-blind treatment phase and, as discussed above, the absolute efficacy of erenumab was maintained and even improved up to 52 or 64 weeks. Therefore, for the comparative efficacy of erenumab versus placebo not to be maintained requires an assumption that any patients who had continued on with placebo would have experienced greater improvements over the period from the end of the double-blind treatment phase to week 52 or 64 than were observed for erenumab. Even if patients had continued to receive placebo and maintained their observed benefit at the end of the double-blind treatment phase, comparative efficacy would still have been maintained. Therefore, it is implausible that comparative efficacy of erenumab is not maintained up to at least 52 weeks (chronic migraine) and 64 weeks (episodic migraine).

Erenumab mechanism of action

Erenumab's novel formulation and mechanism of action are expected to minimise the likelihood of waning, which has been supported by pharmacokinetic studies. Erenumab is a fully human IgG2 monoclonal antibody that acts as a potent and selective calcitonin gene-related peptide receptor antagonist. These properties mean that it is not expected to be associated with neutralising antibodies; IgG2 antibodies generally have little to no activation of the immune system, and erenumab targets the calcitonin gene-related peptide receptor directly, meaning that it does not require activation of the immune system.[4, 5] Accordingly, pharmacokinetic studies demonstrate that anti-erenumab antibodies have a low occurrence rate, are mostly transient in nature, and do not impact upon the efficacy of erenumab. In an analysis of 1,388 patients across four phase II/III clinical trials of erenumab (including Study 295 and STRIVE), anti-erenumab antibodies occurred in only *6.3% (56/884)* of patients treated with erenumab 70 mg, and *2.6% (13/504)* of patients treated with erenumab 140 mg, with over 50% of these patients reverting to an antibody-free status with continued treatment. Specifically, the incidence of neutralising antibodies in these patients was very low *(*[redacted] *patients treated with erenumab 70 mg and* [redacted] *patients treated with erenumab 140 mg) [italics indicates new data not provided in original submission]*. Furthermore, long-term treatment with erenumab was not shown to be associated with an increased incidence of anti-erenumab antibodies compared to those observed during the double-blind treatment phases of the clinical trials.[6] Importantly, patients found to have anti-erenumab antibodies did not experience a loss of efficacy: the mean change in monthly migraine days from baseline to month 6 for patients without anti-erenumab antibodies was *−3.5 (0.2) and −3.8 (0.2)* for patients treated with erenumab 70 mg and 140 mg, respectively, compared to *−3.2 (0.9) and −5.2 (0.9)* for patients with anti-erenumab antibodies *[italics indicates new data not provided in original submission]*.[6]

Therefore, the evidence available to date supports a low occurrence of anti-erenumab antibodies and provides no indication that the formation of anti-erenumab antibodies will lead to a waning effect in the long term. An assumption of no treatment waning has been accepted in appraisals of biologics in other chronic, non-progressive diseases (including omalizumab for previously treated chronic spontaneous urticaria and mepolizumab for severe refractory eosinophilic asthma) on the basis of results from pharmacokinetic studies that have similarly demonstrated that antibodies are typically transient and do not impact upon efficacy.[7, 8]

Expected use of erenumab in UK clinical practice impacts waning considerations

Another important consideration – not acknowledged in the ACD – is that it is expected in clinical practice that patients will not be maintained on erenumab treatment in the long-term. This aligns with the summary of product characteristics for erenumab, which states that "consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment", and that "evaluation of the need to continue treatment is recommended regularly thereafter".[13] Accordingly, it is anticipated that patients will discontinue erenumab if they no longer continue to experience a clinically meaningful response to treatment (i.e. negative discontinuation). This is reflected in the cost-effectiveness model presented by Novartis through the modelling of discontinuation on non-response at the assessment time point, and also a further 2.38% annual discontinuation rate in the long-term that reflects patients withdrawing from erenumab, including for reasons of loss of efficacy. The cost-effectiveness analysis therefore already accounts for the potential for loss of efficacy in a small number of patients in the long-term, and appropriately addresses this by modelling – in line with the summary of product characteristics as quoted above – that these patients terminate treatment with erenumab and thereby lose both the benefits of erenumab treatment but also the costs. This approach follows the precedent set by the appraisal for ocrelizumab in relapsing multiple sclerosis, whereby an annual treatment discontinuation rate was accepted as a means to account for the potential for treatment waning in the absence of evidence for a waning effect after four years.[14] Furthermore, continued stakeholder feedback and UK advisory boards have indicated that, in the UK, clinicians would expect to also apply a positive stopping rule to the use of erenumab. Under such practice, patients who are continuing to benefit from erenumab would not continue to receive erenumab

	indefinitely, but would undergo "positive discontinuation". Newly published guidelines from the European Headache Foundation support this, citing an expert opinion-level recommendation that anti-CGRP monoclonal antibodies be stopped after 6-12 months of treatment. The expectation is that some patients will need to return to treatment. Incorporation of a positive stopping rule was presented as a scenario analysis in the company submission (scenario 6; further information re-presented in appendix document). In the context of application of a positive stopping rule in UK clinical practice, waning is no longer a relevant consideration as patients would not be expected to receive continuous erenumab treatment in the long-term. In summary, it is inappropriate to include the impact of treatment waning in the cost-effectiveness analysis, as patients will only continue to receive erenumab and incur erenumab treatment costs if they continue to respond to (i.e. benefit from) treatment, and this is currently reflected in the cost-effectiveness analysis. ***Conclusions*** In conclusion, Novartis believes that the combined evidence available from long-term follow up and pharmacokinetic studies of erenumab support the assumption that there is no waning effect with long-term treatment with erenumab. This assumption is also supported by the acceptance of an absence of a waning effect in the appraisals for biologics in other chronic non-progressive diseases, which have had a similar duration of long-term follow-up data and similar supporting data from pharmacokinetic studies.[7-9] Novartis does not believe that treatment waning is applicable. However, in response to clarification questions Novartis provided a scenario analysis exploring long-term effectiveness by reducing linearly over time the health state costs and health state utilities for erenumab and botulinum toxin, to reflect the health state costs and health state utilities associated with BSC non-responders. In this scenario, treatment waning was applied from 12 weeks. However, with more time to reflect on this issue, and given that Novartis has provided longer-term data which shows that treatment benefit of erenumab is maintained over 1 year in open-label studies (52/64 weeks; see ACD response document point 3), applying treatment waning from 12 weeks does not, in hindsight, accurately reflect the available evidence base. Therefore, we have provided alternative waning scenarios applying the treatment waning beginning from year 5, to further explore alternative treatment waning assumptions. This is in line with appraisals in the progressive disease multiple sclerosis where waning was applied after 5 years treatment. In the context of the discussion above, Novartis does not believe a treatment waning effect should be applied however it considers that if a waning effect is incorporated to explore any remaining uncertainty, then anything less than a 5 year treatment effect followed by 10 years of waning would be inappropriate based on the clinical evidence and HTA case precedent. An updated scenario analysis, which incorporates this waning scenario is presented in the Appendix document. **Novartis request:** We request that the Committee reconsiders the assumptions regarding waning in light of the long-term clinical data for erenumab, the body of evidence from pharmacokinetic studies, the precedent set by previous NICE appraisals of biologics in non-progressive indications, and the fact that (i) the model discontinuation rate already accounts for the potential of some loss of efficacy and (ii) waning is not relevant as a consideration if patients are not expected to receive continuous erenumab treatment in the long-term.
4	**Results of the indirect treatment comparison between erenumab and botulinum toxin should be used in evaluating the cost-effectiveness of erenumab in the chronic migraine population** The Committee requested the results of "a scenario in the economic modelling in which erenumab and botulinum toxin type A are considered to have similar effectiveness".

	The results of cost-effectiveness analyses in which erenumab and botulinum toxin are considered to have equal efficacy are provided in the Appendix. It must be noted that this is an extreme scenario analysis and these results represent an unrealistic and highly conservative estimate of the incremental cost-effectiveness of erenumab versus botulinum toxin. They are presented solely to illustrate the sensitivity of changes to the odds ratio assumption. Whilst Novartis acknowledges the limitations of the indirect treatment comparison presented in Section B.2.8.2 of the company submission, erenumab was associated with a numerical benefit versus botulinum toxin for all outcomes assessed, meaning that these results are suggestive of a clinical benefit of erenumab versus botulinum toxin, and that cost-effectiveness results assuming equal efficacy as presented in the Appendix should be interpreted as highly conservative. Limits of statistical significance are arbitrary, and as stated in Claxton *et al*., "decisions should be based only on the mean net benefits irrespective of whether differences are statistically significant", with failure to do so by "accepting the arbitrary rules of inference" imposing costs in terms of resources or health benefits foregone.[15] This is supported by the precedent for considering results of indirect treatment comparisons despite lack of statistical significance, such as the appraisal for ocrelizumab in relapsing-remitting multiple sclerosis in which the Committee accepted a cost-effectiveness model informed by the results of a network meta-analysis in which the differences between treatments were not statistically significant.[14] Furthermore, while the benefits of erenumab in 5 RCTs were consistent across the full spectrum of migraine (EM and CM), 7 randomised studies of botulinum toxin versus placebo failed to show a significant benefit for patients in EM. In addition, outside of direct efficacy benefits as evaluated by any indirect comparison, erenumab is also associated with further benefits versus botulinum toxin. This notably includes the reduced burden of administration and benefits to service capacity. As discussed in the company submission (Section B.1.2.2), botulinum toxin requires frequent intramuscular injections, which place a high burden on patients, clinicians and healthcare resources.[16] In contrast, erenumab is self-administered subcutaneously, providing a treatment option that is significantly easier for patients, and less burdensome on the NHS than botulinum toxin. As discussed in Document B of the company submission, Section B.3.4.4, and Appendix U.2, the results of a time trade-off study have indicated that the administration of botulinum toxin results in a considerable utility decrement relative to erenumab; this was not acknowledged or discussed by the Committee during the Committee meeting or in the ACD. The scenario which incorporated the disutility associated with the mode of administration of erenumab and botulinum toxin is presented again in the Appendix. A further benefit of erenumab versus botulinum toxin is the earlier timepoint for assessment of response (3 months with erenumab versus 6 months with botulinum toxin). This allows non-responders to be identified after a shorter time period with erenumab, meaning that ineffective treatment can be discontinued earlier in these patients. In light of the evidence which suggests there is some clinical benefit of erenumab versus botulinum toxin, Novartis also present results in the Appendix whereby the difference between the two treatments represents a midpoint between the odds ratio of the ITC (Section B.2.8.2 of the company submission), and an odds ratio of 1 (an assumption of equal efficacy, as per the Committee-requested scenario analysis). **Novartis request:** We request that the results of the extreme scenario in which erenumab and botulinum toxin are modelled to have equal efficacy are considered as highly conservative and unlikely to reflect clinical reality, and viewed in the context that they do not capture all benefits of erenumab over botulinum toxin, as outlined below: [redacted]

	• Erenumab offers a reduced burden of administration compared to botulinum toxin and this has been confirmed by headache specialists. Erenumab is therefore significantly easier for patients and will reduce the burden of treatment for clinicians. This is captured as a resource use in the cost-effectiveness analysis • Erenumab will alleviate the substantial burden imposed by botulinum toxin on patients, which is a benefit not captured in the cost-effectiveness analysis Erenumab offers the potential to provide access to treatment for a patient population with a high unmet need, given the reduced administration requirements compared to botulinum toxin
5	**Inclusion of a fourth oral preventive treatment as a comparator to erenumab is not reflective of clinical practice and is inconsistent with NICE's previous view on the migraine treatment pathway** The ACD states that "a fourth oral preventive treatment would also be a relevant comparator for erenumab". It is suggested that "botulinum toxin type A or another oral preventive treatment [are] the relevant comparators in chronic migraine, and that another oral preventive treatment or best supportive care [are] the relevant comparators in episodic migraine". Novartis does not believe that a fourth oral prophylactic accurately reflects the treatment pathway of patients with migraine in the UK managed by headache specialists, and hence is not a relevant comparator to erenumab under its expected positioning. Relevant comparators in the Novartis submission were based on combined consideration of clinical guidelines, feedback from UK neurologists and the precedent set by botulinum toxin in chronic migraine, which together indicate that a fourth oral prophylactic does not represent an appropriate comparator for this appraisal.[16] As per the positive recommendation resulting from the NICE appraisal for botulinum toxin in the treatment for chronic migraine (TA260), botulinum toxin is recommended in patients with chronic migraine for whom ≥3 prophylactic treatments have failed. Botulinum toxin is therefore a direct comparator for patients with chronic migraine for whom ≥3 prophylactic treatments have failed.[16] In the appraisal for botulinum toxin, "standard management", comprising rescue medications such as analgesics, was accepted as the single relevant comparator in the population of patients with chronic migraine for whom ≥3 prophylactic treatments have failed. As TA260 is the only previous NICE appraisal in this disease area, this establishes the precedent that there are no further prophylactic treatment options available for chronic migraine patients for whom ≥3 prior prophylactic treatments have failed at the time of this appraisal.[16] To consider a fourth oral prophylactic as a relevant comparator for the chronic migraine population is therefore to imply that there has been a change in the treatment pathway since the appraisal of botulinum toxin as part of TA260 in 2012. Consideration of the relevant comparator in the botulinum toxin appraisal was informed by the 2012 NICE clinical guideline for the diagnosis and management of headaches in over 12's (CG150). This guideline has not been updated since the publication of the guidance for botulinum toxin in chronic migraine; therefore, CG150 continues to be the relevant guideline for assessing current clinical practice. It should be further noted that this guideline does not distinguish between chronic and episodic migraine, and therefore provides the appropriate reference guideline for considering both the chronic migraine population and the high frequency episodic migraine population; with the exception of the recommendation of botulinum toxin for chronic migraine patients as per TA260, the treatment pathway for patients with chronic and high frequency episodic migraine is the same in current clinical practice.[16, 17]. CG150 provides clear recommendations for use of oral prophylactic treatment, and states that topiramate, propranolol and amitriptyline should be considered as treatment options.[17] This guideline does not recommend any other therapies as options for the prophylactic treatment of migraine, and therefore clearly establishes that these three oral prophylactics are the only recommended

	current treatments in both the episodic and chronic migraine pathway, supporting that there are no further recommended oral prophylactics for patients in whom ≥3 prophylactic treatments have failed. Feedback from headache expert neurologists collected in 2017 has stated that clinical practice has been largely unchanged for several years, confirming the ongoing relevance of CG150 and hence the relevance of the precedent set by the appraisal for botulinum toxin in terms of comparators, which can be considered relevant both for the chronic migraine setting and the high frequency episodic migraine setting.[18] This is supported by the most recent surveillance update for CG150, conducted in 2016, which sought to identify clinical and cost-effectiveness evidence for other prophylactic treatments in chronic and episodic migraine, including antidepressants, beta blockers and calcium channel blockers.[19] As discussed in the company submission, Document B, Section B.1.1.2, the current options for the prophylactic treatment for migraine (topiramate, propranolol and amitriptyline) have been in use for many years, and there has been little research into the safety and efficacy of these treatments since the publication of the original guidelines in 2012. The authors of this surveillance update concluded that new evidence was unlikely to change guideline recommendations, confirming the continued relevance of topiramate, propranolol and amitriptyline alone as the key prophylactic therapies for patients with migraine.[19] In the context of the lack of evidence for efficacy and safety of these treatments, use of a fourth oral prophylactic treatment would be poor practice from a patient quality of life perspective, requiring headache specialists in practice to prescribe ineffective interventions, unsupported by evidence, that may be associated with considerable side effects. Importantly, no oral prophylactic therapies have been licensed for the treatment of patients with migraine as a fourth oral prophylactic, and there is no high-quality clinical evidence to support the efficacy of a potential fourth-line prophylactic treatment. As such, it would be inappropriate and methodologically impossible to conduct a robust indirect treatment comparison to consider the cost-effectiveness of erenumab versus a fourth oral prophylactic therapy for the population of patients for whom ≥3 prophylactic treatments have failed. In summary, there has been no change in the treatment pathway for episodic migraine or chronic migraine since the appraisal of botulinum toxin, as supported by expert headache neurologist feedback and the surveillance update to CG150. Furthermore, there is no robust evidence to support the safety and efficacy of a fourth oral prophylactic treatment in patients with migraine. As such, botulinum toxin is the relevant comparator in the chronic migraine population as per the NICE appraisal TA260, and best supportive care, defined by continued treatment with acute medication and healthcare resource use in line with the monthly migraine days experienced, is the relevant treatment comparator to erenumab for high frequency episodic migraine patients for whom ≥3 prophylactic treatments have failed.[16] **Novartis request:** We request that the Committee accepts botulinum toxin as the relevant comparator for erenumab in the population of patients with chronic migraine for whom ≥3 prophylactic treatments have failed, and best supportive care as the relevant comparator for erenumab in the population of patients with high frequency episodic migraine for whom ≥3 prophylactic treatments have failed, based on NICE HTA precedent and the NICE Clinical Guideline.

6	**Inclusion of additional service set-up in the cost-effectiveness analysis is inappropriate and not reflective of the service implications related to the introduction of erenumab** The ACD states that "additional resources would likely be needed, and that the cost of setting up these additional services should be accounted for in the economic model". This refers to an anticipated requirement for initiation and additional monitoring within secondary care specialist headache clinics with the use of erenumab. Erenumab is expected to be initiated by headache specialists experienced in the diagnosis and management of migraine in the NHS, in accordance with the summary of product characteristics which states that "treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine". However, subsequent to this initiation, erenumab can be self-administered (as per the summary of product characteristics); it is anticipated that ultimately subsequent administration of erenumab and follow-up will therefore not require specialist services and that ongoing treatment with erenumab will therefore place a much lower burden on specialist services compared to botulinum toxin. Furthermore, as a self-administered treatment, erenumab directly supports the NHS's long-term focus on promoting patient self-care and self-management, as set out in the most recent NHS Long Term Plan in 2019.[20] Insight from headache specialist with experience in setting up headache specialist service was missing from the Committee discussions. There is the possibility that whilst clinicians gain experience in the use of erenumab there may be a requirement for specialist follow-up beyond the initiation of treatment for patients being treated with erenumab; however, such follow-up would involve a straightforward evaluation of a patients' response to erenumab, and it is likely that such follow-up could take place through telephone or video conference, or via a nurse. Furthermore, it is important to note that the patient population considered in the revised cost-effectiveness analyses (patients with chronic and high frequency episodic migraine for whom ≥3 prior prophylactic treatments have failed) are likely to be managed within headache specialist services already. In addition, the reduction of migraine days in responders to erenumab within these patient populations would be likely to result in a reduced number of unscheduled physician visits and emergency room visits (see Table 58 of the company submission for data supporting resource use associated with migraine frequency). This would contribute towards alleviating the burden of migraine on the healthcare system. Therefore, the introduction of erenumab is not anticipated to lead to a substantial increase in the requirement for specialist headache services or the need to establish a specialist service where none currently exists and may help alleviate pressure on existing services over time. As discussed in the company submission (Section B.1.2.2), treatment with botulinum toxin, which has been recommended for the treatment of patients with chronic migraine for whom ≥3 prophylactic treatments have failed, involves intramuscular injections to between 31 and 39 sites in the head and the back of the neck every 12 weeks, which must be performed by a trained specialist.[16] Treatment with botulinum toxin therefore requires in excess of four appointments with specialist services per year, placing a substantial burden on headache services. Once clinical experience with erenumab has developed and specialist services are only required for patient initiation on erenumab, introduction of erenumab would therefore be expected to reduce the burden of migraine treatment compared to that of botulinum toxin by 3–4 specialist appointments per patient per year. This would have a considerable impact on the lives of patients currently receiving treatment with botulinum toxin, who may have to travel long distances to attend one of the few clinics that currently administers this treatment. In freeing up space within clinics, this also has the potential to reduce the length of time patients currently have to wait to access life-changing treatment, as the high administrative burden means that waiting lists for botulinum toxin are lengthy. Accordingly, the introduction of erenumab would not only save resource for the NHS compared to the current use of botulinum toxin but would also bring potential benefits in terms of capacity pressure release.

	Furthermore, healthcare professionals must undertake lengthy training in how to initiate patients on botulinum toxin due to its administration requirements, which limits the capacity within clinics. This lengthy training is not required for specialists initiating patients on erenumab; with erenumab, any member of staff within headache clinics will be able to perform the initial training. The above considerations have been supported by feedback from advisory boards and a recent meeting with 3 healthcare professionals in England experienced in the management of migraine, who have stated that they do not believe that there would be any additional service set-up or maintenance costs associated with the use of erenumab, and that the use of this treatment would be less burdensome than botulinum toxin and would allow their services to run more efficiently. In summary, it is not anticipated that erenumab will increase the requirement for specialist headache services, as it is likely that the majority of patients with chronic and high frequency episodic migraine will already be managed within secondary services. Furthermore, the reduced administration requirements for erenumab versus botulinum toxin are expected to lead to substantial resource *savings*. The introduction of erenumab would also directly support the NHS's long-term focus on promoting self-care and management.[20] Finally, erenumab would bring substantial benefits to patients, who would have access to a treatment which is considerably less burdensome than botulinum toxin. This burden encompasses not only the treatment itself, which consists of a single, self-administered subcutaneous injection for erenumab versus multiple unpleasant injections to the head and neck for botulinum toxin, but also the time and financial burden resulting from the requirement for patients to travel to clinics – often covering long distances – for frequent treatment with botulinum toxin, which will not be necessary for erenumab. **Novartis request:** The cost of additional services is not relevant to this appraisal and should not be incorporated into the economic model.
7	**<u>The ACD does not acknowledge the magnitude of the clinical benefit for patients who respond to erenumab</u>** Whilst Novartis is pleased the clinical benefit of erenumab has been recognised, it is important that the magnitude of the clinical benefit gained for responder patients is understood, as this was not discussed at the Committee meeting. The difference in monthly migraine days between responders and non-responders is provided in the response to Clarification Question B12 (response status defined on the basis of ≥50% reduction from baseline in MMDs, as per the response definition used of the cost-effectiveness analysis). In patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed, responders treated with erenumab 70 mg and 140 mg had [redacted] and [redacted] monthly migraine days at 12 weeks, compared to [redacted] and [redacted] days for non-responders, respectively. Similarly, a pooled analysis of STRIVE, ARISE and LIBERTY demonstrated that responders treated with erenumab 70 mg and 140 mg, respectively, had mean monthly migraine days at 12 weeks of [redacted] and [redacted] days, respectively, compared to [redacted] and [redacted] days for non-responders. This demonstrates the substantial benefit which can be attained by patients treated with erenumab who respond to treatment, which is masked when considering outcomes from clinical trials for the entire study population, including non-responders. In clinical practice, non-responders would discontinue treatment: as per the Summary of Product Characteristics for erenumab, "clinical studies have demonstrated that the majority of patients responding to therapy showed clinical benefit within 3 months" and therefore "consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment". Patients who continued treatment would be those who have responded to therapy within 3 months, and would therefore be expected to experience important clinical benefits; a one-day reduction in monthly migraine days is considered to be the minimally important difference, a value which is far exceeded by responders to erenumab.[24]

	Novartis request: We request that the ACD includes a statement that acknowledges the substantial clinical benefit of treatment with erenumab for patients who do respond to treatment.
8	**The ACD does not take into account the strength of the clinical evidence for erenumab in the chronic migraine population** The ACD states that "given the uncertainty in the clinical evidence and utility values, an acceptable ICER would be around £20,000 per QALY gained". Novartis does not believe this statement is an accurate reflection of the clinical evidence in the population of patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed. Clinical evidence for erenumab in this subgroup is provided by Study 295, which was a large, high-quality, randomised, double-blind, placebo-controlled trial of erenumab in 667 patients with chronic migraine. As discussed in the company submission, Document B, Section B.2.6.1, erenumab demonstrated statistically significant benefits versus placebo in the subgroup of patients for whom ≥3 prior prophylactic treatments have failed. Patients treated with erenumab 140 mg achieved statistically significant reductions in mean monthly migraine days from baseline to Week 12 compared to placebo (difference: −4.09 [95% confidence interval: −5.84, −2.33; p<0.001]). In total, 38.5% of patients in the erenumab 140 mg arm achieved a ≥50% reduction in monthly migraine days from baseline, compared to 15.3% of patients in the placebo arm, which corresponded to an odds ratio of 3.48 (95% CI: 1.64, 7.39; p=0.001). Patients treated with erenumab 140 mg also achieved significantly superior outcomes versus placebo for several other outcomes, including the change in the monthly severity of migraine pain, and change in monthly headache days, highlighting the consistency of the observed benefit. Accordingly, we believe that the statement claiming that there is uncertainty over the clinical evidence for erenumab provides a misleading interpretation of the data supporting the efficacy of erenumab in the population of patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed. **Novartis request:** We request that the Committee interprets the cost-effectiveness results presented in the Appendix document with reference to the strength of the clinical evidence in the population of patients with chronic migraine for whom ≥3 prior prophylactic treatments have failed. On this basis, in chronic migraine, we believe that a cost-effectiveness threshold of greater than £20,000 per QALY is appropriate.
9	**Technical correction to the description of the indirect treatment comparison** Section 3.9 of the ACD refers to the output of the indirect treatment comparison as a hazard ratio. The relative effectiveness statistic produced by the indirect treatment comparison is an odds ratio, not a hazard ratio. The wording should therefore be adapted accordingly for technical correctness.

Insert extra rows as needed

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Erenumab for preventing migraine [ID1188]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 31 January 2019 **email:** TACommD@nice.org.uk/NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Migraine Trust
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Erenumab for preventing migraine [ID1188]

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Example 1	We are concerned that this recommendation may imply that ……..
1	The costs for erenumab would be expected to be cheaper as the doses are self administered and no cost for a health professional to inject 31 sites as in Botox
2	Self administration of the treatment allows the patient a sense of control. This feeling of control should not be underestimated as to how important this is to the patient.
3	The Migraine Trust understands that nothing works for everybody, but we are aware that people on the trials of this drug saw real benefits. The side effect profile is good and many people were able to resume living and working normally as opposed to being on sick leave and unable to take part in family life.
4	The cost to society of people unable to work is huge. Access to a treatment that works for them benefits everybody. For these reasons the provisional recommendations are not sound.
5	The preliminary recommendations discriminate against women. Three times more women than men experience migraine. Migraine generally affects sufferers in their most productive years.
6	In some circumstances chronic migraine can be classed as a disability. To deny people the chance to contribute more to society is simply unfair.

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Migraine Trust
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have been on advisory boards and received funding to attend conferences from Novartis and Teva.
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	There is an unmet need for better treatments for patients with treatment resistant migraine. There is evidence that erenumab can be effective in some patients who have not had a good response or cannot tolerate (3 or more) preventatives. Tolerability is a major problem amongst migraineurs and in the literature and in our limited experience using it in the FOC scheme erenumab is well tolerated. I cannot comment on long term tolerabilty
2	With regards to set up costs, after the first/ second injection they can self-administer. Botox requires a 3 monthly hospital attendance (time off work etc) and a trained clinician to administer.
3	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Neurologists Advisory Group on headache and pain
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Has all of the relevant evidence been taken into account?** Yes, all currently available peer reviewed trials have been included in the analysis
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, however: A. There is no currently available phase 3 trial evidence for chronic migraine B. The trials do not completely reflect the expected patient cohort who may receive erenumab in the UK: i) 2 of the published phase 3 trials of episodic migraine ('ARISE' and 'STRIVE') excluded those who had no therapeutic response to more than 2 classes of migraine preventative treatment, only the smaller phase 3 trial 'LIBERTY' included patients who had previously failed 2-4 preventative treatments, whereas in practice we expect eligibility criteria for erenumab to be in line with Botulinum toxin therapy ie failure of at least 3 previous migraine preventative drugs ii) patients were excluded from the phase 3 trials if they had co-morbid psychiatric disease, whereas in real life the frequency of depression and anxiety is high in chronic migraine populations and should not be basis for exclusion C. The duration of treatment and waning effect of utility over time is uncertain. The general standard of care with migraine preventative treatments is that if migraine is well controlled on a given preventative agent for 6-12 months then treatment is re-evaluated and often withdrawn usually without immediate return to former state. If a patient requires longer term use we would certainly advocate re-evaluation of need for treatment at least every 18 months. The cost-effectiveness model presented assumes that longer term treatment would be the standard of care. However, we are aware that there are no long-term studies supporting continued benefit after cessation of successful treatment D. We agree that it is appropriate to consider the 70mg and 140mg dose separately, not as a 'blended' dose
3	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Whilst the committee recommendations may reflect the mean response of the patient population to erenumab, the data support the concept that there is a cohort of patients who have an exceptional response with, in some cases, a 75-100% reduction in mean monthly migraine days and a significantly improved quality of life. It may be appropriate to evaluate this group of responders separately and consider a 2-3 month clinical trial of erenumab appropriate to determine the level of response.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association for the Study of Headache
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Has all of the relevant evidence been taken into account?** Yes
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** BASH would like to make the following comments: 1. The Phase III trials STRIVE, ARISE and LIBERTY are for episodic migraine. The trial 295 for chronic migraine is Phase IIb. There are no published phase III studies in chronic migraine. 2. Whilst the reduction of monthly migraine days is the standard outcome measure for clinical trials in migraine, the 50% (and where available 75% and 100% responder rates) are a truer reflection of the efficacy of treatments in everyday clinical practice. 3. The 50% responder rate for Erenumab in Chronic Migraine Study (295) is 38.5% (140 mg) and 34.8% (70mg) compared to placebo 15.3%. The comparable figures for OnabotulinumtoxinA are 48% versus 36%. The therapeutic gain versus placebo, especially at the higher 140 mg dose, is therefore very significantly greater than for onabotulinumtoxinA. Moreover, patients receiving onabotulinumtoxinA are required to attend the out-patient clinics in secondary or tertiary care centres up to 5 times a year, and are given 31 injections by the treating physician/specialist nurse. 4. There is no direct comparison for onabotulinumtoxinA and Erenumab, however, direct comparison for any new treatment is rarely available. The best comparator for new therapy is best supportive care. Hence for the purpose of recommendation the committee should consider Erenumab in the standard manner that was used when considering the cost effectiveness of onabotulinumtoxinA, i.e. versus best supportive care. 5. There has been no significant change in standard clinical practice with regard to the use of oral preventive medication since the publication of NICE guidance on the management of headaches (CG 150), and on the use of onabotulinumtoxinA (TA 260), both of which are based on the accepted clinical practice that after three failures with oral preventives, patients are unlikely to respond to further oral treatment, and should be offered alternative effective treatments at that point. It is not appropriate to consider use of a 4th oral agent as a comparator due to the side effect profile and poor tolerability of oral preventives beyond the two first line agents of beta-blockers and amitriptyline. 6. The decision to use new treatments such as onabotulinumtoxinA after failure of three treatments is not evidence based. In PREEMPT trial a third of patients never received prophylaxis and others had failed one or two treatment, yet recommendations were to recommend following failure of three treatments. Such recommendations were based on economic modelling rather than clinical trial evidence as the cost of the new treatments is very high.

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	7. ARISE and STRIVE excluded those who had no therapeutic response to more than 2 classes of migraine preventive treatment, but it is standard practice in randomised control trials to exclude very refractory populations, and the decision to recommend in refractory population is need-based, not evidence-based. To consider that Erenumab is given to those that have failed three treatments is not unreasonable, as a high cost treatment will thereby only be made available to a small refractory patient population. 8. Medication overuse is not seen in patients with episodic migraine as they are more likely to be suffering from chronic migraine. Patients with Chronic Migraine and medication overuse were not excluded from the trial (295). 9. We agree that there is lack of data confirming long term effectiveness, although this applies to any new high cost drug. Real life data remains the only source of such information and that can only be available once a recommendation is made to treat a limited refractory population, based on cost effectiveness. 10. We feel the committee will have to make reasonable assumption for duration of treatment in chronic migraine based on the data with existing prophylactic agents. We suggest the treatment should be stopped if there is no response at three months (negative stopping rule). Most prophylactic agents are required for 6-18 months, with only a small proportion of patients continuing treatment for longer duration. Duration of treatment of two years would be reasonable for modelling purposes, and the treatment could be stopped earlier if the patient is successfully converted to a low frequency episodic migraine (positive stopping rule). 11. We agree that there are no long term studies on any agent for continuing benefit, nor there is any data for relapse after cessation of successful treatment.
3	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The draft recommendation will deprive a potentially effective treatment to a highly disabled population with chronic migraine who have failed three first line treatments (or four, including onabotulinumtoxinA or have not been able to tolerate some or all of these treatments. A 3 month trial of Erenumab in such patients would be highly appropriate before considering more invasive and expensive treatment options such as intravenous dihydroergotamine, occipital nerve stimulation or even some of the non-invasive neuromodulation therapies that have limited NICE recommendations without mandatory funding.
4	
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Allergan Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Allergan welcomes the opportunity to respond to the Appraisal Consultation Document for erenumab for migraine. In this response, we will focus specifically on chronic migraine, for which our product BOTOX® (onabotulinumtoxinA) is licensed and recommended by NICE, and is therefore a comparator in this appraisal. (On a point of terminology, we will refer here to onabotulinumtoxinA rather than botulinum toxin A, which is NICE's preferred usage, but a generic term that is not specific to BOTOX®. It should be understood that all references to data in what follows are specifically for onabotulinumtoxinA [i.e. BOTOX®], and that it is the only botulinum toxin product licensed for the treatment of chronic migraine.) Allergan Response – Key Points • **Allergan concurs with the Committee's assessment that the long-term effectiveness of erenumab is uncertain. In contrast, the long-term effectiveness of onabotulinumtoxinA has been demonstrated extensively in both clinical trials and real-world settings.** • **Allergan concurs with the Committee's assessment that there is no robust evidence that erenumab is more clinically effective than onabotulinumtoxinA.** • **We agree with the Committee's assessment that erenumab is unlikely to be cost effective compared to onabotulinumtoxinA for chronic migraine patients who have failed at least three prior preventive treatments. We note that this is consistent with the view reached in other international health technology assessments of erenumab, including a recent review by the Institute for Clinical and Economic Research (ICER) in the United States.** • **Allergan believes that the economic evidence provided to the Committee underestimates the degree of uncertainty regarding the cost-effectiveness of erenumab compared to onabotulinumtoxinA, and that the range of the cost per QALY gained is likely to be substantially higher than the estimates in the Appraisal Consultation Document.** We believe that it would be of most assistance to the Committee if we concentrate this response on the substantial body of evidence that exists to support both the long-term effectiveness and safety of onabotulinumtoxinA for chronic migraine. We note that, while it was argued during the Appraisal Committee meeting that there is a significant unmet need for erenumab, and that this argument in part rests upon what are supposed to be difficulties for patients getting access to onabotulinumtoxinA, this argument has not been endorsed in these terms in the ACD. Allergan agrees with the Committee that effective and well-tolerated treatment options are needed and, as our response below shows, onabotulinumtoxinA meets these criteria so far as chronic migraine is concerned. We

	further acknowledge that onabotulinumtoxinA must be administered by properly trained practitioners who either are, or who operate under the supervision of, a neurologist or headache specialist. There are, however, a large number of centres across the UK where onabotulinumtoxinA is administered for chronic migraine and service capacity continues to expand. Allergan is also working with the NHS to increase capacity and access for patients, recently concluding, for example, two Joint Working Agreements, one at the Salford Royal Hospital and the other at University Hospital Birmingham, both with this intent. The studies summarised in this response comprise a total of over 5,600 patients (including over 1,200 from the UK) treated with onabotulinumtoxinA with up to five years of patient exposure. **They show that the clinical efficacy of onabotulinumtoxinA is sustained or improved in patients over an extended period of treatment, as well as that the product is generally safe and well-tolerated. Additionally, HRQoL (measured by HIT-6 [Headache Impact Test], MSQ [Migraine-Specific Quality-of-Life questionnaire] and EQ-5D [EuroQol five-dimensional questionnaire]) and work productivity were improved following onabotulinumtoxinA treatment in clinical trials and observational studies**.[1–8] The evidence for the long-term effectiveness and safety of onabotulinumtoxinA in chronic migraine comes principally (though not exclusively) from the following sources: • A prospective analysis of a total of over 650 CM patients treated by the Hull Migraine Clinic going back to 2010 and providing data for patients in some cases treated for as long as two years (n=508) and as long as five years (n=211).[8–11] • Two-year data from the prospective observational REPOSE study, involving over 600 patients in seven European countries, including 94 from the UK.[5,12] • Two-year data from the Phase IV long-term open label prospective COMPEL study, involving over 700 patients in the USA, Australia and Korea.[13] • Two-year data from a prospective observational study of 275 patients treated at the Sant Andrea Hospital in Italy between 2010 and 2015.[14,15] These data are in addition to those reported in the two pivotal randomised control trials for onabotulinumtoxinA in chronic migraine (PREEMPT 1 and PREEMPT 2) that together provide data for a further 1,384 patients up to 56 weeks.[16] The CM-PASS study further demonstrates the safety of onabotulinumtoxinA over 52 weeks, involving over 1100 patients, including 422 from the UK; no efficacy data were collected in this study.[17] **A summary of the key characteristics and findings from the trials and studies relevant to this response is set out in tabular form in the attached appendix.** It may be helpful to refer the Committee to the recent ADIS drug evaluation[18] in which the long-term effectiveness and safety of onabotulinumtoxinA for the prevention of chronic migraine have been summarised. The studies covered in this review include the PREEMPT programme[16,19,20]; the CM-PASS study[17]; the multinational, open-label COMPEL trial (N=715, 108 weeks of follow up)[13]; the multinational, post-authorization REPOSE study

(N=641, 2 years of follow up)[5]; as well as observational studies at the Hull Migraine Clinic,[8] Sant Andrea Hospital in Italy (N=275, 2 years of follow up),[14,15] and a multicentre study in Spain (N=725, 1 year of follow up).[21] The authors of the ADIS paper conclude that "the totality of evidence from clinical trials and real-world studies indicates that [onabotulinumtoxinA] is an effective and generally well-tolerated option for the prevention of CM that may be particularly useful for patients who have previously failed to respond to or are intolerant of commonly prescribed oral prophylactics."[18]

Studies and analysis carried out at the Hull Migraine Clinic since 2010[8,9] provide the largest consolidated source of UK real-world evidence for the effect of onabotulinumtoxinA in CM prophylaxis, and results extend for up to five years of treatment. In this dataset, all patients had failed at least three prior preventive treatments, except for 14 patients who initiated treatment before the NICE guidance came into effect in 2012.[8] This makes the evidence from Hull particularly relevant to the decision problem in this appraisal.

In the Hull studies, onabotulinumtoxinA treatment was stopped if there was no response after two consecutive cycles (response being defined as at least a 50% reduction in headache days, a 50% reduction in migraine days, or a 2-fold increase in the number of crystal clear [headache free] days to at least six crystal clear days per month).[8,9] Patients who met the initial criteria for response were also permitted to stop treatment if their condition converted to episodic migraine, defined as less than 10 headache days for three consecutive months (Hull modified positive stopping rule), and to recommence treatment if they relapsed to chronic migraine (more than 15 headache days for at least three consecutive months).

The sustained benefit of onabotulinumtoxinA is clearly evident:

- In a three-year analysis, a majority of patients (66%) demonstrated a response in at least one of the endpoints, i.e., at least a 50% reduction in headache days, a 50% reduction in migraine days, or a 2-fold increase in the number of crystal clear days to at least six crystal clear days per month.[8] The results of a more recent analysis of 687 patients treated over a seven-year period were generally consistent with the earlier results.[9]

- In 294 patients with an initial response to onabotulinumtoxinA, 87.4% (n = 257) experienced a successful treatment response over two years of follow up, i.e., were either still on treatment or had successfully withdrawn treatment without relapse to chronic migraine.[10]

- Over five years of follow up, 80.2% (n = 101) of initial responders (N = 126) experienced a successful treatment response, i.e., were either still on treatment or had successfully withdrawn treatment without relapse to chronic migraine.[11]

- In all these analyses, the most common adverse events were consistent with the known safety profile for onabotulinumtoxinA.[8,9]

	OnabotulinumtoxinA was originally licensed on the basis of data from two phase III studies (PREEMPT 1[19] and PREEMPT 2[20]). In these pivotal studies, onabotulinumtoxinA was generally well tolerated and effective in producing statistically significant and clinically meaningful improvements in headache symptoms, acute headache pain medication usage, headache impact and health-related quality of life in adults with CM. Pooled analyses of the PREEMPT studies demonstrated that patients who received five treatment cycles of onabotulinumtoxinA experienced improvement in all efficacy endpoints between the end of the double-blind phase (week 24, two treatment cycles) and the end of the open-label phase (week 56, five treatment cycles), as well as statistically significantly greater reductions in headache days and migraine days from baseline to week 56 than patients who received three cycles of treatment during the open-label phase.[16] One third of patients in these trials had not responded to ≥ 3 prior oral preventive therapies.[22] The findings from the PREEMPT programme have been both confirmed and extended by the results of a long-term phase IV study (COMPEL),[13] in which patients received up to nine treatment cycles over a period of 2 years, and by findings from several real-world clinical practice studies from Europe,[14,15,21,23–26] including the prospective multinational REPOSE[5] and CM-PASS[17] studies. Beyond confirming the PREEMPT programme findings, COMPEL assessed the impact of onabotulinumtoxinA on comorbid symptoms of anxiety, as measured by the Generalized Anxiety Disorder 7-item scale (GAD-7), and depression, as measured by the Patient Health Questionnaire (PHQ-9).[27] The presence of these comorbidities can exacerbate chronic migraine and increase migraine related burden in those already impacted; therefore, addressing and treating these common comorbidities is part of appropriate management for chronic migraine.[28–30] Findings demonstrated that onabotulinumtoxinA improved symptoms of depression and anxiety among those treated for chronic migraine. No new safety signals were identified in either COMPEL[13] or REPOSE,[5] while adverse events in the 52-week CM-PASS study (N=1160) were also consistent with the product label and the results of the PREEMPT trials.[17] In real-world studies conducted in clinical practice settings, adverse events were mild to moderate and transient,[14,15,21,23,24] and the most common types of adverse events were consistent with the known safety profile of onabotulinumtoxinA.[8,9,14,15,23–25] **In response to the question of whether the summaries of the clinical and cost effectiveness provide reasonable interpretations of the evidence, Allergan concurs with the Committee's assessment as follows:** • **The long-term effectiveness of erenumab is uncertain. In contrast, as described above, the long-term effectiveness of onabotulinumtoxinA has been demonstrated extensively in both clinical trials and real-world settings.** • **There is no robust evidence that erenumab is more clinically effective than onabotulinumtoxinA.** • **Due to the high uncertainty in the clinical evidence for the subgroup of interest and key model inputs, erenumab is unlikely to be cost effective compared to onabotulinumtoxinA for chronic migraine patients who have failed at least three prior preventive treatments.**

We further note that the Committee's assessment is consistent with the view reached in other international health technology assessments of erenumab, including a recent review by the Institute for Clinical and Economic Research (ICER) in the United States. ICER's view in summary is that there is insufficient evidence to demonstrate a net health benefit for erenumab compared with onabotulinumtoxinA.[31] Its review omitted a comparison between the two products from the primary cost-effectiveness analysis due to lack of sufficient evidence to demonstrate a net health benefit for erenumab compared to onabotulinumtoxinA.

We would also like to make a number of comments arising from our review of the manufacturer's economic model for this appraisal to which, as a commentator, we were granted temporary access, albeit in a heavily redacted form.

Based on this review, Allergan concurs with the Committee's feedback on the modelling approach, assumptions and data inputs which are discussed in the ACD. We also agree that, due to lack of long-term effectiveness data for erenumab, modelling long term treatment effects required a range of assumptions that contributed to considerable uncertainty of the model results. However, due to the extensive redaction of the model that obscured several important input parameter values it was impossible to verify the reliability of how the economic evaluation of erenumab vs. comparators was performed.

One key issue in the economic model is that in the scenario analyses that incorporate utility decrements for adverse events and method of administration, it is assumed that onabotulinumtoxinA patients have lower utility scores than placebo patients with equivalent monthly migraine days. This is contradicted by the evidence in the PREEMPT trials. These demonstrated that onabotulinumtoxinA patients had generally higher utility scores than placebo patients with equivalent monthly headache days.[32]

The PREEMPT trials also demonstrated that onabotulinumtoxinA had a statistically significant effect on headache severity compared to placebo. In a pooled analysis of the intent-to-treat population, onabotulinumtoxinA patients experienced a significantly lower proportion of headache days rated as severe and a significantly higher proportion of headache days rated as mild than placebo patients.[33,34] In a subgroup analysis of patients who failed to achieve at least a 50% reduction in headache days, onabotulinumtoxinA patients were significantly more likely than placebo patients to achieve at least a 1-grade improvement in the HIT-6 questionnaire item "When you have headaches, how often is the pain severe?"[35]

These assumptions regarding utility decrements are also inconsistent with the NICE guidance for onabotulinumtoxinA (TA260). The Committee took note of comments from consultees and commentators, and supportive data from a survey of chronic migraine patients in the UK, that onabotulinumtoxinA is associated with a range of benefits beyond the reduction in headache days. The Committee's preferred approach was to apply different utilities to onabotulinumtoxinA and placebo in the economic analysis, although there was considerable uncertainty regarding the degree to which differential utilities existed within each health state.[36] The US ICER review also incorporated a utility benefit for onabotulinumtoxinA into its economic analysis, based on the evidence of its beneficial effect on headache severity.[31,37]

Finally, Allergan notes that the cost-effectiveness analyses of erenumab compared to onabotulinumtoxinA submitted by the manufacturer and the Evidence Review Group did not

incorporate the evidence demonstrating the long-term effectiveness of onabotulinumtoxinA that has been published since the NICE guidance was issued in 2012 and which is summarised in this response. The scenarios explored in the economic analyses assumed that erenumab maintains higher effectiveness than onabotulinumtoxinA for anywhere from five years to a lifetime horizon, despite the absence of robust evidence demonstrating that erenumab is more clinically effective than onabotulinumtoxinA. **Therefore, Allergan believes that the economic evidence provided to the Committee underestimates the degree of uncertainty regarding the cost-effectiveness of erenumab compared to onabotulinumtoxinA, and that the range of the cost per QALY gained with erenumab is likely to be substantially higher than the estimates in the Appraisal Consultation Document.**

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Erenumab for preventing migraine [ID1188]

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Appendix to Allergan commentary in response to the NICE Appraisal Consultation Document Erenumab for preventing migraine [GID-TA10302]

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
PREEMPT 1 and PREEMPT 2 (NCT00156910 and NCT00168428)[1] Canada, Croatia, Germany, Switzerland, UK, USA	Two randomized, double-blind, placebo-controlled phase 3 trials, each followed by an open-label, single-treatment, onabotulinumtoxinA phase DB phase: 24 weeks OL phase: 32 weeks Total: 56 weeks	Adults meeting the ICHD-II diagnostic criteria for migraine (except "complicated migraine") with ≥15 headache days per month Randomized (N): O/O: 688 P/O: 696 Total: 1384 Enrolled in OL (N): O/O: 607 P/O: 629 Total: 1236	Age [mean (SD)] O/O: 41.1 (10.4) P/O: 41.5 (10.7) Female (%) O/O: 87.6 P/O: 85.2 Caucasian (%) O/O: 89.7 P/O: 90.5 Headache days per month [mean (SD)] O/O: 19.9 (3.7) P/O: 19.8 (3.7) Overuse of acute headache medication (%): O/O: 64.8 P/O: 66.1	Change in frequency of headache days [mean (95% CI)]: Baseline to week 24: O/O: −8.4 (−8.90, −7.92) P/O: −6.6 (−7.07, −6.08) Inter-group difference: −1.8 (−2.52, −1.13) P<0.001 Baseline to week 56: O/O: −11.7 (−12.17, −11.20) P/O: −10.8 (−11.32, −10.31) Inter-group difference: −0.9 (−1.53, −0.14) P=0.019 Change in frequency of migraine days [mean (95% CI)]: Baseline to week 24: O/O: −8.2 (−8.69, −7.70) P/O: −6.2 (−6.69, −5.68) Inter−group difference: −2.0 (−2.67, −1.27) P<0.001 Baseline to week 56: O/O: −11.2 (−11.71, −10.74) P/O: −10.3 (−10.82, −9.80) Inter-group difference: −0.9 (−1.52, −0.14) P=0.018	≥1 TEAE [n/N (%)] DB phase: O/O: 429/687 (62.4) P/O: 358/692 (51.7) OL phase (pooled): 703/1205 (58.3) ≥1 TRAE [n/N (%)] DB phase: O/O: 202/687 (29.4) P/O: 88/692 (12.7) OL phase (pooled): 245/1205 (20.3) ≥1 serious TRAE [n/N (%)] DB phase: O/O: 1/687 (0.1) P/O: 0/692 (0) OL phase (pooled): 1/1205 (0.1) Discontinuation due to AEs [n/N (%)]: DB phase: O/O: 26/687 (3.8) P/O: 8/692 (1.2) OL phase (pooled): 31/1205 (2.6)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
COMPEL (NCT01516892)[2] USA, Australia, Korea	open-label, single-arm prospective study Enrollment period: December 2011 – October 2013 Intervention phase: 108 weeks (up to 9 cycles of treatment)	Adults with a diagnosis of chronic migraine Safety population N=716 Intent-to-treat population N=715	Age [mean (SD)]: 43.0 (11.3) Female (%): 84.8 Caucasian (%): 81.3 Headache days per 28 days [mean (SD)]: 22.0 (4.8) Acute headache medication overuse (%): 63.7	Change from baseline in headache days per 28 days (mean): Week 24: −7.4 Week 60: −9.2 Week 84: −9.8 Week 108: −10.7 P<0.0001 for all comparisons with baseline Change from baseline in moderate/severe headache days per 28 days (mean): Week 24: −6.5 Week 60: −8.1 Week 84: −8.4 Week 108: −9.5 P<0.0001 for all comparisons with baseline	≥1 TEAE [n (%)]: 436 (60.9) ≥1 TRAE [n (%)]: 131 (18.3) ≥1 serious TRAE [n (%)]: 1 (0.1) Discontinued due to AEs [n (%)]: 25 (3.5) Incidence of AEs in patients who discontinued treatment [n (%)]: ≥1 TEAE: 32 (4.5) ≥1 TRAE: 13 (1.8)
CM-PASS (NCT01432379)[3] Germany, Sweden, Spain, UK	prospective, observational post-authorization study Observation period: 52 weeks	Chronic migraine patients receiving onabotulinumtoxinA Analysis population: N=1160 UK cohort: N=422	Age [mean (SD)]: 46.6 (11.8) Female (%): 84.2 Caucasian (%): 97.8 Medication overuse (%): 24.7	No efficacy data were collected	≥1 AE [n (%)]: 478 (41.2) ≥1 TRAE [n (%)]: 291 (25.1) ≥1 serious TRAE [n (%)]: 1 (<0.1) Discontinued due to AEs [n (%)]: 51 (4.4)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
REPOSE[4–6] Germany, Italy, Norway, Russia, Spain, Sweden, UK	prospective, non-interventional, observational, open-label study 2 years	Adults prescribed onabotulinumtoxinA for chronic migraine Received at least one dose of onabotulinumtoxinA: N=633 3499 total treatments administered	Age [mean (SD)]: 45.4 (12) Female (%): 85.3 Headache days (mean): 20.6	Change from baseline in headache days per month (mean): Treatment 1: −8.2 Treatment 2: −9.1 Treatment 4: −11.4 Treatment 6: −13.0 Treatment 8: −13.3 P<0.001 for all time points	≥1 AE [n/N (%)]: 116/633 (18.3) Most frequent (>2%) adverse events [n/N (%)]: Eyelid ptosis: 34/116 (5.4) Neck pain: 19/116 (3.0) Musculoskeletal stiffness: 17/116 (2.7)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Hull Migraine Clinic, 3-year study[7] UK	prospective observational study July 2010 – May 2013	Adult patients with chronic migraine treated with onabotulinumtoxinA Total treated with onabotulinumtoxinA: N=284 455 total treatment cycles Analysis population: N=254	Age [mean (range)]: Male: 58.6 (19–77) Female: 44.1 (19–91) Female (%): 78 Medication overuse [n/N (%)]: 122/242 (50.4) Failed prior migraine prophylaxis [n (%)] ≥1: 254 (100) ≥2: 252 (99.2) ≥3: 240 (94.5) Headache days [median (IQR)]: 27 (22, 30) Migraine days [median (IQR)]: 15 (10, 19)	Change from pre-treatment to post-treatment [median (95% CI)]: Headache days (n=254): −7 (−8, −5) Migraine days (n=254): −6 (−8, −5) Crystal clear days (n=254): 7 (5, 8) Mild days (n=254): −1 (−2, −1) Painkiller days (n=242): −3 (−4, −3) Triptan days (n=241): 0 (−1, 0) Days off work (n=58): −2 (−3, −1) HIT-6 score† (n=177): −9.7 (−11.0, −8.4) P<0.001 for all endpoints Response rates [n/N (%)]: Reduction in headache days: ≥30%: 118/254 (46.5) ≥50%: 80/254 (32) ≥75%: 36/254 (14) Reduction in migraine days: ≥50%: 128/254 (50) ≥75%: 58/254 (24) Increase in crystal clear days: ≥2-fold: 128/254 (50) ≥3-fold: 79/254 (31)	Adverse events observed [n (%)]: Pain at the site of injection for at least 24 hours: 38 (14.9) Neck stiffness: 37 (14.6) Ptosis: 28 (11) Reported but did not complain of inability to frown: 15 (5.9) Exacerbation of headache for five days: 11 (4.3) Difficulty in swallowing: 5 (1.96) Fainting during injection: 3 (1.2)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Hull Migraine Clinic, 7-year study[8,9] UK	prospective observational study July 2010 – December 2017	Adult patients with chronic migraine treated with onabotulinumtoxinA Total treated with onabotulinumtoxinA: N=796 4571 total treatment cycles Analysis population: N=687	Age, years [median (range)]: Male: 45 (14–79) Female: 45 (17–91) Female (%): 81.7 Failed 3 preventive treatments (%): 97.8 Medication overuse (%): 58.2 Duration of chronic migraine, years [median (range)]: 4 (0.5–67)	Change from pre-treatment to post-treatment [median (95% CI), P-value]: Headache days (n=687): −4 (−5, −4), P<0.001 Migraine days (n=687): −5 (−6, −5), P<0.001 Crystal clear days (n=687): 5 (4, 6), P<0.001 Mild days (n=687): 0 (−1, 0), P=0.06 Painkiller days (n=687): −3 (−4, −3), P<0.001 Triptan days (n=657): 0 (0, 0), P<0.001 Days off work (n=67): −2 (−2, −1), P<0.001 HIT-6 score† (n=596): −7 (−8, −6), P<0.001 Response rates [n/N (%)]: Reduction in headache days: ≥50%: 163/687 (24) ≥75%: 61/687 (9) Reduction in migraine days: ≥50%: 288/687 (42) ≥75%: 114/687 (17) Increase in crystal clear days: ≥2-fold: 281/687 (41) ≥3-fold: 169/687 (25)	≥1 AE [n (%)]: 88 (12.8) Adverse events observed [n (%)]: Neck stiffness: 88 (12.8) Pain at the site of injection for at least 24 hours: 83 (12) Ptosis: 52 (7.5) Reported but did not complain of inability to frown: 22 (3.2) Exacerbation of headache for five days: 22 (3.2) Difficulty in swallowing: 10 (1.5) Fainting during injection: 3 (0.4)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Hull Migraine Clinic, 7-year study: 2-year follow-up[10,11] UK	Prospective observational study July 2010 – December 2017 2-year follow-up period	Adult patients with chronic migraine treated with onabotulinumtoxinA, with treatment data for at least 2 years (24-60 months) Analysis population: N=508	100% of patients had failed at least one oral preventive migraine therapy	Initial response within 2 cycles of treatment [n (%)]: Non-responder: 214 (42.2) Responder (≥50% reduction in headache days or migraine days, or ≥2-fold increase in crystal-clear days): 294 (57.8) Responder per NICE criteria (≥30% reduction in headache days): 243 (47.8) Outcomes at 2 years in initial responders [n/N (%)]: Still on treatment: 162/294 (55.1) Never stopped: 117/294 (39.8) Restarted after relapse: 45/294 (15.3) Stopped treatment: 132/294 (44.9) Sustained response (≤15 headache days per month): 95/294 (32.3) Resistant (reverted to chronic migraine on treatment): 20/294 (6.8) Pregnancy: 13/294 (4.4) Lost to follow-up: 4/294 (1.4)	Not reported

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Hull Migraine Clinic, 7-year study: 5-year follow-up[12,13] UK	Prospective observational study July 2010 – December 2017 5-year follow-up period	Adult patients with chronic migraine treated with onabotulinumtoxinA, with treatment data for at least 5 years Analysis population: N=211	100% of patients had failed at least one oral preventive migraine therapy	Initial response within 2 cycles of treatment [n (%)]: Non-responder: 85 (40.3) Responder (≥50% reduction in headache days or migraine days, or ≥2-fold increase in crystal-clear days): 126 (59.7) Responder per NICE criteria (≥30% reduction in headache days): 101 (47.8) Outcomes at 5 years in initial responders [n/N (%)]: Still on treatment: 28/126 (22.2) Never stopped: 13/126 (10.3) Restarted after relapse: 15/126 (11.9) Stopped treatment: 98/126 (77.8) Sustained response (≤15 headache days per month): 73/126 (57.9) Resistant (reverted to chronic migraine on treatment): 15/126 (11.9) Pregnancy: 5/126 (4.0) Lost to follow-up: 5/126 (4.0)	Not reported

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Sant Andrea Hospital: 155 U study[14] Italy	prospective, open-label, single-center observational study Patients initiated treatment between October 2010 and November 2011 2-year follow-up period	chronic migraine patients with medication overuse headache treated with 155 U of onabotulinumtoxinA Total patients treated: N=155 Analysis population (completed 2 years of treatment): N=132	Age, years [mean (SD)]: 43.2 (13.5) Female (%): 81.8 Diagnosis of CM, years [mean (SD)]: 7.6 (4.3) Monthly headache days [mean (SD)]: 22.3 (4.1) Monthly migraine days [mean (SD)]: 21.4 (4.3)	Monthly headache days [mean (SD)]: Month 3: 16.3 (2.7) Month 6: 12.9 (2.6) Month 9: 11.6 (2.2) Month 12: 9.4 (2.9) Month 15: 9.0 (2.8) Month 18: 8.6 (2.6) Month 21: 8.0 (2.3) Month 24: 7.3 (2.1) P<0.001 compared with baseline for all time points Monthly migraine days [mean (SD)]: Month 3: 15.9 (2.8) Month 6: 12.4 (2.5) Month 9: 11.3 (2.3) Month 12: 9.2 (2.8) Month 15: 8.3 (3.0) Month 18: 7.9 (3.0) Month 21: 7.3 (2.7) Month 24: 6.8 (2.3) P<0.001 compared with baseline for all time points	≥1 TRAE [n (%)]: 23 (17.5) ≥1 treatment-related SAE [n (%)]: 0 (0) Treatment-related AEs [n (%)]: Injection-site pain: 4 (3.3) Neck pain: 5 (3.8) Musculoskeletal weakness: 5 (3.8) Eyelid ptosis: 4 (2.9) Headache: 5 (3.7) Discontinuation due to TRAEs [n (%)]: 0 (0)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Sant Andrea Hospital: 195 U study[15] Italy	prospective, open-label, single-center observational study Patients initiated treatment between January 2012 and January 2013 2-year follow-up period	chronic migraine patients with medication overuse headache treated with 195 U of onabotulinumtoxinA Total patients treated: N=172 Analysis population (completed 2 years of follow-up): N=143	Age, years [mean (SD)]: 44.9 (12.7) Female (%): 79.7 Diagnosis of CM, years [mean (SD)]: 8.4 (4.7) Monthly headache days [mean (SD)]: 22.2 (4.9) Monthly migraine days [mean (SD)]: 21.6 (4.8)	Monthly headache days [mean (SD)]: Month 3: 14.1 (3.4) Month 6: 10.2 (2.8) Month 9: 7.4 (2.2) Month 12: 5.7 (1.7) Month 15: 5.4 (1.2) Month 18: 4.9 (1.3) Month 21: 4.4 (1.2) Month 24: 4.1 (1.0) P<0.001 compared with baseline for all time points Monthly migraine days [mean (SD)]: Month 3: 13.5 (3.6) Month 6: 9.7 (2.7) Month 9: 6.9 (1.6) Month 12: 5.4 (1.2) Month 15: 4.8 (1.0) Month 18: 4.5 (1.0) Month 21: 4.1 (1.0) Month 24: 3.8 (1.0) P≤0.05 compared with baseline for all time points	≥1 TRAE [n (%)]: 29 (20.3) Treatment-related AEs [n (%)]: Injection-site pain: 5 (3.5) Neck pain: 6 (4.2) Musculoskeletal weakness: 7 (4.9) Eyelid ptosis: 4 (2.8) Headache: 7 (4.9)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Domínguez et al. 2018[16] Spain	Multicentre, prospective observational study Patients were recruited between March 2014 and December 2015 12-month follow-up period	Patients fulfilling the diagnostic criteria for chronic migraine eligible for treatment with onabotulinumtoxinA after failure of at least two prophylactic agents (one required to be topiramate) or after tolerability failure N=725	Age, years [mean (SD)]: 46.8 (12.0) Female (%): 85.8 Time since CM diagnosis, months [mean (SD)]: 20.4 (18.7) Number of headaches per month [mean (SD)]: 21.8 (6.4) Number of migraines per month [mean (SD)]: 13.8 (7.0) Analgesic overuse (%): 58.2	Number of headaches per month [mean (SD), P-value compared to baseline]: 3 months: 10.6 (6.1), P<0.01 12 months: 8.4 (5.7), P<0.01 Number of migraines per month [mean (SD), P-value compared to baseline]: 3 months: 7.0 (4.9), P<0.01 12 months: 6.0 (4.7), P<0.01 Responder rates: Reduction in headache days per month from baseline to 3 months: ≥50%: 480 (66.2) >75%: 141 (19.4) Reduction in headache days per month from baseline to 12 months: ≥50%: 575 (79.3) >75%: 198 (27.3)	≥1 adverse event after first treatment cycle (%): Adverse events: 12.3 Mild adverse events: 10.2 ≥1 adverse event after month 12 (%): 5.1 Discontinued due to intolerability [n (%)]: 5 (0.7%)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Vikelis et al. 2016[17] Greece	open-label, single-arm, prospective, multi-center clinical study January 2014 – April 2016 Follow-up for 3 treatment cycles (9 months)	Adults diagnosed with chronic migraine scheduled to receive onabotulinumtoxinA ITT population: N=119 Efficacy analysis population (completed 3 treatment cycles): N=81	Age, years [mean (SD)]: 43.5 (9.8) Female (%): 90.1 100% inadequately responded to or were intolerant of previous preventive medications Number of previous medications failed [mean (SD)]: 2.9 (1.3) Medication overuse headache (%): 48.1 Headache days per month [mean (SD)]: 21.3 (5.4) Days of acute headache medication per month [mean (SD)]: 16.2 (7.8)	Change from baseline to after 3rd treatment cycle [mean (SD), P-value compared to baseline]: Headache days per month: 7.7 (4.8), P<0.001 Acute medication days per month: 5.2 (4.3), P<0.001 Responder rates (reduction in headache days/month from baseline to after 3rd treatment cycle) [n/N (%)]: Efficacy population: ≥30%: 71/81 (87.7) ≥50%: 65/81 (80.2) ≥75%: 45/81 (55.6) ITT population [n/N (%)]: ≥50%: 65/119 (54.6)	Adverse events recorded [n (%)]: Wheals in the injection site: 5 (6.2) Mild ptosis: 5 (6.2) Lateral eyebrow elevation: 3 (3.7) Shoulder and/or neck pain: 3 (3.7) Discontinued due to intolerability [n/N (%)]: 2/119 (1.7)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Vikelis et al. 2018[18] Greece	open-label, single-arm, prospective, multi-center clinical study 3-year follow-up period of responders in the core study (Vikelis et al. 2016[17])	Adults diagnosed with chronic migraine that responded after 3 treatments with onabotulinumtoxinA (≥50% reduction in average monthly headache days from baseline) Analysis population (remained on treatment for 3 years): N=56	Female (%): 89.3 Age, years [mean (SD)]: 43.3 (9.5) 100% inadequately responded to or were intolerant of previous preventive medications Number of previous preventive medications [median (range)]: 3 (1–7) Headache days per month [mean (SD)]: 21.5 (5.1) Acute headache medication days per month [mean (SD)]: 16.5 (7.3)	After 3rd treatment cycle [mean (SD)]: Headache days/month: 7.2 (3.8) Acute headache medication days/month: 4.7 (3.2) After 2 years of treatment [mean (SD), P-value compared to after 3rd treatment cycle]: Headache days/month: 5.4 (2.6), P<0.001 Acute headache medication days/month: 3.4 (1.7), P<0.001 After 3 years of treatment [mean (SD), P-value compared to after 2 years]: Headache days/month: 3.4 (1.7), P<0.001 Acute headache medication days/month: 2.8 (1.3), P<0.001	Few cases experienced transient and mild adverse events, at comparable rates with those of the core study (Vikelis et al. 2016[17]) Discontinued due to intolerability [n (%)]: 0 (0)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Guerzoni et al. 2016[19] Modena University, Italy	retrospective observational study May 2012 – May 2015 Follow-up period of 7 treatment cycles	Patients diagnosed with chronic migraine associated with medication overuse who received at least 7 treatments with onabotulinumtoxinA N=57	Age [mean (SD)]: 50.5 (13.7) Female (%): 80.7 MOH (%): 100 Headache index‡ [mean (SD)]: 0.98 (0.09) Analgesic daily consumption§ [mean (SD)]: 1.79 (1.59)	Headache index‡ by treatment cycle [mean (SD)]: Month 3 (n=57): 0.86 (0.24) Month 6 (n=50): 0.77 (0.30) Month 9 (n=36): 0.72 (0.34) Month 12 (n=20): 0.69 (0.29) Month 15 (n=13): 0.52 (0.29) Month 18 (n=7): 0.65 (0.36) P<0.0001 compared with baseline for all treatment cycles Analgesic daily consumption§ by treatment cycle [mean (SD)]: Month 3 (n=57): 1.47 (1.67) Month 6 (n=50): 1.33 (1.90) Month 9 (n=36): 0.96 (0.97) Month 12 (n=20): 0.70 (0.43) Month 15 (n=13): 0.53 (0.30) Month 18 (n=7): 0.61 (0.42) P<0.0001 compared with baseline for all treatment cycles	Patients with adverse events [n (%)]: ≥1 AE: 24 (42) ≥1 SAE: 0 (0) ≥1 TRAE: 12 (20)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

Table 1. Long-term studies of onabotulinumtoxinA

Study/Location	Design/Duration	Patient Population	Baseline Characteristics	Efficacy Outcomes	Safety Outcomes
Guerzoni et al. 2017[20] Modena University, Italy	retrospective observational study January 2013 – February 2017 3-year follow-up period	Patients diagnosed with chronic migraine complicated with medication overuse headache who were treated with onabotulinumtoxinA N=90	Age, years [mean (SD)]: 45.21 (10.12) Female (%): 84.4 Failed ≥3 prior preventives (%): 100 Headache index‡ [mean ± 95% CI]: 0.98 ± 0.16 Analgesic daily consumption§ [mean ± 95% CI]: 1.98 ± 1.69	≥50% reduction in headache days from baseline [n/N (%)]: 1 year: 14/90 (12.6) 2 years: 2/18 (11.11) 3 years: 1/13 (7.7) Headache index‡ by treatment cycle/month [mean ± 95% CI]: T7/M18 (n=27): 0.52 ± 0.34** T8/M21 (n=21): 0.5 ± 0.27** T9/M24 (n=20): 0.51 ± 0.3** T10/M27 (n=18): 0.53 ± 0.3** T11/M30 (n=18): 0.49 ± 0.31** T12/M33 (n=15): 0.48 ± 0.3** T13/M36 (n=13): 0.49 ± 0.29** * P<0.05 compared with baseline ** P<0.01 compared with baseline Analgesic daily consumption§ by treatment cycle/month [mean ± 95% CI]: T7/M18 (n=27): 0.53 ± 0.42** T8/M21 (n=21): 0.5 ± 0.27** T9/M24 (n=20): 0.48 ± 0.28** T10/M27 (n=18): 0.53 ± 0.3** T11/M30 (n=18): 0.47 ± 0.28** T12/M33 (n=15): 0.49 ± 0.29** T13/M36 (n=13): 0.49 ± 0.29* * P<0.05 compared with baseline ** P<0.01 compared with baseline	≥1 AE [n (%)]: 12 (13.3) Most frequent AEs [n (%)]: Erythema: 7 (7.7) Injection-site edema: 3 (3.3) Itching: 3 (3.3) Treatment-related AEs [n (%)]: Muscle weakness: 3 (3.3) Headache: 2 (2.2) Transitory palpebral ptosis: 1 (1.1) Discontinued due to TRAE [n (%)]: 0 (0)

† Data represent the mean change in HIT-6 score and 95% confidence interval.
‡ Headache index is defined as the number of headache days/days observed.
§ Analgesic daily consumption is defined as number of analgesic doses/days observed.
Abbreviations: AE, adverse event; CI, confidence interval; CM, chronic migraine; DB, double-blind; HIT-6, six-item Headache Impact Test; IQR, interquartile range; ITT, intent to treat; MOH, medication overuse headache; O/O, onabotulinumtoxinA/onabotulinumtoxinA; OL, open-label; P/O, placebo/onabotulinumtoxinA; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UK, United Kingdom; USA, United States of America.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Please consider this further for chronic sufferers, I am unable to work now and spend 3/4 days a week sometimes more in bed due to this condition. I am desperate for my life back and have always enjoyed working. I now just exist, please reconsider.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	Off work for past 2 years due to chronic migraines.
Comments on the ACD: This is devastating to read that the decision has been made to not approve Aimovog on the NHS. There are so many of us waiting for this to come out to hopefully change our lives back to being normal. This will impact so many lives. I had prepared myself to carry on with this disability in the hope that in a couple of years this would be available to us sufferers and may help many of us, I didn't even realise that it was an option that it might not be available to us! I'm totally gutted maybe the people that come up with this decision would like to come and live with me for a month to see the true impact of this condition? People in America already have seen massive success with this drug so how can this be right! I am a mother of 2 young children and I very often have to call my mum up to look after my children, my husband is late for work on many occasions as I can't get out of bed and look after them. I've not worked since Feb 2017 because of this illness so it has even affected us financially. My family's lives have been totally ruined by my chronic migraines and this was a chance for us to maybe get our lives back to normal. I really hope you reconsider your original decision as it has a massive impact on many people's lives and could be a total life changer for many. Thank you.	

Name	[redacted]
Role	Patient
Other role	Migraineur
Organisation	None
Location	England
Conflict	None
Notes	Off work for past 2 years due to chronic migraines.
Comments on the ACD: You clearly do not understand how debilitating migraines are to a lot of people outside of the normal range. I understand that the new drug will work some, not for others like every other drug out there. But please give us that chance of leading a more normal life where migraines do not dictate my whole being 24/7. If you were in my shoes for just one day, let alone a week or more, you'd want that chance. Listen to the proper experts at the top neurology and neurosurgery hospitals in London. Please listen and help give us a chance of a less painful life.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have suffered with Chronic Migraines since the age of 15 (now 42). I have tried Optical Nerve Blocks, numerous triptans all to no effect. Aimovig was one of the last resorts for my neurologist to trial me on as they affect my life so much. I lost nearly 45 days of work last year due to migraines and my employer may not support me long term. The cost of trialling all these meds, numerous doctor then neurologist appts all mounts up as well as 1000's costing employers per year so I am not sure why you are preventing this for helping hundreds of migraine patients who live with this chronic illness and who struggle so much. I am praying this is reviewed.	

Name	[redacted]
Role	Carer
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: My daughter has suffered from chronic migraines since 15. She has been under the care of neurologists, tried every medication available and this was the last resort for her neurologist to try her on. Migraines has such an impact on her life and she is often housebound for weeks due to this. I really believe that this needs to be reviewed.	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: This should be given a try as could help so many suffers. Can they not test these on a select few to see the risks and if all ok push forward with this drug? If it will help a whole nation that suffer with migraines the incurable disease live a more fulfilled life why not try it?	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	N/A
Comments on the ACD: As a chronic migraine sufferer struggling with this disease for nearly 30 years, I am devastated that a lifeline for people like me is being denied. I suspect cost is a huge driving factor, but compared with the millions of pounds lost to the economy in terms of sickness absence, disability payments and lost productivity, I would have thought approving the drug would be more cost effective. This news is so disappointing.	

Name	[redacted]
Role	NHS Professional
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I would like to tell you a bit about myself and how much I suffer and gone through as a migraine sufferer. Six years ago I was diagnosed with vestibular migraines, it changed myself completely. I used to be a bubbly outgoing fun person, now I'm in pain day after day depressed and hate my life. I was referred to a migraine specialist up London where I had tests and tried not 1 or 2 prevention meds, but the total of 10 in 4 years. 9 out of 10 didn't help me at all, the side effects were horrendous and I put on 3 stone making me I've see, I now have a fatty liver due to this and now live in pain as well as my migraines. Only 1 prevention med Propranolol has help some, but not enough to enjoy my life again. I was then asked if I wanted to try nerve blocks up London, bad idea as soon after these injections my headaches got a lot worse. I then got clinically depressed and took many months off working for the NHS, a job which I love. Months later I was asked if I wanted to try Botox, yes I jumped at the offer. I tried Botox for a year, sadly Botox worked for a couple of months but a year later it stopped working completely. I'm new at the end of my tether and was building my hopes up getting approved to try the new prevention injection which I've read and know so many people which this has helped and changed people's lives. Now today I've read NICE won't be available on the NHS, I'm absolutely gutted and disappointed people won't be given the chance to try this because it's too expensive. Why are you playing with people's lives and building people's hopes up!! I want my life back and enjoy my job I love in the NHS. This injection might be the only prevention what might do this. Please, please reconsider and allowing it to be available on the NHS!!! Thankyou	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I cannot begin to express how disappointed I am that NICE have not approved this drug. Many of us know from fellow sufferers in the US what a help the drug has been. I have NDPH, this started on 30/1/2013 and although I think my headache specialist is really good, haven't yet been offered Botox or anything other than preventatives (Gabapentin and Sodium Valproate currently). That's 5 years of suffering with this disgusting syndrome. I had to give up my career, my social life and I now have an existence rather than a life. Please rethink your decision on these new drugs - we desperately need them. [redacted]	

Name	[redacted]
Role	Patient
Other role	Photographer
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: After participating in the trial for this drug with amazing results I have had the worst 18months as going from something that worked to using Botox which is not as affective has made be very depressed. The only thing that has been giving me hope of a reasonable pain free life the hope that the drug will be available soon. To read that it's not been approved today is the worst news possible for me (and my family) **After participating in the trial for this drug with amazing results I have had the worst 18months as going from something that worked to using Botox which is not as affective has made be very depressed. The only thing that has been giving me hope of a reasonable pain free life the hope that the drug will be available soon. To read that it's not been approved today is the worst news possible**	

Name	[redacted]
Role	Migraine Sufferer
Other role	Customer Relations Officer
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: I've had migraines for 32 years, I've had countless days off sick from school, university, then in my working life, I've lost YEARS of my life to lying in bed in my dark bedroom, had GPs visit me at home, countless times to give me medication. How can this be more cost effective than erenumab? The decision not to approve it for NHS use is very short-sighted, I was desperate for it to be approved, I cannot afford private treatment, I work full time, but earn £16k p/a, gross, I take home £1k per month, 2/3 of my wage goes to mortgage & commuting. I don't get company sick pay, if I'm off sick with migraine for 1-3 days, I don't get paid, statutory sick pay starts from 4th sick day. How is this cost effective? Millions of migraineurs will benefit from erenumab, many even work for the NHS, please reconsider and approve erenumab! It's the only migraine specific drug, it is ground-breaking! PLEASE!	

Name	[redacted]
Role	Private Sector Professional
Other role	Dispensing Optician
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Imagine being in constant pain every waking moment of every single day. Picture waking up to a beautiful morning where the sun is bright and the birds are tweeting and your head feels like it is being crushed in a vice and you can't look at the sun because it hurts your eyes and any noises drive you insane. You've tried 11 different drugs that are made for epilepsy, depression or other diseases that aren't what you have and none of them do anything except cause horrible side effects. It's been 10 years now that you have been in constant pain, with no crystal clear days and you can't remember how many different alternative treatments you've tried - from Botox to DHE. This is my reality.

But then one day you are given an injection which gives you the relief you have been longing to have for the past ten years. The injection that brings your daily pain down from an 8/10 to a 3/10 within days. The injection that means you can go to work and do your job properly without having to sit in a dark room and leave work early to just sleep.

Please re-evaluate the decision you have made that is taking away the opportunity for so many people to feel the relief that I have finally found after the long and painful journey I have had.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: This is disappointing. I'd been waiting a year for this to be available on the NHS only for it not to be approved.

I'm averaging a migraine every two days. The medication I'm on currently thankfully heads them off pretty well within a couple of hours but it doesn't stop them occurring, and I'm left drained afterwards. And every med I've ever been on eventually loses its effectiveness.

I was really hoping to find a preventative and this has proved so successful in its use so far. I've had an almost lifelong struggle with migraines, starting from the age of 8. I am now 43. At their worst, they are completely debilitating and I am unable to function at all. This means that holding down a job, and making a useful contribution to society is nigh on impossible.

Preventing migraines might mean I can re-enter the economy and make a useful contribution again.

Surely the cost of prevention drugs is preferable to the cost of constant pain meds and indeed the cost of welfare being paid out to those unable to work due to this condition?

I really hope NICE listen to the views put forward and reverse this decision.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a lifelong chronic migraine sufferer, I am devastated by this decision. Migraine has ruined my life and prevented me from working or having a social life. Having tried all available preventative treatments, including Botox, without success, Erenumab was my last hope. Sufferers like me need a treatment specifically developed for migraine such as Erenumab, as there are none and to deny us this is to discriminate against migraine sufferers.

Name	[redacted]
Role	Patient
Other role	Ex-teacher
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: The denial of this treatment has come as a devastating blow to those of us whose lives are blighted by daily chronic migraine and have tried every other treatment including BOTOX. I was an active member of my community who held a professional and important career and lived a life that included contributing to our society. This condition has left me housebound for approximately 50% of my "new" life for the past 15 years. The days that I can function it is at a low level (enough for self-care and a short time out of the house).

My husband is self-employed and it affects his working hours and productivity. My mother has had to leave her job to help care for me and my daughter and we receive no government funded financial help.

Chronic intractable migraine may not be a terminal illness but by denying people whose lives are enveloped by this condition you may as well be condemning them to a death sentence.

Name	[redacted]
Role	NHS Professional
Other role	Mental Health Nurse
Organisation	None listed
Location	Scotland
Conflict	None
Notes	None

Comments on the ACD: I think it's really sad that you aren't going to consider Erenumab as a treatment option on the NHS. As a migraine sufferer myself- I have went through all the non-migraine treatments (as the medication is not produced to treat migraines) and they have horrific side effects. As a sufferer it cripples my life. It stops me being as effective at work (and causes sick days) - it affects my family life as some days I cannot spend time with them as I'm bedded with migraines. This not only affect the person physically but also emotionally and psychologically. Please consider erenumab as a treatment on the NHS to reverse this awful condition on the people who are suffering so badly in the UK

Name	[redacted]
Role	Patient
Other role	Unemployed due to chronic migraine
Organisation	None listed
Location	England
Conflict	None
Notes	None
Comments on the ACD: Devastated at this news, having followed the American trials and distribution to see the amazing results this drug is getting it was mine and thousands of other people's last hope at a break in this horrendous disease. I like many others have no quality of life due to migraine and have tried all preventatives, Botox, acupuncture you name it!! When you consider how many people have to leave work or have to take numerous days off work with this disease surely the costs are minimal. Hoping that this will be reviewed and that it will be available to the people who need it desperately	

Name	[redacted]
Role	Patient
Other role	Sales Assistant
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I was really hoping that this would be approved, I have suffered 25 years, tried lots of meds and nerve block etc. I really struggle to go to work and can only work limited hours because of my migraines. I get maybe 7 free days a month in between violent episodes I am keeping my fingers crossed it will be available on the n h s because of affordability. I live in hope Please let it be available on the n h s in the very near future	

Name	[redacted]
Role	Public
Other role	Work based assessor
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: No comments listed	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	The Netherlands
Conflict	None
Notes	None
Comments on the ACD: Erenumab (Aimovig) has changed my life so far. I've had migraines for 25 years, chronic for 7 years. Have not been able to work the last 6 years. Aimovig gives me all these new possibilities. No side effects at all! Whereas my previous medications ALL did have very serious side effects and really didn't work. If you take this away from me, you take my future, my life. The future of my family. The last vacation with them was actually the first one I could go swim with my son, go to the playground with him. It was incredible. Please consider. **Greetings from The Netherlands.**	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: As a chronic sufferer I would happily welcome a drug that can enable me to have a quality of life, prevent taking time off work and enable a normal lifestyle. My pain levels vary and at its worst I can be in bed for 5 days with pain before and afterwards continuing.	

Name	[redacted]
Role	Patient
Other role	Private Client Lawyer
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I suffer with migraine. I am 50 and I have done so since 18. My mother suffers with migraine although for me they tend to be hormone related. I have no food triggers but other triggers are smells and temperature. After trying various prescribed meds over the years for both preventative and reactive measures I now take 10mg Rizatriptan at the onset of an attack. Rizatriptan for me has to date been the most effective drug for an attack but I have not found an effective preventative drug. The attack will subside but only temporarily. Currently I have a poor quality of life. My attacks have increased to weekly. I am frequently absent from work which has been noticed and referred to by my employer. I work full time and I suffer terribly with photophobia and sickness. I have no social life for I let people down or am unable to attend and I cannot be relied upon. My spouse's role is more that of a carer so our relationship is affected by the impact of my migraines. In turn my confidence has plummeted and my emotional/mental state is not in a good place. I have exhausted all known avenues and I find few people, including friends, those in the workplace and many in the medical profession, to be sympathetic and understanding. I spend most of my time in a dark room physically rocking, grasping my head and in tears and now I hear that this new breakthrough drug, which scientists have spent years researching for people like me, is not going to be made available to the NHS. This is nothing short of an act of cruelty. It makes no sense that in the 21st century in the Western world this drug, which could save the country millions in sick leave and other meds, is only available to the wealthy! I am a Lawyer and I cannot afford to buy this privately! I don't smoke. I don't drink. I eat well. I exercise. I take supplements where appropriate. My work helps the elderly and those suffering a bereavement. Now I need help. You have it in your hands to make my life better. It pains me to say it but I really believe I would get more help and understanding if I were a drug addict or alcoholic in recovery. I ask you to reconsider and make this drug available to all on the NHS. Thank you for your time.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: This medication has the potential to be life changing for migraine suffers. This must surely have to be available on NHS for moral, financial and political reasons! Migraine is an invisible illness and is debilitating for all sufferers the invention of this medication is nothing short of miraculous! PLEASE DO NOT DENY OUR CHANCE AT A GREATER QUALITY OF LIFE!	

Name	[redacted]
Role	Patient
Other role	Senior Aircraft Maintenance Manager
Organisation	None
Location	Scotland
Conflict	None
Notes	None

Comments on the ACD: The decision to reject Erenumab treatment on NHS based on cost is disgusting to sufferers (like me) who have tried everything available and live in pain every single day.

I have waited over 10 years for ANYTHING to provide relief and regain my life. This was one of the last things to try and as I read the success stories in the U.S I am bereft of words on how this makes me feel and as usual driven by cost.

There are millions of sufferers but far less that have met a strict criteria of trial and error and done every other thing available. At the very least a controlled roll out to gauge its success! While it hasn't been all victorious in the counties that have made the move to release, the very nature of migraine treatment is hit&miss, trial&error and we in the UK (Scotland) should be at least allowed that chance. The last 10-12yrs of my life have been miserable. I am unable to socialize, exercise properly or enjoy many of the activities I once thought nothing of. Not to mention the holidays this condition has ruined or the struggle to maintain a senior position of employment.

I would urge (beg) to reconsider the draft stance and give NHS patients the chance they deserve.

Name	[redacted]
Role	Patient
Other role	Cabbie
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: please reconsider your decision regarding eremunab on the NHS, the cost of this drug privately is out of reach for the majority of migraine sufferers. I am a 47 year old male and was diagnosed with migraine in my teens, if anything they have got progressively worse over the years, I have lost jobs, relationships due to the pain, dizziness, vertigo and resulting anxiety and depression from dealing with this condition, I have lived a somewhat sheltered existence over the years as they would come on at the slightest bit of stress, and have caused me to become very isolated. I have tried sumatriptan, run of the mill headache pills beta blockers, which caused me to gain weight and become depressed as this is a horrible side effect. The cefaly device the alpha stim device and had somewhat limited relief from all of these treatments also tried Botox which helped at the beginning then gradually stopped working, also tried various dietary changes, exercise. I am somewhat lucky in that because I am self-employed I can take days off but this is not good as I am losing money, the hardest part is that my family need support and sometimes I just can't be there for them, as my brother suffers bipolar disorder and my mother is being treated for bladder cancer. I had been watching this drug with hope feeling that at last there is a light at the end of the tunnel, something that might truly work, please reconsider your decision regarding availability on the NHS.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Rejecting this exciting new treatment on cost-effectiveness grounds is wrong. Botox involves several injections and has to be administered by trained practitioners, most sufferers like me are taking several drugs (sumatriptan, zolmitriptan, propranolol, betahustine and amitriptyline on prescription, numerous others over the counter). This along with numerous days lost from the workforce must represent a considerable cost, which could be potentially replaced with one prescription.	

Name	[redacted]
Role	Patient
Other role	Teacher
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a chronic migraine sufferer with New persistent daily headache. I have been having Botox for the last four years alongside trying every drug and device available on the NHS and privately.

I was lucky enough to be offered erenumab privately by my neurologist at a huge cost to my family. But I want functioning well on just Botox. Nothing else has worked. I am a teacher and would not be working without the aimovig. I have literally tried everything. With no relief and the migraines have been getting worse and worse. To say that Botox is a good enough primary treatment when it hasn't done anything to Control my Migraines is madness. To know you have been offered every drug available and none have worked until now and I am not the only one. There are 1000s of others like me. Who are now having this treatment that could change their lives denied.

What about the people that have tried every preventative and every abortive available. Where is their hope? Botox is not a good enough answer for some that have tried everything and experienced no relief. Before the erenumab I had no life. Everything was a trigger. Nothing helped when the pain was so bad I wanted to hit my face off a brick wall. That is the reality of migraine that some people have to live with day in day out. By denying those people access to this specific migraine drug that has been developed to help us... This in effect is stealing people's lives; their opportunities. Their ability to work and leave the house and have a more normal semblance of a life. I beg you to reconsider this decision as it has been the source of much hope to those in the migraine world. And now this hope has been taken away.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have struggled with chronic, severe migraine for 50 years. None of the current preventative treatments help, and I have tried them all. Once again I am struggling with MOH, due to taking too much Sumatriptan as I get a least 15 migraines per month.

I have no life. I am on the verge of getting fired. Again.

If only a new treatment had been developed purely for migraine, instead of relying on treatments for epilepsy, depression, blood pressure etc. Oh wait, there is, but we're being denied it unless we're wealthy enough to go private.

There have been occasions where the pain has been so severe, and so unrelenting, and with no end to the constant migraines, that I've seriously considered ending it all permanently. I need the hope of a new drug. I realise that it may not work for me. There are never any guarantees, but to be refused any chance of trying it is cruel.

Please, reconsider the decision to allow Erenumab to be available on the NHS.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a migraine sufferer I am struggling to even get to the stage of seeing a neuro for Botox so am not eligible for new treatment. BUT the frequency and severity of my migraines have left me unable to work for 5 years and at times suicidal. This is not uncommon amongst chronic sufferers so removing any hope of trying a new drug when everything else has been exhausted is inhuman. It may not be considered cost effective to the NHS but overall it could be if it helps a few people return to work, form better family relationships, be better parents to their children, work longer hours, less sick pay etc. If the drug cannot be approved mainstream then at least expand trials to wider sector of sufferers. We need hope. If anyone on the committee was a chronic sufferer you would understand who desperate we are to find relief from pain and all the other issues constant pain gives. Please help.

Name	[redacted]
Role	Patient
Other role	DAILY chronic migraine sufferer
Organisation	None
Location	Northern Ireland
Conflict	None
Notes	None

Comments on the ACD: My life has been put on hold in my mid 20s due to daily migraines. I have tried everything. I suffer intense pain daily & this drug was my final hope. If this drug worked, it would be cheaper as I wouldn't require sumitriptan injections, diclofenic, etc. etc. as well as numerous appointments. It would also mean I get my life back, have a job, have a social life, get active etc.! Consider only allowing chronic migraine sufferers the new drug? I have migraines daily, I will give permission for you to view my records of everything I have tried.

I am a member of a chronic migraine support group and many, many people in America have found relief.

Please, please reconsider this decision. Contact me if you need more information.

Thank you for your time.

[redacted]

I have tried many different preventatives. I have tired Botox. Acupuncture. Physio. Spring tms device. Had the spheno Palatine ganglion radio frequency. I have tried diet changes and many, many more.

Please reconsider.

Please reconsider. View my records.

Name	[redacted]
Role	Patient
Other role	Temporary unemployed
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: My migraines come and go which can be the worst type as I never know when it will hit I am unable to work as they never know if and when I will be able to be there so because I'm unreliable they don't want me. I can't plan a day out with family I can't say I will look after grandad while mum goes away as I never know if I will be well enough to drive etc. this type of drug would stop all this would lead me to be able to live a much improved life and I understand it's not a cure nor a quick fix but it's about the quality of life and right now migraine sufferers have very little quality of their life it's a very lonely existence when you don't know if you're coming or going. The stress of not being able to work and having to let people down can easily bring on another migraine the very thing I'm trying to avoid! So when all is said and done if I was able to pay for this privately I would certainly be giving it a go. Surely it's worth giving migraine suffers the chance to try and see if they can be improved as otherwise u are stopping us from being us!	

Name	[redacted]
Role	Patient
Other role	Customer Sales Assistant
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: I think it is a disgrace that you have decided to refuse the use of Erenumab, by the NHS, especially since this is the first preventative medication treatment in 20 years to have been tested, for the sole purpose of preventing Migraines, I have had "Chronic migraines" and have had now for over 15 years, and I am currently receiving Botox from the NHS, and to know that you have now taken away the only option and little bit of hope left to me, if the Botox does not work, after years of trying, all other preventatives, is totally sole destroying, that you can never imagine, if you have never suffered from this debilitating condition, that we have no control over, and have not caused ourselves to have. I do not have a life, I struggle to go to work and keep my independence, I often need to be signed off work, due to the effects of my migraines eg fatigue, depression, to list a few, let alone the normal symptoms of my migraines themselves, which are 3-4 days every week, at least. You should really try and live a life of a Chronic Migraine patient, or there family and friends, to see the impact it has on all our lives, therefore we should at least be given a vote, on this, and not just people that have never suffered, or think they have, by thinking, "it's just a headache", well let me tell you, it definitely is not, just a headache and you don't have a clue. I really hope you reconsider your decision, and please authorise the use, of this new preventative treatment, and let us see if it can give us some normality back into our lives that migraines have stolen from us.	

Name	[redacted]
Role	Public
Other role	Retired General Practitioner
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: To Whom it May Concern

I would like to comment on this guidance that Erenumab is not deemed suitable to be available on the NHS.

I am a severe migraine sufferer - I get migraines 24 days out of 28, and I was forced to retire from General Practice when I was 45 as a result of them. Subsequently I was tried on every oral preventive drug available, as well as trying Botox, and having several surgical procedures including neck facet joint injections and sub occipital nerve blocks. None of these treatments worked, and eventually I was able to enrol in a trial testing one of the other CGRP inhibitors (fremenezumab).

Fremenezumab helped my migraines significantly, and I became optimistic about the idea the once these drugs were licensed and available on the NHS, that I might be able to look forward to some kind of relief from my pain, and possibly be able to return to work.

However, I see now that this is possibly not to be. I am therefore writing to ask, whether the committee would consider making these drugs available to selected individuals, who have shown to gain significant improvement from them, in the face of other failed treatments.

I believe, as an individual and as a doctor, that this compassionate approach, would be a valid and acceptable policy, which would help select people who suffer from chronic, intractable pain on an almost daily basis.

Name	[redacted]
Role	Patient
Other role	Nurse
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a migraine sufferer and currently take 5 meds a day (topiramate 125mg BD and amitriptyline) when I get a migraine I take diclofenac PR)

I am a nurse and my migraines prevent me from working and caring for patients. They have stopped me from working nights, as a lack of sleep and sleep disruption is a trigger.

I have 2 small active boys.

My migraines prevent me from looking after my children.

This drug has been shown to reduce and prevent migraines NICE need to reconsider letting the NHS prescribe it.

Name	[redacted]
Role	Patient
Other role	Carer
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am devastated that NICE have not agreed to let migraine suffers try the new treatment that has become available. I have been a migraine sufferer for 43 years and for the last 7 years they have been chronic I suffer agonising head pain every other day I am absolutely shattered, I can't make any plans to go anywhere I have a very restricted diet all I do is work often in pain and stay home. I have thought many times of suicide but hang on hoping for some new treatment to help. I'm lucky in that I have an understanding GP but he has said to me I'm sorry but there is nothing else we can try. The neurologist can't help. The headache clinics can't help this new treatment was the only hope a lot of us sufferers had and now that's not going to happen. I really hope you can reconsider your verdict. Imagine every day how it feels to think that your head may explode, because that's how you feel you spend your life in agony sat in the dark away from noise. Please help us.

Name	[redacted]
Role	Patient
Other role	Senior Research Manager
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am shocked and horrified that this drug has not been recommended by NICE, despite the evidence that was presented to them. I have suffered chronic and hemiplegic migraine for a number of years. This has affected my mental well-being and the vast array of drugs that I have had to take over the years have led to further complications, devastating side effects and ultimately resulting in oesophageal surgery.

Migraine sufferers must suffer in silence, with most people thinking it is a headache. The truth is far from it and I have been hospitalised twice as a result of the devastating effect it has had on my body. GPs know little about the condition and getting a referral to a consultant with the relevant experience is a real fight - my consultant is over 100 miles away, but is the closest to me, having been through the humiliation of a local neurologist telling me that it wasn't a real illness and I should pull myself together.

I do not feel that the committee has taken into account the devastating nature of chronic migraine, its effect on the workforce and the economic cost to both businesses and to the person involved. Migraine is the biggest cause of sickness absence in the UK.

Botox has been cited as the recommended treatment. This is not available to everyone, those who have it have to travel many miles to receive it and, in many cases, it makes the situation worse.

I urge you to take an holistic approach and reverse your decision.

Name	[redacted]
Role	Patient
Other role	Unable to work!!
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: This seems to be about two things: cost and effectiveness compared to other treatments. I can no longer work due to chronic migraines, a position many are also in. Therefore I cannot contribute tax payments towards the NHS and loss of employment or sick days costs the economy millions. It's pretty clear that this is something that has been taken into consideration. For over 20 years the amount I have cost the NHS through countless GP time, specialist appointments, painkillers, nerve block procedures, trips to A&E would probably pay for this drug four times over.

In regards to the point about Botox, NHS staff are clearly not offering this to everyone as in over 20 years of countless GPs and at least 4 different Neurologists across several locations of pain clinics have NEVER mentioned this to me as an effective, available and EASY treatment for my condition. I also read every article on migraines and patient experiences and what few articles I have seen on Botox have not inspired me to seek this out.

Botox appointments and treatments are numerous and administered in a specialist way, therefore the cost to the NHS isn't exactly the cheapest method to pit this new drug against.

I have tried Betablockers, anti-depressants and recently anti-epilepsy. These drugs have intolerable side effects and have not worked, a process which takes you over a year on each to come to a conclusion on. These drugs are not engineered for Migraine, this new one is!

It may not work for everyone but at least it would be a much shorter timeframe. Saving time and money on ineffective treatments and staff appts.

We have managed as a migraine community to have this drug developed, ground-breaking in its nature of being the first drug engineered for migraine, to deny all of these patients including myself at least the ability to try this is unacceptable, frustrating and damaging to our mental health. I have often thought that I no longer want to be in this world not just due to the pain I have to endure on such a regular basis, but mainly due to the lack of hope, support and fear that there is no future in sight where I can be better and live a life to a reasonable standard, this decision only goes to fuel these feelings and once again at a cost to the NHS.

With regards to unproven effectiveness of this new drug, I would argue that there are so many drugs available so easily on the NHS that do not prove themselves as effective so this put this as a barrier given the trials that have been done and the research behind it is very short-sighted and loaded with unfairness.

If this is not approved, it will only serve to those who can afford it privately, a notion that we should not have to deal with still in 2019.

Without the numbers of people having access to this drug, how on earth are we meant to give you more data to prove its worth???

Please reconsider.

Thank you.

Name	[redacted]
Role	Patient
Other role	Unemployed
Organisation	None
Location	None
Conflict	None
Notes	None

Comments on the ACD: I have suffered from chronic migraine for 15 years. I have not been able to work for the past 13 years because of this. I have tried every medicine and treatment that my neurologist has had available to him and nothing has ever worked. I have tried Botox several times at my own expense and this did not work either. The possibility of a new drug being available had given me a glimmer of hope that I might be able to "get my life back". This decision has taken away any hope that the misery of living with this condition will ever go away. People who have never had a migraine do not understand the pain and misery of living with this condition every day, it has such a huge impact on day to day life, I do not feel as though I live a life anymore, for several years now I have felt as though I merely exist.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	Scotland
Conflict	None
Notes	None

Comments on the ACD: Dear Sir / Madam,

I would like to comment on the decision of NICE not recommending Aimovig for use on the NHS.

Having suffered Chronic Daily Migraine for over 12 years, and having tried all treatment options to say I was excited for a new Migraine preventative treatment was an understatement. I can't explain the disappointment I felt seeing the news that it would not be recommended.

I am currently 23, and Chronic Daily Migraine has affected me and my life in every possible way. I was a straight A student before I developed this condition. I started to miss a lot of school, my grades fell terribly which affected my exam results which then affected my career after school. I lost friends due to me not being able to get out of bed. The emotional pain that myself and my family feel is heart breaking. I can't describe the isolation that this condition causes. I have no social life, no friends, and no relationships because no one understands how debilitating this condition is. I have currently need in work for 6+ months, I have my own house and have to rely on help from my family to keep it. I have no will to live, I have to take anti-depressants to help me cope. I'm taking 4 migraine medications that provide no relief. Over the years I have tried;

Pain killers

Migraine preventative medications

Triptians

Unlicensed medications

Hormone related medications

Acupuncture

Homeopathy remedies

Herbal remedies

Chiropractic treatments

Blood tests, hormone tests, intolerance tests

Food diaries, food elimination, diet changes, nutritionist

CBD oil

Nerve blocks

Psychological techniques

Currently on the botox waiting list, I've been waiting 6 months and still currently waiting

These are only some of the things I have tried with no relief. CDM has ruined my life in every way. And for a new treatment that could improve my quality of life, to not be approved is heart breaking. I don't want to suffer for the rest of my life, CDM sufferers deserve the opportunity to try Aimovig. I beg NICE to reconsider.

Thank you,

[redacted]

Name	[redacted]
Role	Patient
Other role	Practice Consultant
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have been a chronic migraine and severe episodic sufferer for about 20 years. I have tried a number of different medications and various treatments the majority of which have failed at some point. The consistent treatment which I have had tolerance and some success is Topiramate. I say some success as Topiramate does not fully block my migraine and I tend to sit on a 2/3 daily pain scale but this is liveable. Not that life should be just liveable. I take Frovatriptan for my acute attacks and this is generally successful. I am not one to attend A&E or my GP as there is nothing that can be done, I work through the pain. I have paid privately for alternative care such as a nutritionist and cranial osteopathy which I have found to be supportive in pain management, however this is costly and not always sustainable. I am now receiving Botox which I have noted a small decrease in migraine days. I count this as a success as any days without headache or migraine is successful. My goal is to bare minimum reduce the amount of Topiramate due to the horrible side effects, including anxiety and bouts of depression. This further impacts on my quality of life.

The point to the above is that a first time treatment for migraine is to be celebrated and should be accessible to those of us with this horrible disability. To have access to something that provides treatment in a way where there are no side effects and is actually designed to treat this illness and not something else is revolutionary. The cost benefit analysis is flawed given the billions (rightly outlined in the papers) that go into lost working hours, additional NHS costs, mental health and social costs which are more qualitative and therefore harder to measure. Part of me wonders if the reluctance to fund the drug is due to this being a more female disease? Perhaps this is why there is less research dollars as well? If there are concerns about the efficacy then extend and widen the study to those with other migraine conditions to see the impact. It is unrealistic to determine that peoples conditions will go away or the drug is a magic cure as in my view neither is true. I retain hope that my migraine will dissipate at some point in my life however accept that it is realistically a life-long condition and therefore live as healthy as I can and work with my medical team and do what I can to improve the condition as best I can. My own experience with various treatments tells me that there should be no expectation that this treatment would be successful for everyone nor work in the long term for everyone either. This includes in dosage or in usage.

Cost obviously needs to be a factor but quality of life for those of us that live with this disease also needs to be taken into account. That includes the impact of the side effects of current treatments and accessibility of current treatments as well.

Name	[redacted]
Role	Patient
Other role	Teacher
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Devastated that you are considering refusing this drug. I have suffered for eighteen months with chronic migraines. I have tried absolutely everything: beta blockers, anti-depressants, epilepsy drugs, right through to acupuncture and vitamin supplements. Nothing works. Chronic migraines destroyed my life. It affects my ability to work, look after my children, my fitness, friendships and my relationship on a daily basis.

After seeing the consultant, erenumab is the best option for me and to me a lifeline. Ridiculously, I don't get enough migraines per month to qualify for Botox but suffering at least 8 a month added to the days recovering, it affects the majority of my life. Living with chronic migraines is a disability.

The cost to cover me at work is £200 a day. £200 x 8 = £1600 per month. Much more expensive than the injection!

If you've suffered from a migraine then you'd know the lifeline this drug is offering to those affected.

Name	[redacted]
Role	Patient
Other role	Retired Police Officer
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: After numerous different trials of different medications/treatments my migraines are now controlled in that I have only 12 - 15 migraine days on a good month.

To achieve this I take sodium valproate, Topiramate and Amitriptyline every day. At the start of an attack I take Imigran injection and also pain killers (if not vomiting)

The Imigran doesn't cure the migraine but it does help me cope. Unfortunately 6-8 is the maximum permitted dose per month and obviously even on a good month I have more attacks than that. I therefore have to choose which days I can take my injection, sleep for a few hours and then just about cope and the remainder of the days I stay in bed all day, usually vomiting.

I would like to return to work but finding a job that I can say I'm not coming in today I've got migraine, I'll make it up to you when I can, is proving difficult.

At 53 I'm too young to never work again

Migraine has had a huge impact on my whole life for as long as I can remember. For the majority of my police service I set aside a large chunk of my annual leave to use instead of sick leave and even then at one point I nearly lost my job. Commendations count for nothing if you take sick leave one day at a time!

A single medication that is actually for migraine that has the possibility of working would change my life and obviously the cost of Erenumab needs to be offset against the cost of all the other medications the likes of myself take.

Name	[redacted]
Role	Public
Other role	Unemployed
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Hello my name is [redacted] and I am begging you to reconsider your recommendations that aimovig not be prescribed on the nhs. I have chronic refractory migraine and new daily persistent headache and have tried all the medicines available aswell as having Botox every 3 mo this and occipital nerve blocks, trigger point injections all of which have failed.

I read that nice were of the opinion it wasn't financially a viable option as Botox was cheaper. What about when you take into account the psychologist I need due to my suicidal thoughts as a result of the pain and my psychiatrist appointments as psychologists can't prescribe medicine add on top of that my fortnightly doctors' appointments. Not to forget my appointments at the pain clinic at the nhnn queens square the ambulance call outs when the pain gets so bad suicide feels like it might be the only way out. Aimovig as well as the other cgrp drugs have shown to have a significant impact on people's migraines even in cases where all other medicine has failed. Because of Facebook we can share our experiences and hopes and we have seen how good it is from the hundreds of thousands in America who have regained some normality to their lives. I can't work because of my pain I struggle to be a parent to my 4 girls because of the pain I'm not allowed to claim benefits as my partner works before anyone thinks I'm some kind of benefit scrounger.

Aimovig could help me get my life back, please can you reconsider your opinion, or at least make it available to those who have tried Botox and nerve blocks. You can't deny sick people the chance of good health based on the opinion Botox is cheaper, Botox doesn't work for everyone.

Please reconsider, cgrp drugs are my only hope the reason I've pushed so far through so much pain knowing there was light at the end of the tunnel.

Have you really not considered the lives people are living that have chronic migraine, it's not a quirk or some kind of trendy illness it's a life changing disability.

I fear my comments will fall on deaf ears but once again please help me.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	Retired doctor- chronic migraine a factor in my early retirement

Comments on the ACD: The non- recommendation of Erenumab for NHS use is disappointing to all who have significant migraine. Whilst the cost for the many people who have episodic migraine would be very high there are smaller numbers that have chronic migraine. For them, the disability caused by this condition should be considered more than the committee has done to date. The effects on families and working life for those with chronic migraine is enormous and there is currently little to alleviate symptoms that doesn't cause significant side effects. The conclusion that Erenumab may be as effective as botulism toxin may be correct, but this treatment is not effective for all, is unpleasant and requires regular clinic attendance for administration. The costs of that are significant, whereas Erenumab can be self- administered.

The committee, as is commonplace, does not appreciate the degree of disability for those with chronic migraine. Surely Erenumab could be approved for use in the NHS at least in those for whom botulinum toxin has proved ineffective?

Name	[redacted]
Role	Parent of patient
Other role	Parent of chronic migraine suffered
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I do not pretend to understand all the data in these reports but from reading posts from The Migraine Trust I believe the report does show to help (similar to Botox) but that cost alone will be the reason for removing the NHS license? **As a parent of a daughter who has experienced Chronic Migraine with Chronic daily Headache since the age of 10 (she is now 20) I am devastated that you may be pulling the only medication that has been promised and developed for so many years for Migraine.** **Personally for us, my daughter is approaching the 7 year anniversary of her 24/7 headache and significant migraines. [redacted] and now [redacted] at [redacted] provide excellent care but they have limited drug options.** **My daughter didn't respond to any treatment although is slightly improved with DHE combined with TMS. She 'survives' and manages to pace her life but constant pain/migraine is incredibly debilitating and it is only her deep strength that has got her to University. 2 years later than her peers and with some concessions but she is there.** **She is due to have her first CGRP injection next week. It is a ray of light to have another treatment to try.** **Please do not underestimate the devastating effect of this illness.** **I feel given the significant variation in people's migraines, that still needs more research and development of drugs. You have a duty not to pull this drug solely developed for Migraine, on cost alone and to allow more time for people to try and benefit from the treatment.**	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: This has the potential to help me. I can only work part time due to migraines. Even under Botox, I still take preventive and triptans, anti emitics, prescribed pain killers to manage those migraines that come. I still feel my life is severely limited by my migraines but there is no other options to try currently	

Name	[redacted]
Role	Patient
Other role	Lending officer (awaiting early retirement due to ill health)
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I know it is all about cost & I hope you can get it for less however as I have had no effective treatment for many years including Botox I am unable to work putting strain on my relationship my mental health & my financial security, you must agree this treatment for chronic migraine patients at least. We are desperate for the hope of a possible break from constant relentless pain & suffering. I am unable to plan a day out with family and friends & have had to miss important functions due to chronic migraines. I have been unable to work as a senior lending officer with [redacted] group for 2 years- I am desperate for the possibility of being able to work in some form with reduction in daily migraines.	

Name	[redacted]
Role	Patient
Other role	Writer
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: The decision not to approve erenumab has ripped the hope from those sufferers of chronic migraine for whom Botox has not proved effective. This is the 6th most common cause of disability in the world. It ruins lives, it costs the economy millions of pounds in lost work days. The first ever drug developed as a prophylactic is being denied to sufferers on the grounds that its effectiveness has been insufficiently proven and that it is too expensive. Only somebody who has suffered chronic migraine to the point of considering suicide can appreciate how deeply disappointing this is. What are we worth as patients? What value is placed upon our lives? This is not some obscure illness but an insidious, invisible and widespread disorder. We are caught once again between the under-resourcing of the NHS and the profit motives of big pharma. Who will advocate for us now?	

Name	[redacted]
Role	Public
Other role	University Lecturer
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Migraine is a term that catches a range of migraine conditions and degrees of severity. I suffer from hemiplegic migraine having less than five times a month. I would not expect to be eligible for this medication- even though those days are hell and I am not able to go to work. In contrast, my daughter, who has had to give up her science based PhD and is unemployable despite a first class honours degree and distinction in her masters, because she is bed-ridden and in agony 15-20 plus days per month. All medication has failed to work. She is due a third round of Botox which has had marginal impact - largely on severity of attack, but this is the last resort. Nothing else is available after this. Moreover, she cannot claim disability. She lives below the poverty line and is struggling mentally because of this disease. For her this drug is a potential life saver.

Perhaps NICE could consider classifying migraine bands of eligibility thereby reducing the number of people able to get the drug which would increase impact - economic as well as medical.

You might also consider inverse subsidies i.e. for those financially affected /unable to work the drug is free, for those in work a contribution is required.

Name	[redacted]
Role	Patient
Other role	Improvement Manager
Organisation	None
Location	Wales
Conflict	None
Notes	None

Comments on the ACD: I would highly recommend erenumab is made available for NHS patients. As a chronic migraine sufferer (4 years since diagnosis) I have struggled with daily life. I have, on average, 3 migraine free days a month. My migraines range in severity and can last anything from 3 hours to 2 weeks.

I have seen multiple doctors and neurologists, and tried a vast array of medication which does not work. It is extremely upsetting when I am told that I have to just put up with extreme side effects of medication - medication that is actually designed for issues such as epilepsy, anxiety and high blood pressure - not migraine.

The results of the trials for erenumab are extremely positive and I strongly believe that others should be afforded the opportunity to use erenumab. Not everyone who suffers from migraine, but those patients, such as myself, who have a long history of extreme migraines and medical professionals struggle to suggest alternative medication options.

Please consider supporting migraine sufferers.

Name	[redacted]
Role	Patient
Other role	Home maker
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: This finding says that the outcomes are not worth it to the NHS based on budget but I can tell you 100% that this would be cost effective for people like myself. I suffer with hemiplegic migraine and have in the last year had several A&E trips with suspected stroke/brain bleed and each time it has been migraine. Every week, without fail, I have a migraine that lasts at least 3 days which means my husband has to take on all household tasks including looking after our 5 and 3yr old, all whilst doing his job which is with the NHS. Any drugs I've been offered actually have worse side-affects than the actual migraines and the DRs are totally clueless about knowing why to treat me with. At times the meds have made them worse!! This drug is a light at the end of a very dark tunnel for me so please consider those people who suffer such debilitating migraines on a regular basis and not just the people who get a bad headache and label it a migraine!!!

Name	[redacted]
Role	Patient
Other role	Management Consultant
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Dear Sir/Madam,

I am very disappointed to hear the news that NICE will not approve the use of Erenumab.

I understand that the drug costs a significant amount of money and I hope a deal can be struck between NICE and Novartis to lower the price of the drug as the clinical trials have proven fantastic results within chronic migraine sufferers.

Fingers crossed!

Kind regards,

[redacted]

Name	[redacted]
Role	Patient
Other role	Migraine patient for 54 years
Organisation	None
Location	England
Conflict	None
Notes	I have tried four or five methods to help control my migraine but nothing works long term

Comments on the ACD: I feel greatly let down, having suffered chronic migraine for 54 years and hopes being raised perpetually to then have them dashed, I have never been able to hold down a long term job and just want some quality in my life, not being able to predict when I will be hit by another episode means I am unable to do things like book holidays, please re consider this decision and give us quality to our lives

I have tried four or five methods to help control my migraine but nothing works long term

Name	[redacted]
Role	Patient
Other role	Researcher
Organisation	Commenting on behalf of self
Location	England
Conflict	None
Notes	None
Comments on the ACD: I'm disappointed that NICE are not going to be recommending erenumab (Aimovig) for preventing migraine. I have suffered with migraines from the age of 10 and now, at 26 years of age, I haven't found anything that prevents them. I wish I could put in to words the pain I have to go. They debilitate me. I can't do anything and I feel completely hopeless. I have had periods of my life where I've been unable to go to school, college and have lost jobs. I have missed out on huge chunks of my life. I understand that the reason behind NICE's choice not to recommend erenumab is due to cost. I plea for NICE to reconsider this decision. Botox isn't an option for people on low income or those out of work (as so many people with migraine are). I feel this unfairly discriminates on young people who also are unable to afford to go private. This needs to be made available on the NHS so that people like me can access the treatment they need.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Chronic migraine has altered my life, causing me to stop working and spending days on end in bed. I have suffered with this misunderstood condition for over 5 years. I have tried all of the medications recommended to me by my neurologist. None of these have altered my migraines, several made my health worse due to the horrendous side effects. There was finally some hope when this drug was developed. I cannot understand why this will not be available on the NHS. Surely treating this neurological condition will cost less than the amount of A&E visits, trial and error of other expensive (and often ineffective) drugs, mental health implications of chronic illness and the amount of time having to be taken off work that currently occur due to migraines? I sincerely hope you reconsider as this condition is seriously debilitating and affects not only the people who suffer with it but also their friends and family.	

Name	[redacted]
Role	Carer
Other role	Customer Services
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: My husband suffers from chronic migraine and is incapacitated on a regular basis 3-4 times a month or more. I have been following the research on this new drug watching for it to be released on the NHS. It is the first time a drug specifically for migraine has come onto the market. It is a really fantastic breakthrough. I really would like to see NICE allow this on the NHS.

My husband's condition means he has to spend 24 hours in a dark room to recover every time he gets a migraine. The Triptans he is currently using do not always help. Due to medication over use the normal over the counter drugs can no longer be used and the Triptans can only be used in the most severe occasions. This drug would hopefully give him his life back.

Name	[redacted]
Role	NHS Professional
Other role	Assistant Procurement Administrator
Organisation	None
Location	Scotland
Conflict	None
Notes	None

Comments on the ACD: I've had greater occipital nerve block injections which made my migraines worse. I've had Botox for TMD with a bad reaction and increased pain. This Erenumab injection was my last hope at getting my life back.

You are not taking into account that not everyone can tolerate Botox and Botox also doesn't work for everyone. Migraineurs are fobbed off with medications randomly discovered helps but never a cure. Erenumab was researched and development specifically for migraine. You can't put a price on someone's disability, pain, poor quality of life and reason for suicide. The cost of migraine through loss of working hours from sickness absence, inability to keep a job and cost of abortive treatments outweighs the cost of this new injection. Botox for migraine is 40 painful injections in the head, neck and shoulders administered every couple of months by neurologist or specialist nurse. Erenumab is only one injection and migraineurs can administer themselves.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I live with migraine and have been waiting for a drug that will prevent me getting migraines. They stop me being able to go into work. I lose time off work and I really can't afford to take time off and lose money. This is the first drug that has been made for migraine sufferers. I think that we deserve this drug to be on the NHS because he myself cannot afford to get in privately. This is a debilitating disease and we as migraine sufferers deserve this drug. Please reconsider	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: As a chronic migraine sufferer who has trialled most other available treatments I am extremely disappointed by NICE current stance around erunanab prescribing. Chronic migraine is a hugely disabling condition with few treatments developed specifically for migraine. It seems very short sighted given the successes reported in current trials of the treatment, particularly given the cost to both the NHS and the economy of chronic migraine. I feel that the treatment should be offered to patients who have exhausted other options whilst we are awaiting the outcome of further trials. Personally I have worked in the NHS for 15 years however due to my condition I have had long periods of time on sickness absence and am now approaching the point of medical retirement due to chronic migraine. I am unable to live a full life, unable to start a family and to contribute to society in the way that I would wish. Without further development of treatments, research and trials I fear I will continue to be disabled with little quality of life.	

Name	[redacted]
Role	Patient
Other role	Student
Organisation	None
Location	Europe
Conflict	None
Notes	None

Comments on the ACD: I feel that it would not only be a life saver for many citizens (as migraine is often accompanied by mental health issues), but it would greatly benefit the economy as migraineurs would be better able to go out and work and thus spend more money.

This is the first ever medication created just for migraines and it's been in the works for over 30 years. It is a massively momentous time for myself and fellow migraineurs. I and many others have been put on scary medicationsfor ailments we don't have. In the past 5 years since I was 19 I've been on Beta blockers, anti-menopause medication, anti-epilepsy, anti-depressants and medication for sever Alzheimers and dementia, done of which I suffered from. I have also encountered many horrendous side effects faced because I didn't have the ailments they were made for. This drug would be a game changer as you'd feel so much safer taking a drug made for your ailment.

I think that it would an amazing, momentous step for thousands of migraineurs across the UK.

Name	[redacted]
Role	Patient
Other role	Deputy Nursery Manager
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have had NDPH with Migraine for over 8 years. That means I have had a headache for the last 2979 days, 24 hours a day, add on at least 20-25 migraines a month on top and you start to get the picture of this condition. It is a horrendous condition to live with for myself and for my family. I am not the same person I was before. There is no logical reason for why I got this condition and no obvious triggers for the migraines. The background headache is just about manageable, but add the migraine pain into the mix and it becomes intolerable.

I do work full time, but that is because have an amazing boss and I am just as stubborn as this condition and I refused to ever let this condition take away my life. Are there days I want to give up, you bet there are. I have banged my head against walls when the pain is so bad.

I have tried all the medications suggested and had Botox for 2 years with some relief, but it stopped working, I was gutted as even though 30 injections in my head was extremely painful at least it worked and when you have this condition you will try anything.

I have cried to my GP, been put on anti-depressants. I can't remember what it is like to not have a headache, or to have a full night's sleep. Whenever I get colds the pain becomes unbearable.

To now be told that the one hope all of us were clinging to is being taken away is devastating. I would love to go privately, but there is no way I could afford to cover the costs.

All any of us want is the opportunity to try, of course it may not work, but hope is all most of us have left.

Name	[redacted]
Role	Patient
Other role	Administrative- but no longer working due to migraine
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I suffer from chronic migraine and have done for the last 20 years. I have tried all of the preventatives over the years including Botox and occipital nerve injections. Unfortunately, none of the above have worked for me. I am unable to hold down a job. I now suffer from depression due to the stresses that migraine has brought. I was so hopeful that the aimovig would be approved so that I could try it and start living again. **Please reconsider.**	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I think it needs to be remembered and considered again that there is still a huge amount of people whom Botox doesn't even work for. What then? Surely the costing of more and more consultations, expensive procedures and hospitalisations completely outweighs the costs of a patient being able to administer themselves one injection a month? And couldn't you put a safe guard in place where patients would be required to give Botox a good go before having access to this drug? I don't think I've heard of an instance where Erenumab hasn't made a difference to someone's migraines in some way. Please don't take away from people who are in severe and disabling pain every single day, a great chance for getting their life back. Please make it accessible regardless if you are rich or not. The news of this latest medicine specific to migraines has sparked hope in so many people's lives - you have no idea - please don't snuff that hope out.	

Name	[redacted]
Role	Patient
Other role	Sales order processor
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Having suffered from migraines since I was around 12, I am now 28 I have never found any medication that has truly helped me. I have tried various types, beta blockers, triptans and epilepsy medications, some with horrible side effects. With no known migraine trigger life can be a worry of when the next migraine will occur. It isn't as simple as 4 migraine days or more s month, I can go 2 months without any but then have 4 in a week. They are unpredictable and inconsistent. I now work in a role where I don't get paid for sick leave which is a major issue when you suffer from migraine. Some days are impossible to go to work and the stress of not being paid adds to the stress of the migraine. A viscous cycle. Any new effective medication that provides relief from migraine is so important to anyone like me. A silent invisible illness that people often doubt is real, it gets you down and often you feel like nobody cares. Nobody knows why they happen, what they really are or how to cure them and it often feels like not enough is done to try and find some sort of cure or relief. If this drug has shown to have a benefit surely it is worthy giving it to people who need it.	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have been suffering with Migraines since I was 16, turning chronic 5 years ago. I am 28 & I have tried everything to help them but no luck. Getting this treatment on the NHS was my last hope. It is extortionate money to pay privately! The fact that this could give me my life back & it could be taken away due to cost is heart breaking. Please make the RIGHT choice.	

Name	[redacted]
Role	Patient
Other role	Waitress
Organisation	None
Location	England
Conflict	None
Notes	

Comments on the ACD: Migraine, though it's not life threatening, is pretty effective at halting any life progress. Having spent the last five years in near continuous migraine I really hate the complacency of rejecting additional treatment for a condition that is so difficult to treat effectively. Many patients like me would love to go back to full time work and maybe even enjoy life.

Cost of travel to one of a few places that can provide Botox treatment is high, especially to people who have had to give up full time work do to frequent migraines and those who are unable to drive during migraines, or can't afford to keep a car. As the erenumab is self-administered, it would improve the equality of access to effective treatment.

Neither of the treatments available will work for everyone and so there will be those few for whom none of them worked. I'm myself down to the last two treatments (Botox, and if that doesn't work, nerve blocks), both of which require regular appointments with the neurologist and time off work.

Migraine, as many other conditions which affect predominately women, has hardly ever been directly treated. It's the first medication developed that is targeting the migraines and while I know it doesn't necessarily make it more effective, I believe it's important to encourage further research in the area.

Name	[redacted]
Role	Patient
Other role	Cleaner
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have migraines seen I was 8 years old and when I was in early 20 they became chronic migraines and a daily headache suffer to I am on daily medication that I take morning and night and in the last two years I be have the General operative nerve injections and I the last 6 months I have been haven't Botox I have not fill in the top part as I have Learning difficulties and do not quite understand it all do get is this new medicine would help a lot of people a specially like me the has been having both lots of injections Very three months wouldn't it save the NHS some money by giving this new medicine a try there's not been a new medicine for migraine sufferers in a long time.

Name	[redacted]
Role	Carer
Other role	Non pharmacist manager/technician
Organisation	None
Location	Scotland
Conflict	None
Notes	None

Comments on the ACD: This is a great achievement to have a new migraine drug after all these years. I think price comparison is nothing compared to overall cost of Botox or DHE. My sister suffers chronic migraines, DHE works however wears off and can't be given regularly as not enough spaces in hospital in Scotland to allow her to get it when needed. This results in her having a short period of time where migraines are manageable then back to being seriously ill with them. Botox made her migraines worse! Both treatments don't take into consideration her life or little quality of life she has. She suffers depression, anxiety, has lost her job, can't work, is bed bound on a weekly basis and relies on others for help and support.

If the new drug even gives her a few weeks each month of pain free then it's better than both Botox and DHE.

I would be willing to pay for this treatment for her as she deserves to have pain free existence.

I look forward to updates and pray it is allowed in Scotland soon!

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a chronic migraine patient I would like to say that although this is bring compared to Botox which I am hopefully trailing in the next week Botox does not work for all patients and so this would provide those patients with another treatment option which can only be a positive trails in America are showing that this drug is very effective and can be used well alongside Botox in stubborn cases or alone for more responsive patients. Migraine is so very debilitating I have been unable to work for over two years and am reliant on benefits as my husband cares for me as a patient who also gets paralysis with their migraines I am often bed bound and so welcome all new treatment options and regardless of cost think they should be used as a treatment line on the NHS even if it means waiting to see if Botox fails first it would be better than having no hope

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: It's hard to put into words how utterly horrible migraines are and how much of an impact they can have on people's lives. People who suffer with them chronically are often left with no options for effective treatment, or are forced to take medication meant for other conditions, often with side-effects. My friend has had daily migraines since she was 8, she is now 62 and this drug is her last hope as Botox has failed. She is one of the worst sufferers in the UK yet she has been made to jump through millions of hoops over her life to access drugs which have side effects and have never been of long term use. I think it is deplorable that you are refusing to allow her to try this new drug	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: As a sufferer of chronic migraine who has tried every other medication option, this is extremely disappointing. I can only control my migraines (15-20 days per month) with strong painkillers which is highly unsustainable. I am close to not being able to work, which would simply make Aimovig even more unaffordable for me if it is not available on the NHS. Please re-consider what a huge impact a 50% reduction in migraines would have for so many of us.	

Name	[redacted]
Role	Public
Other role	Regional Manager
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I think it's quite surprising this has been turned down, given the few solutions to chronic migraine there are available. A disabling condition that affects a lot of young people and takes them out of the labour market and away from social interactions too. The resulting costs of such a person over a number of decades are surely also significant? My husband has ulcerative colitis and was lucky enough to benefit from 4 different biologic home injectebles, so I'm not sure what the difference is here?	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I understand that there is a huge cost implication in administering this drug across the NHS, yet when you look at the impact migraines have on people's lives, in my opinion, the cost should not be factored into. If it were to be available in the NHS, surely, the economies of scale would ensure that long term, the price would fall. **As a migraine sufferer, for 2 days a week, I am non-functioning, by this I mean I stay in my bed and wait for the symptoms to pass. I suffer from a migraine attack in average every other week. What employer is going to employ me?** **With this drug being made available, it would be life changing for so many people.**	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: This drug needs to be available on the NHS. You cannot compare this to Botox which may work for some and not others, and was not designed to target migraines specifically. What about those people who have tried many other options? This has proven to work for a lot of patients, it needs to become mainstream for others who suffer.	

Name	[redacted]
Role	Carer
Other role	Biomedical Student
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I am a carer for a daughter who is a chronic migraine sufferer who has tried numerous drug treatments included in your document pathway. This has included Botox and acupuncture as well as cranial osteopathy. The only treatment that gives some relief are nerve blocks which are steroid based. We are both devastated to hear that this drug is not going to be made available on the NHS. This could be a life saver to many migraine sufferers like my daughter who lives with constant pain daily. I urge you to reconsider this decision.	

Name	[redacted]
Role	Patient
Other role	Unemployed Housewife
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: This is the first specially designed drug for migraine prevention in 20 years, it is extremely important for the 6 million suffers in the UK of whom 700 thousand are chronic, I have had migraine since I was 15, I am 48 now, they became chronic in 2010 and I had to give up work in 2014, I am receiving Botox but that doesn't work for everyone, we should be given the chance to try this drug, migraine is so much more than a headache.

For me a migraine is not just pain in my head, its nausea, then vomiting, motion sickness, being too hot then too cold, having cold feet and nose, increased urination, diarrhoea, excessive burping, the inability to find the right word, or comprehend what someone is telling me, lack of sleep which then leads to another migraine because sleep is a trigger for me. I always say it's like being drunk, hungover and having a dose of food poisoning all at the same time, at times in my life I've wanted to kill myself because of the pain.

Aimovig is not a cure but it is a chance to live as normal a life as possible.

Please reconsider your decision.

Name	[redacted]
Role	Carer
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: A wide variety of medication is needed to manage conditions for different individuals, such as diabetes, hypertension, epilepsy - chronic neurological conditions need a variety of medications to reduce both severity and frequency of attacks.

1/3 of the population is estimated at being affected by this unexplained and incurable condition, resulting in a loss of work, income, family, and well-being.

The lack of medical options increases pressure on the benefit system in supporting both patients and their families.

The number of affected patients in this group surpasses the number of people with diabetes, epilepsy and asthma combined, yet receives a fraction of the funding.

Unmanaged conditions result in an increase in A&E and GP visits, who are often under-trained and unaware of the current developments and options in both diagnosis and treatment.

Insufficient primary care increases the strain on specialist neurologist referrals, as the only specialists able to properly diagnose this condition.

Every unmanaged diagnosis results in huge economic and social change, from medical retirement to poverty, isolation and divorce, increasing the demand on pain management and psychological therapies.

In addition to the socioeconomic effects, there are often additional comorbidities, from depression and anxiety to fibromyalgia and stroke, requiring more medication and cost.

Current medical options result in unwanted effects from unpurposed medication, preventing people from starting families, living in semi-comatose states, and living unfulfilled, frustrating lives.

The increased risk of suicide cannot be underestimated. From unintended brushes with the law, to feelings of hopelessness and finding an escape from the pain, this condition is so debilitating and consuming that many patients have considered or even attempted suicide in preference to the treadmill of trying one unsuccessful, unpurposed medication after another.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I wanted to comment and say recent news that this is not going to be put into the NICE guidelines is hugely disappointing and frightening, it is something myself and my loved ones have been awaiting for so long and given hope that this may be the treatment that releases me from the hell that migraine has meant for me. How can it be that it has been researched, evidenced to help so many but yet that not being important enough for it to be put into the nice guidelines. I hope this decision is reconsidered and changed for the many, many people in the desperate situation that I am also in.	

Name	[redacted]
Role	Carer
Other role	Housewife
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I'm writing on behalf of my daughter who suffers from chronic migraines most of her life. She cannot work, she has no social life and at 28 years old it's not very nice. She has been under [redacted] for a few years, she tried all migraine pills, injections and Botox , nothing really work, we were all putting our hopes on Hannah getting a chance to try this new drug , but there is no way we could afford this medicine privately . It's shameful that this drug is being turned down because of the cost.it could change my daughters and many, many others life around.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I was very disappointed to hear that this new treatment for migraine would not be available on the NHS. I have experienced migraines from a young age and they are truly debilitating. In the last two weeks I have experienced 4 migraines, and although beta blockers are taken regularly to help ease the regularity of a migraine occurring, this is having a huge impact on my work and personal life. This is the first preventative treatment for migraine to come through the initial stages of research and been approved for patient treatment. To hear that the treatment is not going to be available on the NHS, as having the treatment privately is not an option, is truly heart breaking. I hope that you can reconsider this decision as this decision does affect the work place and if people with migraine are unable to work and function this will have an impact on the economy. Please reconsider this decision.

Please reconsider this

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have had migraines since I was 6; I am now 46. I have lost count of the number of treatments I have tried, how many days off school and work I have lost or been guilty of 'presenteeism', how many appointments and events I have had to cancel. For me they work for a while then stop. I've gone in cycles over the years of being bad with migraine and then being ok. At the moment I'm in a cycle of a bad few years and I'm lucky my employer understands otherwise I would be in trouble for my absence level. I have paid privately for various eye sight etc. tests to try and improve my health. The medication I'm on is quite new to me and working right now but it's a question of how long for. The next option will be Botox but what if that doesn't work? If a medication has been developed that is known to work on migraine then it should be available, to those who have tried everything else. I am the same with my other illnesses - I'm on adalimumab for my arthritis and Crohn's as nothing else worked. I know these medications are expensive, but these are a lifeline to keep those of us who want to work in work, or for those who run a family to continue to do so. Without the help of the NHS and the medications they provide I would be another burden on the welfare state, not being able to work when I really want to. Please, consider allowing this medication to be available to those who have no other option left.

Name	[redacted]
Role	Patient
Other role	Individual patient and also Occupational therapist and CBT therapist in NHS
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a lifelong migraine patient - from the age of 6 years to my now 54 years and having moved from episodic when younger to chronic in the last 10 years I am disappointed and upset at the NICE decision. I have tried every oral treatment I am able to and failed. I currently have Botox from which I get some reduction in frequency but which does not touch all the other symptoms that mean I still am forced to come home from work because I cannot see or speak to my patients, to ring in sick and cancel NHS patient's appointments because I have woken up and am unable to stand up without vomiting, to have little to no social life and to limit my holidays because travel and flying trigger migraines. It has been suggested to me that because all the associated symptoms are so debilitating that I would potentially be a candidate for Erenumab, given it is the ONLY group of drugs that is migraine specific and treats these symptoms. This decision removes that option.

I have continued to work my whole career but lost days, had disciplinary sick reviews, fought for disability adjustments and curtailed my ambitions, promotions, hours and thus income because of migraine. My children suffered when they were young because of the hours spent being popped in front of the TV because I had to go to bed. There are thousands of people like me. The committee's decision reads as though we haven't tried hard enough to control our migraines. Most people, if they can ever get to see a neurologist who has any real expertise in migraine, have been bullied into taking a plethora of medications NONE of which are specific to treating migraine and ALL of which have life impairing side effects at the so called therapeutic doses. Many people have to suffer the migraines rather than the side effects. This leads to acute medication overuse and episodic turning into chronic at which point we do not fit the criteria for Botox - and that is assuming you can access Botox in your health authority.

The cost effectiveness which the decision appears to have been based on compares Erenumab with Botox - at less than £2000 difference for chronic migraine. Whilst Botox does work for many people there are a group for whom it doesn't BECAUSE all the other associated migraine symptoms - nausea and vomiting, cognitive dysfunction, visual impairment, neurological impairments in limbs etc. are not treated by BOTOX. It only reduces pain and frequency. This chronic population for whom NICE admits Erenumab is most effective are the ones being penalised by this decision because the criteria being considered by the committee is looking at ALL the types of migraine and making a generalised costing decision. It is insulting to infer that people who have tried and failed on 3 treatments should just try another oral medication. They very likely have - but again only if they can access a neurologist who is prepared to keep on prescribing and supporting. The figure of 3 failed treatments is an arbitrary number that NICE came up with in the first place when considering Botox. I was told by a neurologist when listing what I had tried that there was nothing he could do for me, he had

'failed me' and promptly discharged me out of sight and out of mind.

This is not a disease of old age where hairs can be split about a couple of extra months of life. This is a disease of young, working age people, mostly women, and consequently having a major impact of a person's functioning, parenting, and quality of life in the years when they should and need to be functioning in working life. The costs to society, employers and ultimately disability benefits are huge and have not been acknowledged in this statement. I would ask the committee to consider reviewing the decision, even if the approval is for a sub group of migraine affecting the people most disabled by it. Thank you

Name	[redacted]
Role	Local government professional
Other role	Community Fire Fighter
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Due to low blood pressure and other side effects I am unable to use recommended migraine prevention treatments. The years spent on beta blockers were abysmal, miserable, and unable to do very much but go to work home and sleep. And I still had the occasional migraine. Beta Blockers were tried as random migraine attacks resulted in disciplinary action at work and the risk of losing my job. I am now a secret sufferer. I am prescribed sumatriptan which is effective but would still mean time off work for it to take effect therefore I go to work and my team mutually conspires to cover my absence whilst I sleep in a dark room for a few hours. I should not drive in the initial stages of a migraine or in the first few hours of taking Sumatriptan. However I frequently do as the alternative is to take a day off which could result in disciplinary action. Aside from work my migraine threshold is so low that a long plane flight, filling the car with diesel, a colleague wearing perfume a bad cough or a power point can trigger a migraine. I am desperate for a useable preventive treatment for migraines, the overall cost to me personally and to the national workforce must be significantly improved by allowing this medicine to be available on the NHS. Countless family weekends, cancelled plans and trip, as well as the affect it has on my personal relationships make this an opportunity which has the potential to be life changing. Currently on my 3rd day of migraine recovery after it has been triggered by a bad cold and blocked sinus's

I would be happy to further trial treatment

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a chronic migraine sufferer for 10 years who has tried most of the preventative treatments including Botox often with significant side effects and little improvements (Botox increased frequency and severity), I think it is crucial that specialist consultants have another possible effective treatment in their amourary. I never take on new drugs lightly but constantly hope I will find a treatment that has a significant effect on my present poor quality of life. Erenumab might be the one if my consultant was allowed to prescribe it.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have been suffering from Chronic Migraine with Aura since February 2016. I have lived with constant pain in my head along with the other migraine symptoms of visual disturbances, nausea and photo/phono sensitivity, fatigue, confusion, forgetfulness and irritability since this date. The pain varies from annoying to disabling. i have had as many as 26 migraine days in one month.

I have tried several medications, including Propranolol, Amitriptyline, Pizotifen, Candesartan, Topiramate and Sodium Valproate as well as two types of Triptans. I have also received the Greater Occipital Nerve Injection and I receive Botox injections every three months.

The benefit I have received from these various drugs has been minimal. I get, at best, three weeks benefit (the headache is still there, but is less likely to become a full migraine) out of 12 weeks from the Botox injections and I still suffer with terrible migraine attacks meaning that I have to take at least one triptan and go to sleep (usually for a couple of hours). Usually the pain is reduced on waking but still not fully recovered from the migraine, this can last into the following day or two.

I feel that Erenumab was the last possible chance I had of returning to a normal life. I have lost my job and now claim benefits due to my inability to work. If Erenumab was to be licensed, there is a possibility that I would be able to return to work and become economically active again. The economic and societal benefits of this drug surely outweigh the cost to the NHS.

PLEASE LET US HAVE A CHANCE AT A NORMAL LIFE. WITHOUT HOPE IT IS A LOT HARDER TO DEAL WITH THIS CONDITION.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a chronic migraine sufferer and I have tried all of the treatments available on the NHS. My migraine is so severe that I wasn't able to continue even in part time work and for two years now I have been forced to be unemployed because of my migraine, with no support from the government.

My only hope through the darkness of my condition has been this new drug, which I have been following the results of the trials on for years and have been so eagerly awaiting its availability on the NHS in the hopes it will enable me to return to employment and perhaps have a life which doesn't revolve around my debilitating pain.

To hear the use of the drug on the NHS being rejected and for the reason of cost is such a devastating blow to me and all of the other chronic migraine sufferers. This was my chance for a normal life and it isn't worth the cost of less than £100 a week. My quality of life, my ability to work, and my chance at living a life is not worth less than £100 a week.

I beg you to reconsider this decision as it has such a profoundly life-changing impact for people like me.

Name	[redacted]
Role	Patient
Other role	Disabled
Organisation	CGRP & Migraine Disease
Location	United States
Conflict	None
Notes	None

Comments on the ACD: Migraine is an incurable and progressive neurological disease. Left inadequately treated it not only has a high risk of greater severity and frequency, but has a high risk of comorbid conditions accumulating, adding both to the cost of medical care and challenge in treatment.

I am writing as a representative of one of the largest CGRP and migraine groups online, with over 5000 members. I'm writing to appeal NICE's decision That Aimovig is not cost-effective for the NHS to approve for migraine patients in the UK. The cost of migraine disease, which is currently incurable, is staggering! It is not as simple as the cost of medications needed to treat this disabling disease compared side by side , but also lost time at work, lost efficiency at work, emergency room visits, side effects caused by medications which are not designed for migraine treatment, GP visits, and more!

[redacted] **with over 5000 active members it has been a rare opportunity for me to see first-hand the impact Aimovig is making. I can say with assurance that a high percentage of people with migraine who take Aimovig are literally getting their lives back. What this means is that many of them are able to go back to work if they were disabled, they use far less, if any, abortive medication, they no longer visit the emergency room, and other doctor visits are reduced as well. This is besides them no longer experiencing the frequently side effects from medications which are not designed to treat migraine disease such as topiramate, gapapentin, botox, namenda, SSRIs, depakote, beta blockers and calcium channel blockers! These other medications are well documented as causing problems with the liver, kidneys, seizures, hyperammonia poisoning, severe depression, palpitations, and more. Many patients simply are unable to tolerate these side effects and so end up with preventive options. This then results not only in lost work and increased medical appointments, but also the high risk of serious side effects from the currently used abortive medications imitrex (& other triptans), DHE-45 & other ergotamines, ketorolac, opioids, & prednisone - these cause heart valve problems, blood clots, vision loss, gastrointestinal bleeding, kidney failure, liver damage, & so the list goes on!**

I am writing, as someone who lives in the USA but who is also a UK citizen and having experienced first-hand for 25 years how migraine is treated in the UK. I implore you to reconsider your decision and allow Aimovig/Erenumab to be covered under the NHS for those patients who have previously tried and failed on 1 or more other medications currently used to prevent migraine.

Thank you for your consideration!

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I would like to appeal against the decision not to approve Aimovig as, for me, this is the last resort. I have tried every medication and none have worked. I have tried botox and nerve block injections 6 times and a Cefaly II device and these don't work either. There is nothing left for me to try.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: It is positive that the committee concluded that migraine, particularly chronic migraine, is a debilitating condition that significantly affects health-related quality of life. However, the consultation document does not adequately acknowledge that this is the first treatment that has ever been developed specifically to treat this condition. In practical terms, in assessing the cost-effectiveness of this new treatment, it would seem appropriate to acknowledge the amount of money expended (by both the state and directly by patients themselves) on treatments that were not designed to treat the condition and, therefore, which have varying positive impacts (and other negative side-effects). That, together with the negative impact that migraine can have on mental health especially given that there is no cure and limited funding dedicated to research, mean that the current situation (without this as another option available on the NHS) increases the financial unsustainability of the condition, especially given the amount of days that people are affected and the prevalence of those people who are of working age. For patients such as myself, who has been affected by migraine for 29 years (since the age of 13), have been receiving secondary healthcare for migraine for almost 20 years, am affected by an average of 23+ days per month, have tried five preventative treatments (including Botox), and for whom acute medication provides no pain relief, this decision is devastating and one that I sincerely hope will be reversed.	

Name	[redacted]
Role	Patient
Other role	Editor
Organisation	None
Location	None
Conflict	None
Notes	These are my personal comments, purely as an independent patient with intractable chronic migraine. I do happen work for [redacted] and I do work on projects funded by Novartis. However, I have not worked on anything relating to erenumab.

Comments on the ACD: The main reason for the rejection of erenumab by NICE seems to be regarding the lack of evidence for any greater effectiveness that Botox. I accept that there aren't any trials that directly compare the two treatments. However, the two treatments have been indirectly compared. I do feel that this is partially irrelevant. The pathophysiology of migraine remains poorly understood. All other preventative drugs were not developed specifically for migraine and we don't fully understand their modes of action. It is well known that patients with migraine may respond dramatically to a preventative therapy and others may be non-responders. Patients often try several before they find one that they respond to, with tolerable side effects. These patients need more options - especially if they have tried 3 or more anti-hypertensives/antidepressants/antiepileptics and Botox and still have had no reduction in their migraine frequency. If Botox and erenumab were compared in a crossover trial, it is highly likely that a large proportion of patients who respond to Botox would not respond to erenumab and vice versa. Therefore, I feel that not having a direct comparison with Botox is irrelevant. Yes, it erenumab to be similarly effective, but just because erenumab isn't more effective then Botox doesn't mean that it won't help people for whom Botox is ineffective. These people are often unable to work due to chronic migraine and therefore claiming benefits that far exceed the cost of erenumab, and are suffering beyond what would be considered acceptable for most other conditions. Please give them a new option to try.

The appraisal does not, in my opinion, apply sufficient weight to the fact that erenumab is self-administered whereas Botox can only be administered by a specialist neurologist. Both treatments would require a consultation with a neurologist to be prescribed (who they'd be seeing for intractable chronic migraine anyway), but those prescribed erenumab would not need to return to the clinic thereafter, once the treatment was found to be effective. In comparison, patients receiving Botox require a lengthy appointment with a highly specialised neurologist every 12 weeks- taking valuable clinician time that could be spent seeing more individual patients.

Name	[redacted]
Role	Mother
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: After years of suffering, trying all treatments and eventually having to give up work therefore struggling financially, my daughter had hope for this drug, the only one developed specifically for migraines. **The results in USA seemed to be positive and I was shocked to hear it was not going to be financed here.** **Please give these chronic sufferers a chance of going back to work and living a normal life again.**	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: This drug has the potent to change the lives of many who suffer chronic migraines. Please go ahead with it.	

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have suffered from migraines since the age of 7 I am now 45 I have tried every preventative medication for them with no joy or unbearable side effects. I am currently travelling from Bristol to Hull every 3 month to receive Botox. I have been desperately waiting for this drug to be made available on the NHS I have had to give up work in December 2017 as couldn't even manage my three day a week job. Migraines have ruined my life, my relationships, friendships and has at times made me want to not be here at all as they rule my life, people do not understand the impact the have on your life and your relationships. I cannot believe with the amount of people who suffer with migraines that a drug specifically created for migraines has not been produced before now & now it has it is not available on the NHS. All the other preventative medications available are for other conditions and come with some terrible side effects. Imagine not being able to plan anything or commit to anything but having to wait until you wake up every day and see how your head is before you decide what you are going to be capable of doing that day. I urge you to rethink the decision on this drug. Migraine coat employers millions each year this could help so much and enable a lot of us to be able to go back into the workplace and feel normal again. I cannot work but cannot claim disability I feel like a complete burden to my husband and family and my migraines and the effect the have on us all make me feel like they would all be better off without me. Give us a chance to feel useful again and be able to function again.

I have always worked since I left

School at 16 paid my taxes and National insurance but am denied access to this the only drug designed specifically for migraines through the NHS and due to the fact I cannot hold down a job because of them I will never be able to afford this drug on private prescription

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I believe NICE should reconsider their decision for erenumba. A lot of migraine suffers have had to wait years for a drug specifically aimed at migraine. Currently we are using prescription drugs that aren't designed for migraine and although they have helped me in the past they have also come with some very nasty side effects, I've had nose bleeds and felt poorly both physically and mentally from others. The dose-ages are changed or the medication is due to them not working which also resulted in me then having to stop as they lowered my heart rate and blood pressure too far. I am currently trying Botox and yet this isn't a drug specifically for migraine it is only half helping, but has come with side effects as well such as a stiff sore neck.

All these non-migraine drugs are not cost effective, they are not designed for migraine and it's a 50/50 chance they will even help. They come with horrible side effects which can make people worse not better and can cause headaches themselves. Medication induced headaches are daily and it can make it hard then to tell which is medication induced and which are true migraine. Thus causing more sick days/ time off work or even having to stop working altogether. Alternatively you can stop the treatments and suffer as there is NO alternative once you have tried everything. Even GPs don't know what to do once you have used the main tablet medication and it can be years of trial and error to have to use all of them before GPs will refer to a migraine clinic! Who only really offer more of the same drugs not initially licensed for migraine and that may or may not work, I have now tried everything and am currently trying Botox with mixed results. If this doesn't work then I don't know what else there is?!

Migraine has caused me to take time off work, change the hours I work to a part time job which offers a lot of flexibility due to having to take time off. It also effects my family life and my ability to care for my kids. I'm lucky I have a supportive husband who cares for them when I'm ill which can include him being called home from work himself. But its hurts me that I can't be with my family enjoy them and activities together.

I have to consider everything and if it will trigger my migraine, such as bright lights, high pitched noises, food, smells and a whole load of other things, migraine triggers are always on my mind when planning to do anything from going to work to going shopping or even just a family trip. It has a major impact on my mental health too as I spend most of a month feeling poorly or in bed due to migraine, which can make me depressed and emotional. Everyday I have some form of migraine, from full blown migraine to medication induced migraine.

If I could stop or even reduce the migraines I could work more, care for my family, increase a more healthy mental health and generally be more proactive and happier in my life.

It was a relief when this drug was announced as a migraine specific drug that may actually work and after reading about it myself it sounds like a positive step, cost effective as is not using drugs licensed for other conditions and has less side effects, therefore reducing the need for doctors' appointments and more medication to combat the side effects, giving people the option of coming off benefits and getting back to work or even being able to commit better to work or family. This drug offers migraine suffers a chance at normal life and the fact it is self-administered is better than Botox for which you have to attend hospital every 3 months again cheaper for the NHS.

Yes it's a new drug and there is no long term data from research, if you don't allow it to be given then there never will be, patients are more than aware of this and migraine sufferers have waited long enough for a drug to be developed specifically for migraine. The trails have offered positive results and these are better than the current results for the treatment already offered now!

I believe erenumab will be cost effective as it will reduce the need for other treatments requiring regular hospital appointments or GP appointments, it will reduce the amount of people claiming benefits or sick pay, it will reduce the need for other medications, and will improve the lives of 1000s of people.

Name	[redacted]
Role	Patient
Other role	Secretary – NHS
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have suffered from chronic migraines for over 40years. I have lost count if the medications I have tried, all with little or no success : including Botox

The announcement of this new treatment gave me hope that I would eventually be able to lead normal life without the constant worry of an attack

I have been threatened with disciplinary procedures at work until I produced confirmation of my disease, I have missed important events due to this debilitating illness. I am covered under the Equality Act due to severity of attacks

The cost of my current treatment, consultant visits and loss of working hours must surely be taken into account.

For all migraine suffers this must be a devastating decision.

Name	[redacted]
Role	Patient
Other role	Research Fellow
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a chronic migraine patient I have been struggling with this disease for many years. This is a very debilitating condition, which affects our work and private lives, forces us to downgrade our expectations on many aspects of life and leads us to loneliness and continuous struggles not to lose our jobs and fall into poverty.

Like many others, I have tried different therapies and cannot try others but I am still suffering for migraine at least 20 days a month.

I have followed the development of this new drug as the first real hope to go back to a decent life. I understand this is a costly drug and I perfectly acknowledge it should be used only when necessary. But taking away this possibility from people who need it so badly would be an offence to all those who have been holding on until now, fought to keep working and being part of this society, knowing that when the time would come, their health system would support them.

Name	[redacted]
Role	Patient
Other role	Education support worker
Organisation	None
Location	Other
Conflict	Yes
Notes	None

Comments on the ACD: I am a patient on Aimovig / Erenumab for preventing migraine [ID1188] 140mg dose that has had amazing results. Even though i have had few side effects i feel that this outweighs the quality of life i have now been given back since being on Aimovig. I Live in Australia. I Am on this in conjuction with my daily medication prescribed by my neuro together this has finally worked well. I believe there will never be a perfect fix for anyone. So to remove any form of possible assistant medication would be a huge injustice.

In the first month I only had 5 Hemiplegic migraine attacks which lasted 24-36 hrs this began towards week 3 and for me was still a huge win. My brain has never felt so functional without pain.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: It is extremely disappointing to see that NICE have rejected this on the NHS.

I currently suffer with chronic migraines all day, every day. This has been for the last two years and I know there are others where this has been their life for many more years! Missing work, not being able to travel, not seeing my friends and family. This is a debilitating disease and ruins lives.

I have tried 3 different types of medication, acupuncture and Botox. Neither have worked, not even giving me one migraine free day.

I've recently had an overnight stay in hospital because of my chronic migraines. CT and MRI scan have both come back with no issues. Bloods are fine.

The consultants reaction - "I don't even know what to do with you". How can you expect someone to live like that?!

My specialist at York hospital has advised that even she doesn't know what the next step is after Botox.

Erenumab was my last hope. I've read that so many people have benefitted from this drug but unfortunately I am not in the position to go private for this treatment.

I've even tried to take out a loan just so I can try Erenumab.

All I am asking for is ONE migraine free day and this could be all I need!

Name	[redacted]
Role	Patient
Other role	Student Nurse
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I suffer from chronic migraines. They massively affect my life. I'm missing half my placements and struggling with essays etc. due to these. It affects my entire life and causes me to suffer from anxiety and depression. Erenumab is the first hope I've had in a really long time. It's the first drug which has been created specifically for migraines. To give people like me the chance to live a normal life is something you can't put a price on. (Unless you get it privately but if I was to pay that amount to get my life back, due to being on the bursary I would no longer be able to afford rent, bills or food) Botox, like every other migraine preventative has been formed for something else. Erenumab had been many years in the making and is designed specifically to treat migraines. I, like many others, would appreciate this chance at a normal life.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I am a chronic migraine sufferer. I have lost my career and social life. I have tried all preventative medications with barely any improvement. The treatments have often caused more symptoms than they solve. Chronic migraine robs people of their lives and yet there is no dedicated preventative medication available on the NHS for sufferers. This is simply not on. We should have access to this new treatment that offers hope out of the prison of chronic migraine. I want my life back, I want to be a productive human being. If this new drug is not made available on the NHS I will not have access to it. This is just so unjust. Please approve it. It will be our only dedicated preventative medication, and we need it. Thank you.	

Name	[redacted]
Role	Patient
Other role	Now unemployed
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: For the past 9 years I have been on this roller coaster of high episodic/chronic migraine. I no longer work I had a great career at [redacted]. I am now reliant on benefits to survive. I no longer socialise, I cannot look after myself at times and lost years of my grandchildren growing up. I am one of the lucky ones that has a good GP and I get to attend a headache clinic. Over the years I have tried many prophylatic medications, including inpatient treatment and devices to prevent migraine episodes. As yet I have not found something that has worked. I have had GON injections and three rounds of Botox. I want to live my life not just survive another day. I don't want to fear each day in case it's another day of pain, sickness isolation, loneliness, depression. On many occasions my 82 year old parents travel many miles to get me to hospital to get intractable migraine under control. The cost of my medication, GP visits, Headache clinic visits, benefits to support me to live. Input of social services to support me and my son who I am meant to be his carer. The cost of all of these things must be much more than the cost of the Erenumab medication. The cost of getting my life back is priceless. We only get one life and I don't want to waste mine If there is something to help me live again.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a 41-year-old chronic migraine sufferer who has lived with migraines almost all my life. I have tried all other available preventatives, including Botox, and all have been ineffective / intolerable. I, like other migraineurs in this position, am incredibly disappointed with this draft ruling. For at least a year the UK migraineur community has waited eagerly for this drug, expectations raised by widespread media coverage. But with good reason: clinical trials of all the CGRPs have shown clinical effectiveness (as you acknowledge) in the order of existing migraine preventatives. Alongside all cost considerations it should be borne in mind that migraine causes £8.8 billion per year in lost productivity. Clinically effective drugs like Aimovig will help to reduce this. However and this is the crux of the issue CGRPs have been shown in trials to have the added advantage over existing preventatives of *notably fewer side effects*.

For me and many other migraineurs, for whom all other preventatives have been ineffective or intolerable, Aimovig is another clinical option to try, and offers the hope of reducing the impact of this condition on our lives. It would only be offered to small numbers of people like myself, for whom Botox and other treatments have failed. Therefore it cannot be considered (in terms of cost and trial results) alongside Botox. It is not an interchangeable treatment with, or comparable to, Botox. It is for sufferers who *cannot use Botox*.

As such it extends a potential lifeline to sufferers for whom all other options have failed. I live the majority of my life in pain, or battling severe fatigue and other migraine symptoms. I can only work four days a week and have only had one child because of this condition. I have not reached my employment earnings potential because of this condition. I regularly suffer from depression and low mood, and my personal and social life is limited, because of this condition. My relationship with my partner is adversely affected, because of this condition. I was waiting so eagerly to try another solution, one which for the first time since the triptans, has been *designed for my condition*. That chance may now not be available to me.

I urge you to please, please reconsider this draft decision, on behalf of all the UK's chronic migraine sufferers, who are waiting desperately to try a tolerable drug that may enable them to live more normal, pain-free lives.

Name	[redacted]
Role	Patient
Other role	Former Palliative Care and Pain Clinic Family Therapist and Counsellor
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am writing from my personal perspective. Normally I would write without such emotion on a document like this but I feel it is time to say how I feel, how deeply let down I feel on my own behalf but also for the many others (mostly women) whose daily life is affected by this dreadful condition. Headache and migraine treatment have been badly under resourced by our health services for years. I am hugely grateful to [redacted] for his work to bring relief to people like me, and to the wonderful support of [redacted] of the City of London Migraine Clinic over the years that I lived in London.

I am 62 and have had chronic migraine for many years, and before that frequent migraine from age 10. I have been determined to 'have a life' and to pursue my career despite living with this painful and distressing condition. Migraine for me means three days for each attack, intense pain which has made me feel absolutely desperate and frightened, and nausea, relentless nausea with vomiting, sometimes until I vomit blood, which doesn't relieve the nausea. It is maybe worse feeling nauseous endlessly than feeling pain. It is suffering in which you cannot relate to people or distract yourself with TV or radio. It is all pervasive. And then, there is the living with dread of the next attack and the uncertainty which means you cannot plan ahead or guarantee your attendance at your child's birthday party. To add insult to injury, when you have been through all the so-called preventatives over years and are left with only the acute medicine to use, triptans (which I thank God for) the triptans are rationed by GPs who are concerned about rebound headaches - but since I had more than 15 days of migraine per month with or without triptans I might as well take the only drug which gave me relief! So then there is the considerable fear of running out of the triptans. It is a sort of hell and I often think death would be preferable.

These days I rarely talk about it to anyone but the neurologists for fear that someone might say something unhelpful and remind me of how extraordinarily isolating and lonely it is living with migraine. So in short, I would like you to consider the considerable suffering!

I was fortunate to have caring employers who valued my work skills, otherwise my sick leave would have meant I could not continue working. So secondly please consider how costly it is to have so many people absent from work with this disease. You will have the statistics on that.

Thirdly, as a woman I cannot help but wonder if this drug might have been developed earlier and approved for use by the NHS if a greater proportion of migraineurs were men. In part, historically this may be women's 'fault' for not being assertive in asking for what they need, but the word 'migraine' conjures up in the mind for many a headache which weak and emotional women experience around their period, and make too much of! Now that we FINALLY have a preventative drug for migraine we women are going to have

to fight for it as we have fought for so many basic needs over the years.

Is there anyone on your NICE committee who has experienced full blown nightmarish migraine or the horror of living with fear of the next one? Or the stigma of having migraine? As a former counsellor, I do of course appreciate that you may have members who have the capacity for great empathy even if they have never had a migraine.

Please reconsider, and allow those of us with this illness to be treated on the NHS. It is shameful that you have to be rich in order to be treated for migraine.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Headache teaching is not on the curriculum for approximately 75% of the undergraduate medical schools in England, despite migraine being ranked the seventh most disabling disease with severe migraine attacks being classified by the World Health Organization as among the most disabling illnesses- comparable to dementia, quadriplegia and active psychosis. This is why it is so disheartening as a chronic migraine sufferer to know that the panel which came to the decision not to approve Erenumab for NHS use did not contain neurologists/headache specialists who understand how disabling migraines can be.

Research into migraine is the least publicly funded of all neurological illnesses relative to its economic impact, which again is why your decision disappointments me as it is the first drug to be designed to specifically treat my condition in over 20 years and I cannot access it.

I am unable to work full-time due to my condition, and therefore unable to fund private treatment. I am unable to enjoy my time out of work because all of my energy has been spent trying to get myself through those few days I work. Migraine impacts on every aspect of my life, and where my peers are progressing both in work and socially- many starting families of their own now- I am unable to do so- constantly missing out on family and social events because I am too unwell to participate.

Migraine is currently estimated to cost the NHS £150 million; however its cost to the economy as a whole is conservatively estimated at £3.42 billion per year. Including all headache disorders the cost rises to £5-7 billion annually. Prescriptions, although costly, are a fraction of the total cost migraine has on the economy.

We do not want to be in pain, we do not want to continue to be excluded from society we want to work, and be productive at work, we want to earn, and to contribute. We want access to a treatment that may allow us to do this. Please reconsider your decision and allow me and my fellow sufferers to try this medication.

Name	[redacted]
Role	Family/Friend
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: My best friend (like a sister) suffers from debilitating chronic migraines. She has had to take voluntary unemployment to maintain even a fraction of quality of life. She has tried the A-Z of the so called "migraine meds", that aren't even targeted specifically for chronic migraine suffers, but are a "side effect". She is a superhero. This drug, which was developed specifically for people like her, could allow her to return to work, have a normal life, not have to cancel plans because she's in so much pain she can barely move! There is no way she can afford to get the drug privately because she's not working; we all pay our taxes so the NHS can provide drugs like this to allow people to function! Please reconsider not offering it on the NHS so that my best friend can live again.

Name	[redacted]
Role	Patient
Other role	Part time Finance Officer
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a chronic migraine sufferer I was disappointed to hear that NICE are not minded to recommend erenumab for use on the NHS. Having struggled with head ache and migraine since the age of 12 I was formally diagnosed with chronic migraine three years ago and have endured a debilitating migraine every day since. 18 months ago I was forced to reduce my full time working hours and moved home to my parents as I needed their support in day to day living both practically and financially.

Having been treated by numerous neurologists over the years, I am currently an outpatient at UCLH. I have tried many different treatments and medications including preventatives, painkillers and botox. None have worked for me and all have had concerning side effects. From what I understand, I would therefore be a candidate for erenumab.

I understand that the cost of this new medication is a concern for NICE. I wonder, however, whether the impact of migraine on the UK economy has been fully considered. Many migraine sufferers are young professionals with full time jobs supporting the UK. A high proportion of chronic sufferers like myself are forced to leave employment, reducing their positive impact on the economy and potentially costing the government in benefits,

I have read that erenamub is suitable for those who have 4 or more migraines per month. Maybe a cost reducing solution would be to recommend this drug for patients experiencing more regular occurrences of migraine and whom subsequently encounter a larger impact on their day to day working and family lives.

In reviewing these and others' comments, please consider that the very nature of the condition makes it difficult for migraineurs to sit at a computer and review and comment on the content of your papers.

I hope these thoughts are useful and properly considered.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	Blank
Conflict	None
Notes	None
Comments on the ACD: I cannot speak as an expert, only a patient with chronic migraine who experiences 15-20 migraine days per month. I have tried seven prophylactic migraine treatments (including nerve blocks and botox), none of which have currently made a significant difference to my quality of life, or management of this condition. I know I am not alone, migraine treatments are notoriously unsuccessful, which is why the whole community was so excited to hear about this new drug, created specifically for treating migraine. We read online of the successes of its uses in the US and privately in the UK and it felt like hope. I understand that the funding for this drug however has been rejected based on the fact that it is no more successful than botox, but what appears to have been missed is that this could cover a group of people who are currently unresponsive to treatments. **Financially I feel that this must make sense. I understand that the cost of this drug is £9000 per year per patient, but that Novartis have offered a significant discount to the the NHS. I admit that I do not know the costs of current treatments, but assume that, for example with botox, when the cost of the drug and administration every three months is calculated that it is considerable. This new drug has the benefit of being self-administered in the patient's own homes. Personally, I am barely able to work part time with my chronic migraines, and saw a drop in my salary after my diagnosis of over the £9000 per year that this drug costs. I also have the costs associated with prescriptions, travel to appointments (I have a 200 mile round trip to each of my consultant appointments and botox treatments) and the limit on my income which means that pursuing treatments such as this privately could never be an option. I feel trapped in this horrible life of chronic migraines, I have lost my career, my personal life, my abilities to take care of myself and lose days, weeks, months at a time to these attacks. I urge you to reconsider this decision for those, like myself, who are trapped in this disabling condition with currently no specific treatment.**	

Name	[redacted]
Role	Patient
Other role	Customer service administrator
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Please think about how much of a difference it will make to the patients who suffer on a daily basis.	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Please reconsider decision not to fund life changing drugs	

Name	[redacted]
Role	Public
Other role	Carer
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: To deny migraine sufferers a drug that would relieve their symptoms on the basis of cost effectiveness is callous and cruel. The effect on quality of life alone, never mind the knock-on effects of improved functioning and participation in the community, society and the economy, would make such a huge difference to migraine sufferers. This decision should be reviewed and taken with compassion, particularly in cases where other medication is not proving effective at controlling or reducing migraines.	

Name	[redacted]
Role	Patient
Other role	Community Nurse
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I urge you to re-consider your decision not to offer erenumab on the NHS. As a lifetime sufferer of chronic migraines, I have to have botox, a preventer and 2 supplements to try to control my migraines and I still have up to 5 a month. My pain consultant feels that erenumab would really be of benefit to me and I am sure others in my position. I know cost wise it is a little more than botox, but not when you add in the other medication I currently need to take. Not to mention each botox visit is a half hour with a consultant and a nurse in attendance. Please, please re consider your decision for myself and all sufferer of intractable migraine out there without the means to self-fund this drug.	

Name	[redacted]
Role	Public
Other role	Retired
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Please reconsider not letting this drugs be used I have good friends and family who suffer from this debilitating condition which affects their daily life even after trying all available drugs thank you	

Name	[redacted]
Role	Patient
Other role	Occupational therapist
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I suffer with chronic migraine and I have tried multiple treatments including Botox, Topiramate, beta blockers etc. and they have had no effect. I am under a specialist at the QE Hospital in Birmingham and I had the opportunity to try this new tailored treatment. Eranumab has been really effective in the two months so far and the prospect of not having access to it is unthinkable. My quality of life is now so much better especially as I'm a carer and I can now perform my work role and caring responsibilities without the difficulty. I can now function most of the time which is amazing! Please reconsider your decision!	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	Scotland
Conflict	None
Notes	None

Comments on the ACD: As a parent of a 32 year old daughter living and working in London who has suffered from severe migraines since the age of 8, I would urge you to reconsider your decision and allow this treatment to become available. As the

[redacted], have stated, they have seen positive results with their patients when the treatment was used.

I also believe that the so called excessive cost to the NHS can be justified if it takes into consideration the additional costs to the NHS for associated treatments caused by the migraines, e.g. mental health issues and subsequent treatments, as well as the cost to UK business in the loss of productivity due to absences from work caused by migraine or associated conditions.

My daughter was only last week told by her NHS Consultant that she would be getting her prescription this month, however sadly that is now no longer the case. This has led her to have another nervous breakdown and depression has set in, as this was her last resort, which she has been hanging onto for several months now. It is heart breaking as a parent to see your child, who has had every other treatment possible under the NHS but with no success, be so disappointed angry and sad after being in a positive frame of mind for the last few months in expectation of what was believed would be a life changing treatment.

Please reconsider and allow the use of this drug/treatment.

I found it a very convoluted process to be able to comment in the consultation.

Name	[redacted]
Role	Patient
Other role	Head of Inclusive Learning and Resources at an FE college
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am asking NICE to reconsider its guidance on making Erenumab available on the NHS. As a mother and an educational professional who lives and tries to work with chronic migraine these drugs may give me hope of a pain free existence. I cannot tolerate other drugs including BOTOX. Without this group of drugs there are no options left for me to try. Without hope, without the possibility of trying these drugs, I may not be able to continue to work or to function as a mother. In short I my mental health will not withstand this condition without the hope of trying these drugs and I fear I will return to feeling suicidal as I have previously experienced due to the never ending pain without hope. At present my condition is managed with IV DHE but I may not be able to have another dose. That leaves me with nothing.

My current acute medication regime costs the NHS almost as much as Erenumab would but the cost to the NHS and the state will be far higher if without an effective preventative treatment I have to stop work.

I appreciate your responsibilities to ensure any new drug is both effective and cost effective and I am begging you to either consider further data or to simply review your assessment as BOTOX is not a viable alternative for many chronic migraine suffers.

I cannot express in writing the devastation I felt when I read your draft guidance. In it I saw my future, my hopes and my options for a pain free future disintegrate. I hope you will take the views of me and many fellow chronic migraine sufferers into consideration and change your decision not to approve Erenumab for prescription on the NHS. I will never be able to afford it privately. Health and pain free living shouldn't be dependent on wealth. Please, I implore you, reconsider.

Thank you

[redacted]

Name	[redacted]
Role	Public
Other role	Writer/academic
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: For people with severe migraine, which other drugs cannot treat, Erenumab could allow them to return to work and family life, and release them from an existence of pain and sickness. It could be life changing and could even be lifesaving, given the number of people with this desperate illness who contemplate suicide.	

Name	[redacted]
Role	Public
Other role	Teacher
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: As a migraine sufferer, I can be debilitated for months at a time. This condition leaves me unable to move and at this point I have no other medication or treatments to try. The prospect of the injection offering relief also offers hope, especially when I work in a profession that you cannot function in with a migraine.	

Name	[redacted]
Role	Patient
Other role	Music Teacher/Freelance Musician
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a chronic migraine sufferer and fortunate to be under the care of GSTT Headache centre. Since the onset of chronic migraine nearly four years ago (caused by the local anaesthetic in a dental injection) I have failed to respond successfully or had bad side effects from at least five different drugs including nortriptiline,amitriptyline, pregablin and topirimate. I was a non-responder to Botox. I currently have nerve block injections every three months but these are no longer effective enough for me. I have a migraine to some degree or another every single day of my life. Whilst on many days I struggle through work (I am not financially in a position to retire yet) it affects the standard of teaching I am able to deliver and I cannot currently pursue my additional career as a freelance saxophonist. My life outside work is affected greatly as most evenings I ill with the resulting bad migraine from the working day and similarly at weekends. This has a big impact on any kind of social life and developing relationships with friends. Shopping is also a nightmare with the lights and atmosphere bringing on many auras associated with migraine. My quality of life is impacted hugely. I had been offered erenamub injections if my condition does not improve in this three month period and hope this may still be possible.

Greater consideration needs to be given in terms of erenamub injections being funded by the NHS for patients such as myself where a large number of other treatments have not been effective. It has been a long journey so far and I, and many other sufferers, desperately need a light at the end of the tunnel. The psychological effects are huge.

Surely the cost of the injections, which I appreciate are expensive, is offset against loss of working days.

Name	[redacted]
Role	Patient
Other role	Hotelier
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a chronic migraine sufferer and am currently a patient at the National Migraine Centre in London. When I heard of the decision to reject the use of Erenumab in the NHS I felt compelled to comment and appeal against this stand point.

I have suffered from chronic migraine for just over four years now. I have seen many top professionals in the migraine field both as a private patient and on the NHS. [redacted] to name just two. Chronic migraine has affected my quality of life immensely, and not just mine but those closest to me. For the majority of the past four years I have been unable to work due to the sheer volume and debilitating nature of my migraine attacks. My social life has been affected as so often I am forced to cancel plans and I have been unable to drive due to vertigo caused by migraine. Migraine has affected every relationship in my life and completing simple daily tasks and caring for my young daughter is a daily struggle.

I have been prescribed a myriad of preventative medications over the years such as amitriptyline, pregabalin, propanalol, topiramate, candesartan, steriods to name a few but without any success of treating my chronic migraine or the side effects were too intolerable to complete a trial of three months to test their efficacy. Last year I was given botox for migraine on the NHS at York Hospital and suffered an extreme reaction which lasted the whole twelve weeks. I was in immense pain, i suffered from severe vertigo and the treatment worsened my condition rather than giving me any relief.

In December 2018 I was prescribed Erenumab by the National Migraine Centre and on Thursday 6th December I self-administered my first injection. Within days there was a noticeable change to my migraines, within weeks I had my first pain free day in years. I have seen more improvement since administering my second injection two weeks ago and finally I feel like I am starting to get my life back after years of feeling like a prisoner within my own body. Not only has this drug immensely improved my chronic migraine I have also experienced very few side effects which is almost unheard of in my medical history. I cannot stress to you enough how valuable erenumab is to me, not only to my physical health but to my mental health also. I am one of the lucky ones who is extremely fortunate to be able to access the drug privately. For all sufferers similar to me who have tried and tested every preventative medication available, who have almost given up hope of ever living a pain free life, who will now be denied access to this life changing medication on the NHS is an absolute tragedy. I urge you to reconsider your decision and make Erenumab available on the NHS to chronic migraine sufferers across the country without delay.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: It is disappointing that NICE have decided there is insufficient evidence to approve this drug; the first of its kind targeted specifically at migraine sufferers. I was diagnosed with chronic refractory migraines in mid-2017 and, despite being told on my first consultation with a headache specialist that Botox was the only thing currently on the market likely to have an impact and offer any relief, I spent 16 months trialling four different preventatives. Each preventative had its own set of side effects from emotional outbursts and depression to extreme fatigue and each had to be trialled for a minimum of three months, plus additional time for titration of dosage both up and down. I am lucky enough that my local CCG accepted my application for funding for Botox however my first session has had no impact on the frequency of my migraines nor level of pain experienced. Whilst I know through forums and the information supplied at the time of first Botox treatment that it does not always work on first occasion, as my second session is now due I am highly conscious that if my second session of Botox does not work then I am left in a position where there does not appear to be any further option available other than trying a greater variety of drugs which are targeted at other conditions and again running the gauntlet of possible side effects and the impact these will have on my physical and emotional well-being.

I appreciate finances are of concern and the results do not appear to show a greater benefit to sufferers than Botox offers however it would be useful if consideration could be given as it being offered as an option on those occasions where Botox has failed to make a difference with applications being made to CCG's for funding and relevant evidence of failure provided in the same way as Botox.

I am a 44 year old female who experiences varying symptoms of migraine and pain levels every day who has to continue to hold down a full-time job and meet all responsibilities. To know that a new drug which may have a chance of offering some relief, has not been approved is incredibly demoralising when already dealing a chronic pain condition.

Name	[redacted]
Role	Patient
Other role	Buyer
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: This document does not take into account sufferers who have tried all of the medications currently available that have not worked. It is also not considering those who cannot afford to pay privately for this drug, the decision not to offer this drug on the NHS is condemning people to a lifetime of misery and disability. It does not consider the 25 million lost work days per year that this condition generates, surely the cost outweighs getting people back in to work instead of laid in bed. Migraineurs have waited years for this condition to be taken seriously and for a preventative specifically for this condition, only for it to be snatched away due to costs. It does discriminate against suffers who are debilitated by this condition. Once again the migraine community are being treated as less important than suffers of diabetes, epilepsy and asthma, bearing in migraine is more prevalent than all these conditions combined and is just as disabling. 1 in 7 people suffer from migraine, surely something that can help so many of the population must be made available to everyone.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a migraine sufferer of over 20 years, I was extremely disappointed to hear that Erenumab has not been recommended for use on the NHS. Having tried eight different preventative medications over the last 13 years and many, many other things, Erenumab was my next option.

Chronic migraine is a debilitating and isolating condition that affects everyday life. Migraine sufferers often feel that the condition is not taken seriously and I feel this decision confirms that. Sufferers have waited so long for developments and new treatments and to be told that Erenumab has not been recommended is devastating.

For the last five years, I have had migraines between 20-28 days per month, while working part-time and bringing up two young children. Last July, I was hospitalised after 5 days of vomiting with a severe migraine. It is not just a headache.

I understand that there are other prophylactic agents available but surely for someone who's tried eight different medications already plus numerous other things, Erenumab should be an option?

Please seriously consider the feedback you receive from migraine sufferers during this consultation who have to live with this condition. We desperately want to feel better, to be able to live a normal life and to spend more time with our family and friends instead of being in chronic pain, often suffering alone in a dark quiet room.

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have had NDPH / migraine for 6.5years. During this time I have tried a large number of treatments.

Erenumab is the first available of a group of medications specifically to treat migraine. This is a huge breakthrough for sufferers.

We need this and other targeted medications available on the NHS for qualifying patients.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I suffer from severe episodic, borderline chronic migraines which are very difficult to treat when they occur. I have tried several beta blockers, vitamin supplements, changing my diet, and my migraines are still very intense. They interfere with my life in every possible way. I miss commitments regularly. I know several people who suffer from migraines who have the same issue. I feel that erenumab could potentially be helpful for myself and others. There is no other medication specifically for migraine. We have to use medications that have an off label treatment for migraines, many of which have unpleasant side effects (notably topamax and gabapentin). Erenumab is along the lines of something I have been hoping and even praying for years, for some respite from my migraines. I want to have the chance to live life without pain all the time. I am asking you to please consider allowing it to be available on the NHS. Life for people with migraines is incredibly challenging and to have a glimmer of hope taken away from us is beyond disappointing.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: As someone who has suffered from chronic migraines for 4 years every single day, this decision was devastating. I saw this as at least a hope. My life could be dramatically changed by this drug, like many others have found. But there is no opportunity for me to try at the time of writing due to the decision made. I have tried 14 different medications to try and treat this dreadful disease. A disease which has taken away by teenage years, chances to reach my educational potential, work full time and live my life. I am seen 3 monthly at the headache clinic who are running out of options and with an entire life ahead of me I do not wish to have this pain for the rest of my lifetime, when treatments such as Erenumb are on the market privately at such great costs. I understand the cost section in regard to the NHS. But maybe it should be considered a further option when literally nothing will work, not available to those with less frequent days but those like me who suffer with chronic migraines daily. The amount that is lost from the economy, the workforce, community, society, relationships due to migraine is so damaging that for someone suffering daily at least a trial will period on the drugs would be potentially life changing. I hope that for the sake of every 1 in 7 person in the UK who suffers from migraine, and the reduced number that is still too high who suffer from chronic migraine symptoms and pain daily our lives and futures can be considered as part of a framework within the NHS. **Thank you for allowing this consultation to take place.**	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	United States
Conflict	None
Notes	None
Comments on the ACD: I am in the US and have been a chronic migraineur with persistent daily headache for 17 years. I started Aimovig almost immediately after it was approved. I have found relief from using it, and know a lot of other people have also had success. I went from needing relief medication 2-3 times a week to needing it 1 time a week (average). My daily headache that used to be a pain scale of 7-8 daily is now a 5-6 daily and these improvements have made a huge difference in the quality of my life. I am able to do so much more than I was able to do before. Please approve the use of Aimovig and similar medications for migraine use in the NHS.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: This is utterly devastating for chronic migraine sufferers like me - I average 24 days a month of incapacity due to this utterly disabling illness. The promise of this drug had been the last strand of hope for myself and many like me and now it has been snatched away. It is unrealistic to deny us it because the evidence suggests it's no more effective overall than botox- as any CM sufferer will tell you We all respond very differently to treatments- for one person, botox is a miracle, for another it does nothing at all. For those who respond well to erenuab it means the difference between living, working (and contributing to the NHS) and just existing in pain and misery. It is inhumane to take that chance away and am beseeching whoever is reading this to reconsider that. The WHO classifies chronic migraine as being equally disabling as Dementia and Quadriplegia. We need all the help we can get.	

Name	[redacted]
Role	Carer
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I am the husband of a woman who suffers with chronic migraine. I have never commented before on any NICE actions or decisions, but in this instance I feel that I have to make my voice and my concerns heard. The announcement that NICE is declining to fund the migraine drug has shattered her. She works full time whilst in constant pain and is resilient and determined. She has received three doses of intravenous migraine drug treatment which involves quite a lengthy stay in hospital, all other migraine medications are not particularly effective at reducing pain consistently. The new drug, erenemab was a source of great hope for her and for us as a family as it raise the possibility of a short term solution to her pain. I would ask you to reconsider your decision and consider the impact of your decision upon the lives of families such as ours, who feel deprived of hope in the wake of this decision.	

Name	[redacted]
Role	Public
Other role	Student
Organisation	Nottingham
Location	England
Conflict	None
Notes	None
Comments on the ACD: I personally know people who suffer almost every minute of their lives from migraines and they can only depend on ONLY this medication. This should be enough of a reason to NOT take it away from them	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	Europe
Conflict	None
Notes	None
Comments on the ACD: I know several people who suffer with migraines and this would medication helps them get through their day and taking this medication away from would cause loads of problems for them it's unacceptable	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Please reconsider your decision, this is the 1st medication to be designed to treat migraine - a chronic, debilitating condition which massively impacts on people's quality of life. Cost should not be the reason people are not allowed access to it. Furthermore consider migraine sufferers who have been forced to give up work, if this drug would allow them to return to work consider the impact on society. Friend of a chronic migraine sufferer, I have seen the impact that this condition has on people's lives.	

Name	[redacted]
Role	Carer
Other role	None
Organisation	None
Location	None
Conflict	None
Notes	None
Comments on the ACD: This is so important for chronic migraineurs in whom other treatments have failed, my mum being one example. She is already under neurology, and has tried everything available already. Her quality of life is shocking, and the cost to her, the rest of the family & wider society really necessitates making this type of treatment available.	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Life is hard enough for people with this devastating condition. Please make this available to all sufferers on prescription.	

Name	[redacted]
Role	Patient
Other role	Retired Clinical Psychologist
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am responding to the appraisal consultation document as a patient, although I have a background in research and have worked in the NHS for 25 years as a clinical psychologist. I have experienced severe migraines since I was a child and they have become steadily worse as I have grown older. I am now 64. I currently experience between 15 and 20 severe pain days per month and have less than 5 pain free days. I spend many of the severe pain days in bed vomiting repeatedly. I have tried >10 preventative treatments and botox. None of these have had any impact on my condition.

My comments are as follows:

1) I wonder if you include in your cost and quality of life analysis such factors as time lost from employment due to migraine and the cost to other aspects of life of remaining in employment. I only managed to remain in work by spending all of my time outside of work in bed - evenings and weekends. Although I was a good clinician with a rare expertise of working psychologically with those people who have the most severe mental health problems, I missed many days from work and eventually had to retire on health grounds. That lost my skills to the NHS and cost at least 5 extra years of pension.

2) Does quality of life include the psychological impact of living with this condition - isolation, loneliness, depression? At times, I have felt that life is not worth living.

3) I wonder if you have given sufficient weight in your document to the fact that this is the first ever migraine treatment specifically developed to treat the condition using current understanding of the condition. All other preventative treatments, including botox, were developed to treat other conditions. I have tried at least 10 of these and their side-effects have been appalling. Also, the very fact of this new drug's existence has increased hope in people with migraine and your decision has damaged that hope and decreased quality of life. As Erenumab is so new and unusual because it is the first, perhaps it is to be expected that further, more detailed research is required. Could this not happen while it is made available to patients who have been waiting for many decades for such a drug?

3) My reading of the document suggests that botox is the treatment of choice for migraine. This has not been effective for me. It requires an appointment at a Specialist Migraine Clinic and is extremely painful, often triggering a migraine. I feel bruised and as if I have been kicked in the head for a day or two after treatment. My understanding from the clinical and research literature on migraine is that the population of people with migraine require a variety of treatments. Could Aimovig not be one those treatments?

4) There is another treatment which is not referred to at all in your document. This is in-patient treatment with DHE (dihydroergotamine) infusion. This a 5 day in-patient treatment which is often the only effective treatment for very severe migraines. It has to be repeated annually. This should surely be included in any comparisons of cost. Also, greater occipital nerve blocks are often used to treat more severe migraines.

5) Does your cost analysis include the average spent on Sumatriptan type drugs for treating individual attacks of migraine as well as all of the preventative drugs an individual might try? I have to use an Imigran nasal spray as the tablets cannot be absorbed and I use between 6 and 8 per month.

6) I hope that the committee's decision has not been influenced by the fact that this condition affects women more than men and is often regarded as 'just a headache' and it is not a newsworthy condition. WHO describe the condition as among the most disabling, comparable to dementia, quadriplegia and active psychosis. Anxiety and depression are significantly more common in people with migraine than in other individuals.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	None
Location	England
Conflict	None
Notes	I am a follower of The Migraine Trust and am filling this form in on their recommendation.

Comments on the ACD: As a migraine sufferer I am very disappointed about the NICE decision not to recommend erenumab (Aimovig) for preventing migraine. I would like my history of migraine and the interventions I have used, to be considered during the consultation.

I have suffered from menstrual migraine since 1971 which in the years after a hysterectomy became chronic. Since then I have tried tablets such as Midrid, Vitamin B6, Sodium Valproate, Verapamil, Topiramate, Gabapentin, Amitriptyline, Clonidine, Propanolol, Metoprolol, Candesartan with no success. I have also had Botox injections 3 times, bilateral greater occipital nerve blocks 4 times, right cervical facet joint injection once, Cefaly trigeminal nerve stimulator, private sessions of physiotherapy, private acupuncture all with very little success. I have suffered from daily headaches for a number of years and the only thing that relieves the dreadful pain is Sumatriptan tablets and Imigran injectors. These of course should only be used sparingly. In December 2018 the consultant who I see privately prescribed Erenumab 70mgs which I have self-funded. In the first month my migraines decreased in severity and I had 8 consecutive days without a headache - which is unheard of for me. I have just taken my second injection and am already starting to feel the benefit again. I have agreed to pay for 3 months' supply but cannot afford to carry on doing this. Surely NICE should talk to current users of the drug before they decide definitely not to recommend the drug for use on the NHS.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: The appraisal appears to be based on definitions of numbers of migraines per month that could be classed as sporadic. It is compared to the use of Botox, which NICE guidance will only recommend for Chronic migraine suffer (at least 15 attacks per month, of which 8 are of a severe scale) who have tried a variety of first line preventive medications. Botox is the current last line treatment for many people but is still not used alone in a significant majority of patients, it is used alongside other preventive medications. The cost of additional treatments need to be taken into account. Erenumab could represent a cost effect last line option for those who gain no reasonable benefit from Botox. This would represent a signficant benefit for patients and be hugely cost effective compared to un managed chronic migraine which is likely to result in significant disability, a high probability of job loss and related social costs.

Why Erenumab has not been looked at with the same access criteria as botox is nonsensical.

I suffer from Chronic migraine and have done for many years. I had a particularly intractable episode during 2018 for which I was absent for 4 months from work.

During that time I had 2 hospital admissions, I use approximately 12 injectible triptans per month, in addition I am prescribed strong antiemetics, ondansetron and IM Cyclizine, I take 2 first line preventives combined, with the addition of botox, which I have every 3 months. The cost of my condition direct to the NHS in 2018, including pharmaceuticals, hospital admissions, around 10 GP consultations, but excluding outpatient specialist appointments and related treatments during inpatient care was in excess of £9,000. Compared to this, a successful treatment with erenumab would represent a significant coat benefit to the NHS

In addition to this, I am a [redacted], my salary cost to [redacted] excluding on costs for the duration that I was absent on full pay. In addition the NHS could have easily paid more than this in locum costs to cover the absence.

The costs of the drug itself only represent the tip of the ice berg. A comparison needs to be made of the sum total of drugs used by the average chronic migraine sufferer, as a single preventive such as botox alone is rarely a real world scenario. The costs of treatment is also excluded, with injectible triptans costing around £90 for 2, the difference in migraine free days could be considerable.

While social costs are not included in the NICE formula, as a chronic disability, with sufferers protected under the Equality Act, the social welfare and wider costs are significant, and failing to approve a successful

treatment option as a last line treatment is a complete oversight in terms of the wider social and economic implications and also immoral.

Name	[redacted]
Role	NHS Professional
Other role	GP
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I would like to emphasise the need for this in chronic migraineurs in whom other treatments have failed and this would be a small proportion of people whom are already under neurology, and have tried everything available already. This is with regards not just the individual but the wider repercussions to society, work, family and cost to NHS in GP appointments, sleep deprivation, depression, other medication, inability to work, health and wellbeing of families. **Note there is only a 3 month trial so it is stopped after this so ongoing costs are not an issue and has a 50% approx success which is huge in relation to the tiny proportion who may benefit.**	

Name	[redacted]
Role	Patient
Other role	International Marketing Manager
Organisation	None
Location	England
Conflict	None
Notes	SAME AS ABOVE

Comments on the ACD: DEVASTATED!!! Literally is the one world that summed up how I feel when I read the news that Erumab has been rejected due to the cost - the first migraine only drug in over 20 YEARS - shocking!!

Honestly, I cannot explain how totally and utterly devastated I'm feeling right now having found this ludicrous and heartbreaking news out! This breakthrough drug was the ONLY piece of hope I've been holding onto this last year, since suffering from these debilitating chronic migraines since I was 8 years old / for 24 years!! Having tired every single drug & treatment available on this planet...I was shortlisted and promised to be one of the first in the UK to trial this on the NHS! Literally heartbroken! Especially after being told a few years ago that there is no other alternative / drug of treatment for the NHS to offer me, as I have exhausted all possibilities.

I know me, and many, many others need to express our concerns for the NHS / NICE to REVOKE this decision!! The effect that migraine has on this country is baffling through physical and mental well-being, loss in productivity in the workforce / economy for those who want to work / have a purpose, rather than being on benefits / giving into their disability - letting in rule their lives. I'm 100% certain that there are other areas of NICE / NHS were costings can be saved / medicines taken off the shelf to prioritise a drug that could change so many peoples' lives for the better...I urge you to revoke this decision and come up with a solve cost wise with the pharmaceutical companies who can have some a positive impact on the health and well-being of the nation!!

Hold On Pain Ends = HOPE - not according to the NHS / NICE

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Dear Sirs, I have been a chronic migraine sufferer since my young teenage years, experiencing countless trips to A&E and innumerable periods in hospital for excruciatingly acute and chronic pain as a result of having had little or no relief from medicines that have been available through the NHS. For over thirty five years I have been within the NHS system trying an abundance of medicines and procedures (including PENS, GONI and Botox), all of which have offered little or no relief, so I continue with longstanding daily migraines that cause me significant functional impairment and decrease my quality of life. I am asking you to reconsider Erenumab's use in the NHS, as this new drug will support me to experience a better quality of life and function within my family, and society, as any mother and good citizen should. I speak for the many, many NHS patients, who as chronic migraineurs, struggle down the same pathway through life as I do. Please do not turn your backs on us, we need your help to release Erenumab into the NHS.	

Name	[redacted]
Role	Patient
Other role	Administrator
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: Very disappointed to hear that this has been rejected as a chronic migraine sufferer who has lost one job due to migraines and under other employer guidelines, despite equality act etc. To be able to maybe see a light at the end of the tunnel and maybe for people like myself to get our lives back instead of constantly will I be okay today, will I have to cancel going to that. Calling in sick to employer. Please reconsider your decision and give many people the chance to get a life instead of constant pain. We only get one life and so debilitating the one we currently have to live. But through this pain we paint on a smile and try to carry on.	

Name	[redacted]
Role	Patient
Other role	Supervisor
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Being a sufferer of migraines since I was 14 and most recently more severe ones for the last eight year and working from being 15 and paying into the system since I started work I'm extremely disappointed that once again you've decided not to help the sufferer with the erenumab injection this tells me you don't understand the debilitating condition or even care.	

Name	[redacted]
Role	Patient
Other role	Unemployed
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I was incredibly disappointed to hear that Erenumab had been rejected as a treatment under the NHS. There hasn't been enough emphasis on how chronic migraine affects lives to the point where someone doesn't actually have a life. It states that, People with migraine can often miss out on family time and find it difficult to make plans. The condition can fluctuate over time; it is unpredictable and can be poorly understood in the workplace. Since last April I haven't been able to work due to the severity of my chronic migraines. I live in daily pain, often unable to leave my bed and also find it difficult to know when one attack ends and another one starts due to the frequency. I am 28 years old and my Mum is now my full-time carer. I have completely lost my independence and am currently living under Personal Independence Payment whilst I am unable to work. I am currently on my 6th and 7th preventative medication and have recently had my first round of Botox. I have heard mixed reviews of the success of Botox and I wonder, if it doesn't work for me, where do I go from here? The thought of having the option of an NHS-funded drug specifically designed for migraine fills me with some hope, but without this option, the hope fades away. I know myself that living on PIP and being unable to work means there is no chance I could access the treatment privately and I am sure that there are many other people in my position. All that we ask for is the full range of options which may help us to get our lives back or at least live an improved lifestyle rather than living in excruciating daily pain.	

Name	[redacted]
Role	Carer
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have a 21 year old daughter whose life has been devastated by daily chronic migraines. She has been bedridden for the past 7 years due to her condition. She has tried nearly all the prophylactic treatments including antidepressants, beta blockers and anti-epilepsy drugs. All of which did not work and gave her awful side effects for example kidney stones. She was unable to complete her education and is not able to work. She suffers headaches/ migraines every single day which intensify if she does anything at all. We had great hope when we heard about erenunab (Aimovig) and read all the great life changing reports from fellow sufferers in the United States, but have been devastated by the response from Nice. Please consider funding this medication on the NHS, especially for those patients with chronic migraine. It is a very cruel, and disabling illness which is much underestimated.	

Name	[redacted]
Role	Chair Elect of the Migraine Trust
Other role	None
Organisation	None
Location	None
Conflict	None
Notes	None
Comments on the ACD: There are many sufferers whose migraine disrupts and spoils their lives. No treatment works for everyone and any help to make more people able to be productive in their working and family lives deserves to be available on the NHS.	

Name	[redacted]
Role	Carer
Other role	Retired life assurance and pensions assistant
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: My daughter has been diagnosed with chronic migraine. Migraines have meant that she has needed to give up full time work and move back to live with me for financial and practical help with day to day life. She works 2 days a week. She is treated at UCL but so far no drug has been found to help her. She has a migraine to varying degrees every day of every month. Working and having a social life is very difficult. She suffers with fatigue as well as pain. Erenumab could transform my daughter's world. The NHS pay for all sorts of self-inflicted illnesses. Migraines are genetic. Compared to the cost of medication/consultants/nurses/reduced working hours/time off sick/benefit claims etc. surely the cost of these new injections is less.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	United States
Conflict	None
Notes	None

Comments on the ACD: To Whom it May Concern,

I, an American, have recently been made aware that the CGRP inhibitors, in this case, Aimovig in particular, is being debated upon whether it should be available to the citizens of the UK. I am reaching out to implore your decision to approve the availability of the CGRP inhibitors. They are the only migraine specific preventative medication ever made, and have been helping a great many people. As a migraineur myself, I would hope that my country allow me to try any possible treatment or hope available, if safe. This is an extremely debilitating disease that needs to be eradicated, or at least manageable. These CGRP's are currently our only hope. Personally, I was on Aimovig for 3 months. While it did not help me, it has helped others. I am currently on the 2nd gen CGRP, and am praying for results. From my personal experience, I had no side effects from Aimovig. Please consider seriously the decision to allow UK citizens the hope that these medications provide, and at best, the relief. Thank you for your time and consideration.

Name	[redacted]
Role	Patient
Other role	Palliative Care Nurse
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: My life is slowly disintegrating due to Migraines. More frequent, more painful, longer lasting as I get older. I care for others, I feel no one listens or cares for migrainuers. I struggle to work and often consider leaving - I would be a burden on the state costing money. I cannot contribute to my family, friends, society. It is a daily struggle, with pain, fatigue, nausea and forgetfulness.

I have tried many preventatives with no success and horrible side effects

This new medicine gave me such hope that I would get my life back. I could participate in family and work activities without worrying trying to avoid triggers.

To say I'm disappointed at your decision is an understatement. I was devastated.

Migraine is a silent, unseen disease. Please do not ignore us.

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a migraine sufferer I wanted to let you know how Migraine has affected my life and why it would be a great boost for me personally for this drug to be available on the NHS. I have struggled with migraine for about 35 years - it has progressed from episodic migraine to chronic migraine and has resulted in me cutting down my hours at work drastically over the years, limiting my career ambitions, with the end result that I am now taking early retirement at the end of this year. I do not want to retire I feel I still have a lot to contribute at the age of 60 but for the sake of my health giving up work seems to be the only option. Throughout all of those years I have had to cancel social engagements regularly at short notice, not being able to take part in many family engagements, have struggled to fulfil parental responsibilities and responsibilities towards my mother who had Alzheimers, all of life was a struggle and still is. I have taken three preventative treatments with very limited success, and was extremely excited to learn that research has actually been done into a preventative treatment specifically for migraine. It felt as though somebody was at last taking my condition seriously. I was aware that there would be a cost involved with the arrival of a newly launched drug, but I already cost the NHS money through repeated visits to my GP, and my use of triptans which are the only drugs that can help me through the very worst migraines. I am aware that there is already a high cost involved with triptan medication and I would assume that if I were able to cut down on taking these drugs there would be some saving to the NHS. Whilst I am aware that Migraine is not necessarily a life threatening condition, except for the fact that it has on many peoples mental health, I do believe that in purely practical terms the cost to this country in terms of lost revenues, lack of ability to care for family, and lost ability to contribute to our communities, aside from the effect that it has on my personal quality of life, all needs to be taken into consideration when looking at the big picture. I personally would be very disappointed if the opportunity to try out a new drug that had specifically been researched and produced for my debilitating condition was not available to me. Thank you.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I've suffered with migraine all my adult life and feel it's the curse of the devil and have felt suicidal at times. I have experienced some horrendous times in my life and in work, it is difficult to recall them all but I've sobbed uncontrollably as I've had to yet again drag myself home in the car (a one-hour's drive) and take yet more time off work feeling so low, so guilty and in pain. I think I've been made to feel guilty so often, even by some friends as if I've brought it on myself, and what did you do this time to bring it on? I've always felt somewhat guilty and made to feel worse by others who think I'm letting them down because I cannot now attend a function or event, drive them somewhere as previously planned or similar. I've missed many events, such as a family wedding, short breaks, trips to the theatre and nights out with friends and family. Holidays have been ruined and hundreds of days of my life spent in pain, in bed with the curtains drawn praying the migraine will lift soon.

I've spent a long time putting myself through an assortment of tests, avoiding certain foods and alcohol and tried a huge array of alternative medicine and other things that I thought might cure me. I went through food intolerance testing, Acapuncture (which is a story by itself as I was finally offered ten free sessions by the acupuncturist as he was so convinced he would cure me and didn't); Homeopothy, stress-relieving treatments like Reflexology, seeing an Osteopath & Chiropractor, trying aromatherapy massage, Yoga & Tai Chi classes. Vitamin B and Magnesium supplements, went to my Dentist to be fitted with a dental brace (in case my teeth grind), herbal remedies, tried a light-mask, a Sea-Band around my wrist and naturally etc. However, nothing really works except prescribed preventative medication, for a while but nothing is a cure-all. I started getting migraines really badly lasting for three days, most of which was spent flat out in bed feeling dreadful trying to look after myself as I lived alone.

I feel that I've tried most relevant medications over the years: migraleve, Beta blockers (Propanolol), Sanomigran each night (was taking 15mg but I put half a stone in weight on so compromised and reduced it), Progesterone only pill (POP), Mefenemic acid for a short while and Naproxin. I've tried most triptans but never felt they had a profound effect stopping my migraines (Almotriptan, Naramig, Frovatriptan, Rizotriptan, sumatriptan etc.), I was using soluble Paramol but then they stopped making it. Tried Ibruprofen or paracetamol in the hope it might slow down or stop an attack but didn't. One of the best prophylactics for me at the time was Amitriptylene (anti-depressant) until the efficacy wore off a few years later. I've been on Venlafaxine, Gabapentin and Topirimate (which made my migraines disappeared for ONE-WHOLE year, then returned as bad as ever), etc....

I think more media attention and awareness of it has helped and people are more supportive now than they ever were in the past. However, you can still get people who think a migraine is just a headache. I've experienced the worse in people and the best. However, even those who show sympathy

have no real knowledge of what it's like to suffer a bad migraine attack, how it feels, how it leaves you feeling and what the impact is. I think there is always more room for more education. Managers in work and other staff members have not always seen migraine as something dreadful to suffer, more an excuse to take more time off or leave work early etc. I had one senior manager who suggested I might want to think about giving up work and letting someone else (more-healthy) take my job. I was once made to drive around 70 miles each day for two-days during a conference.

Name	[redacted]
Role	Patient
Other role	Managing Director
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Section 3.1 clearly states the impact of chronic and episodic migraine. This is my experience of it. I currently miss about half of my life. My children do not get to do fun stuff as I can't plan anything. I miss work. I have to work for myself as a result of having migraine, and the work time is severely limited by this. It affects my income, and my life.

Like many people I have tried more than 3 preventatives and nothing works. I have had nerve blocks done which don't work. The only thing that works for me is migraine-specific abortive medication and To avoid medication overuse headache I need to limit the number of these I take. Which I then results in me suffering intense pain during 3-day migraines. A preventative which is proven to work in many cases, like the 140mg dose of erenumab, would be a life saver for so many people. If after 3 months it doesn't work for the person then stop, but it has to be worth a try. The quality of life for those with migraine, and for their children, is severely limited by this disease. And the disease is not included in the "disability" list for any sort of benefit so people have to struggle to work in order to make enough money to survive. Another tool to reduce the impact of migraines has the potential to allow me, and so many others, to begin to have a normal life again.

I currently have chronic migraine and nothing reduces the frequency or intensity of the disease.

Name	[redacted]
Role	Patient
Other role	Data developer
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have had a chronic migraine for a year. I have tried many preventatives, none of which have worked. This treatment could give me my life back. This could also affect many peoples' lives and should be provided on the NHS to stop this debilitating condition.	

Name	[redacted]
Role	Patient
Other role	Unemployed
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I've suffered with chronic migraine for 20 years, a constant migraine for the last 3. I've tried many medications, they've all failed to give any relief. Amovig would have been the next thing for me to try but this is only possible for me on the NHS as I am unemployed due to chronic migraine. This leaves botox as the next step which I am unsettled about because unlike Amovig the specifics of how this works on migraine is unknown, botox is around 35 injections which is likely to push my migraine to savage and must be administered at a hospital. Traveling is difficult for me so this presents the first problem, the second being the hospital in my area gives botox every 20 weeks rather than the recommend 12 so I wouldn't even be receiving a full treatment. I urge those involved to push for Amovig to be NHS approved.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I suffer with chronic migraine with aura with 25 migraine days a month. I work part time and have 2 children. I struggle to work. I have had Botox for 4 years and preventative medicines have failed. Suffer side effects. Acute treatments are also ineffective. There is nothing more I can take. I am having pain management counselling.	

Name	[redacted]
Role	Public
Other role	Civil Servant
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am commenting on the consultation as the mother of a daughter who suffers from chronic migraine and has done so since she was 14 (now 22). I think the document underestimates the impact of this condition. It is described as headaches throughout and that it is debilitating. The truth of this condition is that when it strikes it can be disabling. And the word headache does not being to describe the impact. Sitting with someone who would be crying with pain except that crying makes it worse, whilst they describe their head as exploding, whilst they need to get up to be sick but can't raise their head let alone move to the bathroom, would persuade anyone this is not a headache. My daughter has tried every one of the so called preventatives which were never developed for migraine sufferers with little to no success, and even worse with one of the anti-convulsants from which she had horrendous side-effects, meaning that she hardly ate for three months, as well as dealing with the headaches. Painkillers sometimes, even usually, work to lessen the effects but some weeks she can be getting as many as five attacks a week. And the whole time it is entirely unpredictable as to how many attacks and of those how many don't respond to the painkillers knocking her out for a day. I am extremely proud that around this condition she managed to achieve a first class master's degree in engineering and is now starting her career but with the continuing concern that she has no idea of the impact on her working life.

The second point I would like to note that that I don't think the consultation has taken into account when looking at cost/benefit is the impact on productivity. Large numbers of the population suffer from this condition and multiplying up the number of days lost to the condition must impact on the productivity of the country. At a time when Government is increasingly concerned at the low average productivity figures and the impact on the economy, I think something that could potentially improve overall productivity figures by improving attendance for people with this condition should be factored into the equation. I think this would balance the so-called high cost of the drug which in my view is unduly influencing the assessment.

Finally you ask about whether the document under consultation could be deemed to be discriminatory in any aspect. Given that it is recognised that migraine affects three times as many women as men, I think the assessment could be deemed to be viewing the economic impact of improving women's lives as less than men's.

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a sufferer of chronic migraine and am disappointed by the current decision. I have tried many of the current preventative options, but none have been very effective. I have suffered with migraines for many years, dealing with them at school, during university and now as I start my career.

One of the main reasons given for this decision is related to the cost effectiveness of providing this option through the NHS. Migraines have a major impact on many people's lives and account for a large number of lost days. This decrease in productivity not only impacts the sufferer, but also their employer and the economy.

I also believe the present cost migraines have to the NHS may not have been fully considered. As mentioned I have suffered for many years, long before I was old enough to pay for my prescriptions. I get preventative medication and medication for during an attack. These were provided and are still supported by the NHS. If I could find a preventative option that worked I would not require such a high level of additional medication.

Finally, it is becoming harder to get hold of painkillers. This is becoming so significant recently that I have seen it in the news. The pharmacies have had issues getting hold of my prescription for the tablets I take when experiencing a migraine. If a better preventative option can be found, this will not be such a significant problem.

As someone who has recently finished University (with all the debt that comes with it) and starting to set up my life, the current cost for this treatment is not something I can consider paying and my only option is to get it through the NHS.

[redacted]

Name	[redacted]
Role	Patient
Other role	Teacher
Organisation	None
Location	Wales
Conflict	None
Notes	None

Comments on the ACD: I have been suffering with chronic migraine (daily persistent headaches) for over 4 years. I have been under the care of a neurologist and a specialist headache neurologist and have tried all drugs that are associated with the treatment of migraines without success. They either did not help, made the headache worse or caused terrible side effects. I have also tried a nerve block and botox injections, both without success.

In addition to my medical treatment I have also tried alternative therapies e.g. chiropractor, reflexology, acupuncture, craniosacral therapy in order to help with my condition. None of these have worked.

My migraines are life changing and this new injection 'Erenumab' was my only hope of trying to lead a normal life. It came as great sadness to read that Erenumab would not be made available through the NHS. I would strongly urge you to reconsider this decision.

Name	[redacted]
Role	Carer
Other role	None
Organisation	Nome
Location	England
Conflict	None
Notes	None

Comments on the ACD: I'm writing as a mum of a 25 year old daughter. She was a healthy bright very sociable young person very keen to work and contribute to society. After graduating she started within weeks at a job in the city. After four months she woke up with a headache which has never gone away and within weeks she was suffering from chronic migraines as well. The last four years she has been unable to work or have a normal social life and has to live with me as she is unable to look after herself. Despite all this she remains positive that one day her headaches will improve.

As someone who has tried three preventative drug treatments and Botox unsuccessfully she was very hopeful that Nice would approve this drug and hoped that she might be allowed to try this on the NHS. We both appreciate that it is expensive and possibly there has not been enough trials done yet and also we have realistic expectations of the chances it will help. Nevertheless, it is the first drug specifically designed for treating migraines and I'm sure if my daughter did benefit from it any costs involved in her treatment would be outweighed many times over by her contributions to society. Thank you

Name	[redacted]
Role	NHS Professional
Other role	Consultant Neurologist
Organisation	Maidstone & Tunbridge Wells NHS Trust
Location	England
Conflict	None
Notes	None

Comments on the ACD: Chronic migraine affects a significant number of individuals and leads to significant negative impact on quality of life. Migraine as a whole is recognised in the top 20 causes of disability worldwide (WHO). A significant number of schooling and work days are lost due to this condition. Botox has provided a real world treatment option that has brought measurable benefits to a small number of my patients over the last 5 years. These patients have all satisfied the criteria for treatment. Unfortunately there is a relatively small number of patients who fail Botox therapy, and have already failed three or more oral therapies. For many patients trying these oral treatments again is of no benefit, and for many intolerable side effects limit the use for these drugs.

I strongly support the placement of Erenumab as a treatment that should be available for patients who have failed Botox treatment, having qualified for that treatment by current prescribing criteria. I anticipate that this would number a relatively small number of patients. Strict response criteria should be applied to sanction continuing treatment.

Erenumab is a novel treatment option based on sound biological evidence regarding the physiology of migraine. At the very least a possible Risk Sharing scheme could be considered?

Name	[redacted]
Role	NHS Professional
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: We are developing a subgroup of patients with refractory chronic migraine who have not responded well to Botox. A new treatment is required for these patients. Given that erenumab is effective in treating chronic migraine, it may be worth assessing the cost to the patient and the economy in terms of lost work days and added use of preventive of abortive therapies if the migraines remain suboptimally treated.

In terms of long term data, there is new emerging data on the long term use of Botox which suggests that it has an ongoing beneficial effect and can increase the interval between treatments. This I suspect is more to do with the physiology of migraine; once the migraine is rendered episodic and secondary sensitisation is reduced, then the migraine may enter a period of relative remission (the CAMEO series) fat which pointy the erenumab may be stopped.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I would like the new preventatives to be reconsidered for patients with extreme migraines which do not respond to any other treatment.

I have suffered for nearly 40 years and have had over 23 years of trying different treatments. Tried all the available prophylactics, been on Botox on and off for years which has unfortunately lost its effect in reducing the migraines. There is currently no treatment available that helps with hardly any pain relief that works. I lose more than half my week to severe pain and it's after effects, no normality of life. While migraines are treated as non-life threatening, the sufferer actually has no life and they are controlled by their pain which at times is so severe that you actually want to die just to end the suffering. There have been suicides as a result of migraines but as the cause of death is reported as overdose etc., rather than the reason for the overdose i.e. Migraine; the doctors, NICE do not take the deaths into account.

When cancer patients who also have suffered from migraine in their lives get asked which is worse, the cancer or the migraine, the answer is always migraine.

For this reason I would like to ask that the new treatment be reconsidered for use on patients like myself who are under neurologist treatment who have tried and not had success with any other treatment, this is our last hope.

I would be grateful if my comments can be taken into account.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As I understand it, Erenumab is the first new drug developed specifically to target migraine, and the results of the trial show it prevents almost half of attacks.

As a chronic migraine sufferer I am bitterly disappointed to learn that it has been rejected for use on the NHS. I appreciate that it is expensive, but it would only be used by patients for whom all the cheaper options had failed, and would not be given to everyone. I have approx 18-20 migraine days a month; I have tried all of the recommended preventative meds (beta blockers, anti-depressants, anti -seizure ones) plus the sTMS device and the Cephaly device, as well as Botox. None of these were effective (they did not work or I could not tolerate them). As such I feel I would be a suitable patient to try a totally new type of preventative treatment.

Botox works for some people, but not all, so it could still be offered before Erenumab to limit the amount of the latter given on the NHS. However, Botox is very invasive -31 injections in all on each occasion it is given.

My chronic migraines mean I no longer work, even part-time, and also limit my social life in many ways. It is definitely a disability, and one which is little understood. Triptans do work for me, but I am restricted to taking them 10 times a month to avoid medication overuse headache. This means that I have no treatment available at all for about 10 migraine days a month. IF Erenumab were made available for last-resort situations like mine, it could give me my life back. Please reconsider your decision.

Name	[redacted]
Role	NHS Professional
Other role	GP
Organisation	None
Location	Scotland
Conflict	None
Notes	I am a co-investigator of the BECOME study which has been sponsored by Novartis. I have accepted honorarium from Novartis for delivering headache education and for a Scottish Advisory Board.

Comments on the ACD: I agree with the conclusion with respect episodic migraine but would like to comment on chronic migraine. Not sure when there is evidence for the 70 mg dose why NICE would not endorse clinicians to use the 70 mg dose. Response was measured for 50% or greater reduction yet committee thought 30% reduction more clinically relevant. This is taken from the CM trials on botox. Surely 50% reduction better than 30% reduction for those patients, furthermore does not account forthe patients who get 100% response as for these patients this is a "cure". I agree that there is no evidence to conclude that erenumab was more effective than botulinum toxin type A but there is no evidence to day it is less effective. Likewise I agree 4th comparable oral preventer would be useful but this was not expected from botox submission. Is NICE suggesting the only place for this therapy would be if botox failed? I am unsure relevance of long term treatment comments as I understand follow up for CM was for 52 weeks. In my clinical practice if patient back in episodic migraine at 1 year I would be planning to stop therapy and see how patient was.

Name	[redacted]
Role	NHS Professional
Other role	Senior Registrar in Neurology
Organisation	None
Location	England
Conflict	None
Notes	I have no competing interests.

Comments on the ACD: In my work with the Armed Forces I encounter a significant number of young patients with chronic migraine. Whilst our preferred treatments, in the form of tricyclic antidepressants and anticonvulsants, work for a proportion of our servicemen and women, our ability to maintain a therapeutic benefit is significantly impaired by the tolerability of these agents. Young people in particular seem to suffer the cognitive sequelae attached to such products. A significant amount of time off work, or time unfit for live firing or exercises, ensues, diminishing our already depleted manpower. Botox is a cumbersome as it necessitates frequently returning for injections, which clearly does little to enhance manpower.

Faced with these difficulties, the ability to use an anti-CGRP medication, with it significantly improved side effect profile, is very much welcomed. We hope that it will be brought into the fold for migraine therapies, at least for those unable to tolerate our first-line agents and for those in whom repeated consultations for Botox would cause significant inconvenience.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have suffered with migraine since the age of 20. I am now just 70 years old. I have tried every single type of new drug, treatment offered to me during the last 50 years and have kept well abreast of new developments and immediately consulted my Neurologist each time a new treatment emerged. I have had absolutely NO success with any of the treatments, right back to Migril, Saniomigram, and copious amounts of codeine based painkillers. I have submitted myself to various other types of treatment which have cost huge amounts of money including Chinese herbal medicine, acupuncture, wheat-free months, dairy free months, Alexander Technique and the list goes on. I gave up alcohol aged 21 in the hope that this would help. I have not eaten cheese (as this was believed to be a trigger in the 70's) since then and injected myself with Sumatriptan and gone through each and every one of the triptans as they emerged onto the market. I then tried Topiramate, propranol, and all these made no difference. I have lost huge sections of my life where I was NOT ABLE TO FUNCTION AND WENT AROUND ALMOST COMATOSE. Events like my own 21st party had to be missed, on the day of my son's wedding I was drugged up to the eyeballs and could not truly enjoy the day etc. I then tried Transcranial magnetic stimulation and used that for months on trial - absolutely no effect whatsoever.

I then read about the Botox and before approved by NICE had to fund Consultant appointments and even the Botox itself as my insurance company treat my migraine as CHRONIC and will fund any treatment. I paid for all that BOTOX for months and absolutely no reduction at all in either number or severity of migraine attacks.

Then I attended the Migraine Symposium in London in last Sept. and herd [redacted] hailing the new treatment Aimovig. As usual I contacted my Neurologist) not via National Health system but privately and finally obtained a private prescription for my first injection in October 2018. MY WHOLE LIFE HAS COMPLETELY CHANGED. I CAN ACTUALLY PLAN EVENTS, DAYS OUT ETC. WITHOUT THE FEAR OF HAVING TO CANCEL AT THE LAST MINUTE OR ARRIVE TOTALLY HUNGOVER DUE TO THE EFFECT OF MASSES OF TRIPTANS ETC. I have been experiencing between 13/16 MIGRAINES every month for all those years and in the 28 days after injection I ONLY HAD 5 MIGRAINES. The second month was incredibly 5 again in 28 days. Third month 4 migraines in 28 days. I AM A WIDOW AND AM SO RELUCTANT TO EVEN TELL MY CHILDREN ABOUT THIS AIMOVIG IN CASE I BURST THE BUBBLE AND THE IMPACT IT HAS ON MY LIFE. My GP was very supportive and obviously had to prescribe those horrific amounts of Triptans for me even to have any sort of life. THERE MUST BE MANY OTHER PEOPLE IN THE SAME SITUATION AS MYSELF WHO HAVE TRIED ABSOLUTELY EVERYTHING ON THE MARKET AND AIMOVIG IS THE ONLY DRUG WORKING. Please NICE reconsider the Approval for Aimovig. It truly seems to be a miracle cure for me. Having been a victim of those migraine attacks for 50 years please let me have the remaining years migraine free.

As a widow I cannot afford to keep funding these injections without huge cost to my personal circumstances. Surely the study must also take into account the amounts of Triptans and other medicines which will not be prescribed if Aimovig is available on NHS and this should be offset against the cost. Indeed it only has been compared to Botox but another plus for Aimovig is it can be administered by the patient and does not require a Consultant - was the cost of the Consultants who administer the Botox factored into the comparison feasibility study? MANY THANKS FOR ALLOWING ME TO AT LEAST VOICE MY APPEAL.

I have had the last 50 years of my life totally ruled and disrupted by migraine - nothing else has even given me a day's grace. Suddenly the Aimovig is my miracle cure and please do not make the remainder of my life the hell it has been because of cost. After all I am already 70 years old.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have tried every drug and every medical and alternative treatment there is for Migraine. I am a chronic sufferer and have been in an acute state for the past 15 yrs. Nothing I have tried has made any impact on the frequency (minimum 3 times a week) , although Botox, which I have 4 monthly, has a honey moon period of about 4 weeks, when the pain is slightly diminished.

Erenumab is the ONLY drug, and I have tried everything else, including medical devices and Botox, that has, so far, stopped me having migraines 3/4 times a week, sometimes more. I have been without a migraine now for 3 weeks. This has never happened, not in 15 years! It is a life saver, and life changing, literally! There is nothing else out there that even comes close to helping me be pain free and able to function, and it would, I'm sure, help so many other long term sufferers.....

I have taken Erenumab at the 70mg for 3 months. Within that time frame, I managed to go without a migraine for 2weeks, the longest I have gone for 15 years, but then it reverted to 3/4 a week. I am now in my second month of taking Erenumab at the higher dose of 140mg. I have currently not had a migraine for 3 weeks! This is incredible, and has totally changed my life...

Name	[redacted]
Role	Patient
Other role	None Executive Director
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have been suffering from migraines since the age of 4, with episodes increasing in intensity and frequency, in my early thirties. I regularly needed to take days off work and suffered from severe pain and vomiting. Over the years, I have been under the care of many different health care professionals and have tried every medication that is available for different periods of time. Some have given me some initial relief, but most have had side effects, some quite severe. I have also tried many alternative therapies - none of which worked. I am now 63. Up until I started on Erenumab 4 months ago, I had settled into a pattern of up to 15 migraines a month which were significantly exacerbated in length and intensity if I ate anything other than a very bland diet. After 4 injections of Erenumab (at monthly intervals) the frequency has reduced to 4 or 5 a month and the intensity by about 50%. I am still careful with my diet but find I can tolerate a broader range of food. I will certainly be continuing with the medication as it has had a major beneficial impact on my life.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	Wales
Conflict	None
Notes	None
Comments on the ACD: For migraine sufferers this drug could be life changing. I have been receiving botox for 2 years now and whilst it has made a huge improvement I still get on average 5 migraines a month. This is not only debilitating but impacts on my ability to work and live my life.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Having suffered migraine for 30+ years and tried most preventatives, now on topiramate, I still have to watch everything I eat and still at best suffer episodic migraine and quite often chronic migraine!! It can rule my life.I am desperate for this new drug and never thought for one minute it would not be licensed by you after it came out in America. I'm horrified that you might block it. There are thousands of people who have their lives run by migraine and ruined and are waiting for something new that actually works, maybe. Please give some hope and reconsider.	

Name	[redacted]
Role	Patient
Other role	Self employed artist
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I'm a chronic migraine sufferer, and I've respond poorly to treatment. Pills in general cause me extensive side effects, so overtime I've tried many pills and progressed to other treatments, this includes the Botox injections which I tried for the recommended amount of time, they did nothing to help me, they had no impact at all, they didn't reduce my migraines by even one in the 6 months I was on them. I have a very mild improvement to the Goni (greater occipital nerve injections) they take the edge off. The Goni are my last option at this time, so for me this means 6 severe migraines a month, around 18 milder migraines a month and the rest of the day's in a month I "just" have a headache the same headache I have every hour of every single day, the headache I've had for over 3 years, every hour of every day for over 3 years... this is me when I'm improved on my last option, so another option is desperately needed. I cannot state strongly enough how much another option is needed by myself and the 600,000 chronic migraine sufferers in the UK.	

Name	[redacted]
Role	Patient
Other role	Medically retired
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I was extremely disappointed to learn of NICE's intention not to make erenumab available on the NHS. I am a chronic migraine patient, and have tried all the preventative medications currently available: beta-blockers, anti-epilepsy meds, tricyclic antidepressants etc. None have been effective, and all have had extremely unpleasant side effects (unsurprising as none of them are primarily for the treatment of migraine). I have had botox and occipital nerve block injections, and have tried alternative therapies: acupuncture, hyperbaric oxygen therapy, chiropractic, plus endless supplements and dietary changes. Nothing has worked, and I consistently experience 20-25 migraine days each month. I have had to take ill health retirement and am now reliant upon disability benefits.

Erenumab represented the only hope for me - it is the first medication developed primarily for migraine prophylaxis, and with minimal side effects. I hoped that this drug would reduce my migraines, give me my life back and enable me to work again rather than being financially reliant upon the state.

I would urge you to reconsider your decision- PLEASE make this drug available to those like me whose lives have been destroyed by migraine and who have exhausted all other possibilities. I cannot afford to obtain it privately and, unless it is made available on the NHS, now have little hope of becoming a fully functioning member of society again.

Migraines have cost me dearly- I have lost the career I worked hard for, my social life, my interests. I have even considered ending my own life. However, as well as the emotional cost to me and many others in the same position, there is a financial cost given that many of us now have to rely on state benefits and are likely to continue to do so without new drugs being made available. Erenumab represented the best chance for me and the many others like me of returning to work, and thus contributing to the country financially again.

Even in those migraineurs who have been able to continue working, migraines cause significant numbers of sick days and lack of productivity, all of which has a financial impact.

Please consider all the financial implications of migraine when assessing cost/benefit in erenumab, as well as its potential to help many people like me whose lives have been destroyed by migraine, and who currently have NO migraine-specific preventative medication available.

Name	[redacted]
Role	Patient
Other role	Retired disabled
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: What appears to be missing here is the massive disruption lifelong Migraine disorder has on family, marriage and stymied work aspirations. It costs the economy billions in lost productivity alone. People like me don't just get the odd attack. It becomes a syndrome you can live with for months, sometimes mild, medium or severe where it paralyzes you with the pain. Erenumab would give people like me their life back. You may take a weekend away or a trip for granted. People like me and many others can't even plan a trip to the pub. Withholding this drug knowing how safe and effective it and others coming are is a decision that's as cruel as it is monstrous. We have a genetic chemical disorder that can be helped. A spike in Calcitonin leading to a chain reaction the misery of which cannot be adequately described. My mother and her 6 sisters all had this disorder chronically. In bed for days untreated. I suffer even worse…getting through with Sumatriptan injections and tablets. It's no way to live a life when relief is now a possibility. Please reconsider for the millions that suffer. **Just a man who is 63 years old who has suffered this terrible disorder since 5 yrs old. Please do not deny this new range of drugs from people like me. Often life is just a world of pain and illness.**	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: People with migraine (a neurological disease) are "missing out" again. Just as when the Triptans were prescribed reluctantly years ago. The decision on Erunamab should be re-considered. Migraine is a life changing affliction for the sufferer, their families and employers - with many days lost to all. If the decision is financial - then it is short sighted - as it was with the Triptans. Migraine is recognised as a disability and medication should not be withheld from sufferers.	

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Re. NICE's decision on Aimovig as a migraine prevention, January 2019.

I was very disappointed to read that NICE is not recommending Aimovig because it is not cost effective.

I have suffered from migraines for thirty eight years despite trying all the prophylactic medications available. It would take too much space in this email for me to describe the misery and disruption that migraines have caused to me during my life. I have eight to ten migraines monthly. I cannot live a normal life because I never know when migraine will occur. I have never worked full time since 1977, and retired from my part time job early, due to migraines.

I hope that NICE will help me and other sufferers by recommending this new medication. I would like to try it and if successful would make the remaining years of my life pleasant.

[redacted].

Name	[redacted]
Role	Patient
Other role	Unemployed
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have suffered with chronic status migraine for over 11 years. I have tried a wide variety of treatments in that time. For about 7 years I was on pizotifen which got me to a point where I could work again, this lasted for close to 4 years, it was never gone but under control. Then the migraine came back to a point that I couldn't work anymore. Once I could see a consultant he put me on Botox as I more than met the requirements. I thought the Botox made a big difference. It improved my quality of life and reduced the severity of the migraine attacks but I was still getting several a week and was still classed as chronic. In November I was taken off the Botox due to NHS rules as I was still chronic after multiple treatments. I'm on a mega dose of vitamin B2 now. I am not getting better, in fact it's getting worse.

I understand you do not think erenumab is not cost effective compared to Botox but what about people, like me, for whom current NHS treatment isn't effective? I know to get the Botox I had to have tried a number of other treatments first, perhaps a similar protocol could be implemented for erenumab were Botox needs to have been tried first before it can be prescribed?

Erenumab is something I been aware of for a while due to its press coverage. Due all the other available drugs failing to treat me I had been eagerly waiting for this treatment to be approved. After looking into it I have read a lot of stories from people in America who have had their lives turned around by this new treatment. I felt like there was some hope in the horizon, even if it was not certain it would help, at least there was something else to move into.

I hope my case will help you change your mind and approve this treatment. If you want to talk to me further please feel free to get in touch

[redacted]

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I personally am disappointed this medication has not been approved for use in the UK. I have suffered with chronic migraine most of my life and have tried many different preventative medications. I was excited by the prospect of a preventative that was developed for the use of migraine specifically and could tackle the cause of my pain directly rather than mask the symptoms of it. I would welcome this decision being reconsidered.

Name	[redacted]
Role	Patient
Other role	Student
Organisation	1994
Location	N.Ireland
Conflict	None
Notes	None
Comments on the ACD: I am a 24 year old female who has suffered from migraine all my life, and chronic migraine for the last 3 years. I have exhausted over 10 treatments - including botox - and am yet to respond to any and find any relief. I understand that this drug may be costly, but it acts as an alternative to the likes of botox and should not be dismissed for those of us who have exhausted the other options. This drug has the potential to restore my quality of life and mental wellbeing and I see no reason why other developed nations should offer this medication and not the UK.	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	None
Conflict	None
Notes	None
Comments on the ACD: My 20 year old daughter is in CONSTANT pain. She rates this as a 9 base level at all time, she is not a drama queen (as a comparison has walked around with broken bones for 3 years after being ignored, due to her young age and our GP calling her an attention seeking teenager, so she knows what she's talking about - MRI finally revealed 2 bi lateral pars, L3 & L5). Her "migraine" has been constant 24/7 for the last 18 months. She has not finished school, she does not leave the house, she is losing all hope of ever having a "normal" life and all she wants is for the pain to stop. This drug may not work for her, most migraine drugs only work on 50% of the people, but to deny her even the chance of some respite is inhumane. Next time you have a headache or tooth ache or any other pain, try not taking any medication and see how you cope with it, may give you some small measure of insight into what migrainurs have to live with.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: Commenting as a vestibular migraine sufferer but also as a medical professional. This is an incredibly debilitating condition, I am at the stage where I may have to give up my career as none of the medications I have tried are working and the side effects are becoming more intolerable. I have tried propranolol, amytryptilyn, pizotifen and topirimate, more than the recommended 3 fails. I didn't even know this was a guideline before reading this document so will be visiting my GP shortly! I would ask you to reconsider approving erenumeb.	

Name	[redacted]
Role	NHS Professional
Other role	Neurology Consultant: Headache Specialist
Organisation	City of Sunderland NHS Trust
Location	England
Conflict	None
Notes	None

Comments on the ACD: Overall the document seems to agree that Erenumab is safe and effective. The main limitations appear to be cost (no PAS price yet agreed) and need for better comparators to Botulinum toxin.

1. I agree it is not cost effective for episodic migraine

2. I disagree that more comparisons to botulinum toxin are required as if it represents 'standard of care' Botulinum toxin provision for chronic migraine is not available in all hospitals but only in specialist headache centres so cannot be seen as a 'standard of care' although it is believed to be the most effective non-oral treatment for chronic migraine currently. Studies have shown equal effectiveness of botulinum toxin to topiramate and I suggest the best oral preventative should be the best comparator (as indeed was the case when botulinum toxin was approved by NICE).

3. I believe that there is no need for head to head trials between botulinum toxin and erenumab and no need for identical trial lengths to compare results (refer to PRE-EMPT trail and available Erenumab trials) as Erenumab should be assessed in its own right.

4. As with botulinum toxin, I agree that the correct place for Erenumab is after 3 failed oral preventatives as with botulinim toxin, but not necessarily after botulinum toxin given reasons as in point 2 and 3.

5. I care for a large population of chronic migraine sufferers who are all limited in their lives at work and at home and are desperate for alternative treatments. It would be unfair to this cohort of patients to deny them the chance of trying a potentially effective and safe treatment.

6. There is already patient demand for this treatment with a few individuals going to their local MP's to ask why they cannot access it with NHS support.

Name	[redacted]
Role	Carer
Other role	Mother of Chronic Migraine Sufferer
Organisation	1952
Location	England
Conflict	None
Notes	My daughter started having aimovig 140mgs on a private basis last month and there has been a noticeable change in her condition. However, the cost makes this unsustainable.
Comments on the ACD: I have read the document and having witnessed my daughter's decline from happy, outgoing girl with everything to live for, to the exact opposite, I implore you to sanction erenumab as genuinely our last hope. Even an occipital nerve stimulator has failed and I know that my daughter is totally at the end of her tether. She is intelligent and hardworking when allowed to be, and would be such a useful member of society if only something would work... Please help us. As a family we are crippled by this problem which has gone on for 12 years. Days out and holidays are a thing of the past for my beloved girl who spends 50% of her life now in a darkened room.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have had severe migraine associated vertigo since I was 6 years old, daily migraines most of my life, heavily reliant on painkillers, took erenumab and only one small migraine in a month. Unfortunately it had no effect on the associated vertigo but was brilliant for the pain. It is extremely important that this is allowed on the NHS.	

Name	[redacted]
Role	Mum of son with chronic migraines
Other role	Civil servant
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: My son is 33 and suffers from chronic daily migraines. He has tried at least 12 medications acupuncture botox and nerve blockers to no avail. He needs a chance to try the Aimoveg. His life is on hold,unable to work and friends losing contact. Unless you live with some done suffering this way you cannot appreciate the need to try and find a cure	

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have suffered from migraines all my life, Now I am retired frequency has increased to four to five times a week.

In my particular case, the aura, which last 8 to 10 hours are the most debilitating aspect of the attacks.

I have taken Amitryptine to prevent these for 10 years, but these are no longer effective at a dose I can tolerate.

I am asthmatic (fully controlled) so my GP will not prescribe beta blockers, a medication intended for heart problems.

I have tried drugs intended for epilepsy, but these caused intolerable side effects.

My GP has told me that there is no treatment he can offer me apart from triptans once an attack has started, which allow me to continue functioning at a basic level during an attack. But have unpleasant side effects. These are also restricted (I believe by the CCG) to 12 per month (originally 6).

Then Erunumab comes along offering hope at last. The first ever medication specifically for migraine. It is considered safe and effective in most cases, and has been licensed in the US and Europe. The only issue with seems to be the pricing. With three similar drugs all at approximately the same price!

I would ask NICE to reconsider it's decision on this, last hope for many migraine sufferers, and leave the competition authorities to address the pricing issue.

According to the WHO, migraine is a genuine disability and is the third most common disease in the world. To refuse patients access to this treatment is like not offering hearing aids or spectacles, or refusing insulin to diabetics.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Please could you approve this drug, I have suffered with migraines for over 12 years, I have tried everything that out there and nothing has work. I have a lot of low in my life and it's my kids that keep me going but I lose out on so much time with them because I'm sick with a migraine. I had to leave my good job because I'm have so much time off. Please let this drug go through it's could help so many people like me to have a better life that we once knew.	

Name	[redacted]
Role	Patient
Other role	Careers Consultant
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I am a sufferer of migraine. Can you look again within the research and explain why ANY improvement is not considered sufficient for recommending this drug? I have not had improvements with many preventatives but this does provide some to some people. Migraine prevents me better managing my CVD and osteoporosis. It is not clear whether it is chronic or episodic migraine but it causes significant disability, absence from work, loneliness and isolation and depression. I have had to reduce my working hours and am at risk of pensioner poverty if I stop work completely. At times I have considered how pointless life is with this condition. Because of medications for CVD I am unable to take triptans and amitriptyline. I have tried other medications without success e.g. propanalol and metrapolol. My GP will not prescribe cander sartan as my BP is too low. I have not found a rescue medicine: the only one I am allowed is aspirin and it doesn't work. **The utter desperation of migraine patients is ignored by the medical profession (with notable but few exceptions); there is stigma around the condition which affects how employers and non-migraneurs deal with it. It is devastating.**	

Name	[redacted]
Role	Patient
Other role	Judge part time
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am aged 57 and have had chronic migraine for many years which affects my work and home life significantly. I can only work part time and cannot seek advancement in my career due to migraine.

I have tried antidepressants, anti-epileptics and beta blockers to no avail. I then had botulinium toxin type A injections without success. I am under the care of the John Radcliffe hospital and there are no further options for me to try without Erenumab. I have had 2 completely drug free periods to rule out medication overuse. One possible benefit of Erenumab is that if it works then it will not only improve my quality of life but will also enable me to reduce my dependence on pain relief medication, lose weight and to take exercise, which will bring other health and therefore cost benefits to the NHS. This may help to break the cycle of headaches which needs to be considered as a long term benefit. I am currently having migraine at least 20 days a month.

Migraine disproportionately affects women and to fail to authorise its use would be to discriminate on the grounds of gender.

I strongly urge you to authorise the use of this new medication which may bring some hope to the many migraine suffers in this country.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I do not believe that the information presented here fully reflects the nature of migraine, e.g. "people with migraine can often miss out on family time and find it difficult to make plans". This does not properly recognise the impact migraine can have on someone's life - it may be true for episodic sufferers, but the main issue for an individual experiencing migraine on a daily basis is more likely to be the extreme and severe pain they are in.

In addition, "symptoms can start in the days leading up to a migraine and that recovery can take a few days, so people with chronic migraine may have few symptom-free days" fails to recognise that it is possible to experience daily migraines and therefore NO symptom-free days.

If this is the understanding of migraine upon which the decision was made, the decision is flawed - I do not believe this information fully explains the extent and impact migraine can have, particularly whilst an individual is experiencing a severe episode of the headache phase. The word 'pain' is not mentioned at all.

This seems odd when this drug surely should be considered for use in people who are chronic migraine sufferers, which includes people who experience daily migraines.

My main concerns about the document are as follows:

- the document makes claims about erenumab vs "best supportive care", however, as far as I can see, the latter term is not defined. Without understanding what this is, it is difficult to assess what this means in practice (and whether this care is something which is or would be accessible across the NHS/cover all circumstances)

- from what I can see, much of the decision seems to turn on the fact that "there was [in]sufficient evidence to conclude that erenumab was more effective than botulinum toxin type A". I do not understand why this is relevant. A (chronic) migraine sufferer may try numerous treatments before finding one which works. The requirements for botox are that an individual has tried and failed three other preventative treatments - I do not understand why similar requirements could not be applied in respect of erenumab (e.g. to require that an individual can only be considered for erenumab if they have tried and failed three preventative treatments AND tried and failed botox OR botox is unsuitable for them. This document fails to recognise that an individual experiencing chronic migraine is experiencing significant periods of time where they are unable to function and the critical importance of sufferers being able to access treatment options.

In addition, I do not believe the consultation period for this consultation was adequate. The consultation has run for an extremely short period, and this

fails to take into account the fact that migraine sufferers (and in particular individuals with chronic/uncontrolled migraine, who are migraine sufferers most likely to have an interest in the consultation) are, whilst in the midst of a migraine, likely to have periods where they are unable to use a computer/process information.

Name	[redacted]
Role	Patient
Other role	Retired Occupational Therapist
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am 63 and have suffered with Migraine for 45 years. This has significantly and adversely affected my life and that of my family. I suffer approx 10 Migraines monthly and over the years have tried every preventative medication suggested by neurologists plus every alternative treatment, all to no avail.

I was ecstatic to hear about Erenumab, my only hope of significantly reducing the frequency of migraines and vastly increasing my quality of life. To hear that Erenumab would not be available on the NHS and it's use had been totally rejected for all by NICE was devastating and quite frankly I feel, unfair. This treatment is the ONLY hope for hundreds of thousands of sufferers. I feel this decision is prejudice against migraineurs because of the cost.

Why has Nice rejected the funding of this drug for use by EVERY person affected by migraine? Surely the provision of Erenumab to those with chronic/higher frequency episodic migraines should be investigated and considered further.

The potential cost of working days lost per month is surely greater than the potential monthly cost of this treatment?

Name	[redacted]
Role	Patient
Other role	Chronic migraine sufferer
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Please do not delay in bringing this new treatment targeted at migraine for prescription. It cannot be underestimated how wholly miserable life can be with this condition, and the treatment at present is mainly with drugs designed to treat other conditions. Please, please do what you can. **Chronic migraine sufferer since 14, sometimes experiencing symptoms on a daily basis.**	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: This drug is one of the first created and targeted just for Migraine with great results, it is making a positive impact on so many patients' lives and the decision to not approve it is both a huge disappointment and a disgrace. It would help cut headache days and enable patients like myself to lead a more normal life.	

Name	[redacted]
Role	Patient
Other role	Chronic Migraine Sufferer
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: As a chronic migraine sufferer I have been waiting for a "migraine specific" treatment for over 40 years, and both of my daughters, now 29 and 33, are developing a similar condition.

If I address my current situation, it will perhaps put my concerns into context. I managed work by combing sickness days, holiday days and putting in extra hours at the weekend and evenings to ensure my work was not suffering. I was able in the latter years to amend my work pattern by negotiating this with line managers. However, the toll on my health was excessive and I had to resign my post on grounds of ill health and rely on sickness benefit in my early 40's. My life situation was dramatically altered as I am sure you can imagine, dropping down from what was then over £35,000 to benefit level. My family life and social life was negligible and I missed out on a number of important family events.

Prior to leaving work I had been studying part time and this too suffered so I was unable to complete my Master's degree, despite having invested time and money into it.

I have tried various treatments recommended by the neurologist/migraine specialist but these have had little impact on allowing me to participate in any meaningful way with any social, family activities (and work is out of the question!). In addition, the side effects have frequently outweighed the "benefit" of the medication. I now receive botox. This has been more useful than any of the medications I have taken, but it still does not reduce the frequency and severity sufficiently. The fact that I can go to bed as soon as a migraine starts - as I no longer have children at home, do not work and do not socialise - has helped to alleviate some of the severity, but there is no life in spending one's time in bed. I average 15 - 20 days migraine a month. This does not include the "down time" that both precedes and follows a migraine.

At the age of 40, I told family and friends that I hoped I would die a natural death before "retirement age" if there was no relevant cure. I also ensured I had an advance directive as I do not wish to remain alive in a worse state than I do already. I reached my 60th birthday last December and was finally hopeful that my next few years could be improved with this treatment.

I understand the issue of cost. However, I do not choose to have migraine. I do everything I possibly can to avoid and treat the condition. I visit Stoke hospital and my GP regularly and now have my prescriptions free. I am angered by constant reports on the TV about obesity and alcohol abuse, causing ill health, and the ability and willingness of the NHS to cover these individuals when they have made a life style choice (I understand that many of these people may have complex issues, but the bottom line is it is a choice and treatment of gastric bands, insulin etc. is being offered at enormous cost per person).

This treatment offers me the opportunity to regain a life. It could enable me to return to work, require fewer prescriptions, contribute to the economy through work and social life, reduce appointments at the GP surgery and Hospital, and contribute to the local community.

I would therefore request that you review your decision and consider the impact this treatment could have on both individuals and the wider community. I repeat, migraine sufferers do not choose to have migraine by abusing their life style. We have no choice. You have a choice to offer us a treatment that could change our daily life dramatically - and if it doesn't work for some people for whatever reason, the treatment would not continue.

Thank you.

I am not sure how well I have expressed my concerns as I currently have a migraine - again - although currently in recovery and waiting for the next one!

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have suffered from chronic migraines since the start of 2015. I'm so debilitated by my pain and other symptoms that I'm unable to work and do so many normal day to day activities. I have tried three preventative drugs along with Botox and nerve blocks with no success for controlling my migraines and daily head pain.

I ask you to reconsider for other chronic migraineurs like myself who have not responded to 3+ preventative treatments including Botox. Chronic migraine is a distinct sub group of the migraine population. It's an even smaller subgroup of chronic migraineurs who have not responded to at least 3 preventative drugs.

Without erenumab we are left with very few options of what to do next. What can we do as a society for these people? Give them a chance to finally try a drug specifically made for their condition.

No long term evidence? Correct, but only because it's the first drug of its kind! It's revolutionary for migraine and I can't stress enough that itâ€™s the only drug that's ever been made specifically for the prevention of migraine. A disease which effects 1 in 7 people.

I appreciate it's a high cost drug but the economic burden of migraine is so incredibly high at £3.42 billion per year in the U.K., that I strongly urge you to give this drug a try for a population who is in desperate need and running out of answers.

If my migraines were successfully controlled by erenumab I would be able to work again and put money straight back into the cycle for other patients.

Please reconsider for migraineurs who are left alone to lie and wait in the dark.

Name	[redacted]
Role	Patient
Other role	Patient
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: As a chronic migraine sufferer I wish to stress the importance of making this drug available on the NHS, due to the disability caused from migraines. I have 25-30 migraine days a month and have tried numerous treatments. Currently financially struggling with self-funding Botox, which has improved my health a great deal, but I still have 10-15 migraines a month. If this ever stops working I may find myself bed bound for a large part of the month as I was before. I think it is completely wrong that this NICE looked at episodic migraine and not chronic migraine, as this would greatly alter the costing. The improvement to a chronic migraine sufferers' life would be far greater and therefore more cost effective, than for an episodic 3/4 days per month. I urge you to reconsider and support the use of this drug for chronic migraine sufferers on the NHS.	

Name	[redacted]
Role	Public
Other role	Technician
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Hi I am a sufferer of hemiplegic migraine and have been for a number of year, I would put myself in the episodic category. I have been under a neurologist from more or less the start and have tried several types of drug to try and control them. I have tried toprimomate, amatriptelin, gabapentin, I suffered terrible side effects on these. At the moment I am on pregabalin and propananol these help slightly in controlling the number of attacks I have but the severity of them remains about the same. I suffer from a number of side effects of the medications (dizziness, confusion, loss of memory and a low heart rate to name a few) I also have concerns regarding staying on the medications long term and their long term side effects. I also suffer from social of mental issues due to the hemiplegic migraines, I no longer like to go out due to the fact if I have an attack how people see me, a full blown attack can look like a stroke. My confidence is low and it has also restricted me in my job, I was hoping that the erenumab would be a new avenue to try reduce and control my migraines better than they are at the moment. A drug for the purpose of migraines is what myself and other sufferers have been longing for, and not having to rely on other medication from other illnesses to hopefully help in migraines. I hope that NICE will reconsider and allow this drug to be passed so that it can give migraine suffers a better quality of life.	

Name	[redacted]
Role	Patient
Other role	Systems Support Specialist
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I, and I am sure hundreds of thousands of others, have been very disappointed to see that this potential new medication has not been approved. I think the potential of this medication has kept a lot of people going in their daily lives, living with the hope of some relief from this disabling condition.

I myself currently suffer with chronic migraine, and it has all but destroyed the life I have spent so long building for myself and my family. This condition does not only impact me, but my family. I rely on them to take time out, sometimes from their employment, to help me when I am suffering. I am currently facing potentially losing my job of 18 years due to this condition, which is then going to impact my life even more so than it already has. It has been highlighted recently that migraine sufferers are left feeling isolated, and although I have very supportive family and friends, I can still be left feeling this way. This condition has plagued my life. I have missed out on so many events over the years, most importantly precious time with my daughter, which I cannot get back. This last week alone I have lost 5 days to migraine. This is no life, and no one should be left to suffer like this.

I sincerely hope that this medication can be reconsidered, as the relief this could bring to so many lives does not have a price. You cannot put a price on a persons' happiness and quality of life.

Name	[redacted]
Role	Patient
Other role	Housewife
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I'm very disappointed so far regarding the chances of Erenumab being made available on the NHS. For many, many years I have suffered terrible migraines and have tried all the medicines available to no avail, nothing works.

Since the availability of Botox for Migraine treatment, I have had this prescribed. Unfortunately the effectiveness of the Botox has lessened somewhat over the last year or so.

Because of this, my Consultant Neurologist feels that Erenumab could be beneficial for me should it become available on the NHS.

Erenumab therefore seems the only hope for me to get some improvement in my terrible condition.

Please can you take this information into account and there must be many others just like me who suffer on a regular basis with debilitating migraines.

I hope that Erenumab will be approved for NHS use and people like me might have the chance of getting a bit of normal life back

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I do not understand how this drug, one of the only drugs created to prevent the on-set of migraines, is not being offered by the NHS.

By the NHS's estimates migraines are a common health condition, affecting around one in every five women and around one in every 15 men. The impact of migraines accounts for 25 million working days being lost, every year.

By restricting access to this drug we are not only effecting the economy and business in a significant way but limiting this medicine, which will be life changing to many migraine suffers, on an individual level.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a person who has had weekly migraines lasting 1 - 5 days and for over 30 years. I have been through all the treatments currently available to help prevent migraine with very little success.

My migraines have limited my work opportunities and the contribution that I can make to society. I currently only work 1 or 2 days a work. It is very difficult for me to make any commitments due to my migraines as I am not sure that I will be able to participate. The symptoms when I have a migraine are very distressing.

I was desperate to be able to try this new treatment as it tackles the migraine in a different way and I was hopeful that it could make a difference.

I understand that the treatment is expensive but if the treatment worked for me even partly it would be outweighed by the fuller contribution I would be able to make to my work in the public sector and enable me to participate in a much fuller way to society.

My situation is by no means unusual, I know of many others who are desperate to find a new approach to managing what is actually a life changing condition and renders them economically restricted.

I really hope that you will reconsider your decision not to make this treatment available.

Name	[redacted]
Role	Patient
Other role	Senior Layout Engineer
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I don't have time to read the document and not sure if decision is down to cost. However I will say there are no decent migraine drugs that work for me, I have to take codeine and caffeine and put up with daily headaches some weeks. As the other drugs have too many side effects to function at work on them.

1 in 3 women get migraines and I had to leave my last job because of them. The cost to society is HUGE. If there is a new drug that works, I cannot understand why it's not being funded. Migraines are disabling and usually chronic. I have no life anymore, as could not cope with health issues and work and i already eat healthily. Exercise makes them worse so cannot exercise as much as i would like as too ill afterwards.

I wish drug funding took into account the cost to businesses and society and quality of life, rather than just money and whether the disorder is life threatening.

Name	[redacted]
Role	Patient
Other role	Registered Nurse
Organisation	None
Location	Scotland
Conflict	None
Notes	None

Comments on the ACD: I as a chronic migraine sufferer I am devastated that this drug has not been approved for use on the NHS. I as a healthcare professional and migraine sufferer have seen and experienced how absolutely debilitating this condition is yet there seems to be a misconception by many that it's just a headache. Migraine has absolutely ruined my quality of life. I have trialled absolutely every oral preventative there (none of which were designed for treating migraine) and am currently receiving Botox which unfortunately hasn't had the effect I was hoping for. Erenunab is my last hope after Botox. Every single day is a struggle and has been for years yet I plod on trying to minimise the amount of time I take off work sick. I have twin toddlers at home so life can't stop for them, and I just pray that they don't take after me as I have taken after my grandmother and mother with mine. I am not an isolated case. I have seen this in my job. Many are worse off than me. And frankly how they keep going is beyond me. Please think of the bigger picture and realise that there are actually few drugs out there specifically aimed at preventing migraine as a first line. This could change many lives.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have had the privilege to take part in a clinical trial for CGRP - this was not Aimovig however. **Even though this trail only lasted 6 months it has been life changing for me and I had had not a single migraine since finishing the trial over 4 months ago. I have suffered from chronic migraine for 20 years. I refused to try Botox as this can go wrong and paralysis of the face can occur. I understand that CGRP is going to be costly however there are 3 more pharmaceutical companies producing CGRP's. Once they are ready to approach NICE surely the cost can be reduced. Migraine suffers have never had a drug created specifically for migraine, this drug could be life changing for thousands of people. Patients should be asked to contribute a small proportion of the cost towards the drug when it is prescribed - believe me if the drug works as well as it did on me patients will find that extra portion of money. I also believe that CGRP allowed me to stop taking all the other medications - so it may well be that 3-6 months of CGRP treatment will be all that is needed to free a patient from migraine. I also believe that patients should be given this drug in headache clinics up and down the country that specialise in migraine. This would allow patients to be educated on lifestyle changes, supplements, diet & exercise and this in turn would create a higher long term success rate. Please do not deny migraine suffers this drug, at the moment this is their only hope of improving their quality of life.**	

Name	[redacted]
Role	Patient
Other role	Unable to work due to migraines
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have suffered from migraine all my life and chronic migraine for the past 3 years. I have tried 9 medications and none have worked. I have had 2 rounds of Botox and tried GONB injections as well as transcranial magnetic stimulation and many other treatments. Could this medication be made available for people like me who have tried so many other options with no relief? This condition is so debilitating that I have had to give up driving and work and spend most of my time in bed. Thank you.	

Name	[redacted]
Role	Patient
Other role	Research Associate
Organisation	None
Location	Wales
Conflict	None
Notes	None
Comments on the ACD: As someone who has suffered from migraines all my life, I was disappointed to read that Aimovig is not going to be recommended for prescription on the NHS. Although my migraines have been managed by beta-blockers, I find there are substantial side-effects (e.g. fatigue) that interfere with my daily functioning. The amount of hours and days missed at work due is migraines, and general levels of wellbeing in those affected, should bear more weight in the decision. NICE should go back to Novartis and try to secure a greater discount to their product.	

Name	[redacted]
Role	Patient
Other role	Executive Coach
Organisation	None
Location	None
Conflict	None
Notes	None
Comments on the ACD: Please approve Aimovig for use in the NHS. Migraine sufferers lose many days of work due to migraines. I'm self-employed so I receive no sick pay and potentially lose clients because they may perceive that I cannot be relied on to deliver work as planned. I have no idea whether this drug will work for me but there will be other migraine sufferers that it will work for.	

Name	[redacted]
Role	Patient
Other role	Teacher
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am a chronic migraine sufferer who has suffered from migraines from the age of 20, until now (47) where they are dominating my life wiping out days at a time each month, preventing me from working full time and maintaining family/social relationships. I have tried all other preventatives without significant effect or unacceptable side effects. This drug gave me hope for the future and seems to be the only help on the horizon for chronic migraine sufferers.

The cost of migraine to society in terms of days sick at the workplace and the fragile situation that this puts chronic migraine sufferers in cannot be underestimated.

For a chronic migraine sufferer, a 10% difference can have a huge impact - 30 - 50% would be an absolute miracle.

Name	[redacted]
Role	Patient
Other role	Vice President, Healthcare Practice
Organisation	None
Location	England
Conflict	None
Notes	I have a PhD in biochemistry and work in strategy consulting for life sciences companies, including pharma companies (but not Novartis), and am very familiar with the migraine treatment landscape.

Comments on the ACD: I believe that NICE has made an error in not recommending erenumab for use on the NHS. Reading through the consultation document, I believe that the error partially stems from identifying comparators for chronic migraine patients. Assuming that current prophylactic medications are the standard of care for chronic migraine patients who have already failed on three medications ignores the reality that many chronic migraine patients (anecdotally, as I am not sure if there is data on this; this is an important data point that was not included in the consultation document) simply give up on finding appropriate treatment options and are dependent on rescue medication to manage their migraines, generally due to side effects or to a wish not to be on medication that is not having the desired effect. If best supportive care is considered to be a comparator for erenumab, then the cost-effectiveness of erenumab for chronic migraines may be clearer. Botulinum toxin A is also not a good comparator due to limited access for patients across the UK; if patients were able to access botulinum toxin A as they can an oral drug such as propranolol, which can be GP-prescribed, then this would be a relevant comparator. I speak from experience here, as a chronic migraine sufferer who has failed on more than three prophylactic medications and was not able to access botulinum toxin A in either Islington or Hackney CCGs, in which case I would seriously question access in other areas of the country. Alongside my questions regarding appropriate comparators, I would like to speak personally regarding my own experience with erenumab. I have been on erenumab for just over eight weeks, prescribed via the National Migraine Centre and paid for out-of-pocket, and have had only one migraine during that time, reduced from approximately 16 headache days per month, 8-9 of which were migraine days (and required multiple doses of almotriptan to control on approximately 4 days). While I understand that my response has been higher than the mean response observed in the trials, I can tell you that the quality of life improvements are massive, both in terms of pain management and how I go about my daily life. I used to be anxious about getting a migraine at any time, and would be anxious to distraction if I forgot to bring medication with me when I left the house, and can now even take short trips without worrying about a migraine. My migraines are strongly triggered by exercise, which had led to weight gain, and I am now able to be lightly active again without migraines, which will have massive benefits for my overall health and decrease my risk of (expensive) conditions such as cardiovascular disease and diabetes. I value erenumab so highly that I will continue to pay out of pocket for it, if necessary, but I hope that you will reconsider the decision (particularly looking at the comparators) not to recommend erenumab for use on the NHS.

Name	[redacted]
Role	Patient
Other role	Head of Buying & Merchandising
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I would ask NICE to reconsider making this available on the NHS. I am a chronic Migraine sufferer and know the impact of migraine to every aspect of my life. Current Treatments and attitude to Migraine is still a challenge with very few people, including medical clinicians, understanding the severity of this condition. I don't think it is right to start limiting treatment for a condition that is so severe and impacts so many people. The benefit, if this treatment worked for an individual, are so far reaching. This is just another indicator that the medical profession, and NICE, don't take this condition seriously.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	I am currently a patient of [redacted] at the National Migraine Centre and have seen some of the best Headache doctors in London, including [redacted]. I have tried Amitriptyline, Propranlol, Botox, 2 TMS devices, Flunarizine, Topiramate, Gabapentin, pizotifen, 5 occipital nerve blocks, as well as several supplements including magnesium and Vitamin B2.

Comments on the ACD: Responding to this quote: Meindert Boysen, director of the Centre for Health Technology Evaluation at NICE, said: Migraine is a debilitating condition that significantly affects quality of life and the committee heard from patient experts that well-tolerated treatments are needed. It's therefore disappointing that we've not been able to make a positive recommendation for erenumab.

Erenumab is a promising new preventive treatment for migraine that has been shown to be clinically effective compared with best supportive care. However, there was not enough evidence to suggest that it is more effective than botulinum toxin type A for people with chronic migraine, which NICE already recommends. And for both the chronic and episodic migraine populations there was no evidence to show that erenumab is effective in the long-term in people for whom 3 previous preventive treatments had failed...", I am shocked. As a chronic migraine sufferer, I do not see how the 2 things are related. It's a false comparison. Most drug therapies help somewhere between 20-30% of the suffering population. However, it is not the same thing to say that the same 20-30% of people, or even with a wonder drug of 80%, will get the same results. I also have a wide array of environmental allergies and none of the newer antihistamines work for me, even though there are a wide array available. They are all around 25-30% effective but I am not covered. I have tried over 10 different therapies, including 2 rounds of botox privately and it did not work AT ALL. So, what is the point here? Because I am an outlier, I do not get access to a proven therapy. Conversely, I am grateful that Zomig is available on the NHS because I have tried all but one other triptan and none of them had any positive effect. Finally, OF COURSE, "there is no evidence to show that erenumab is effective in the long-term in people for whom 3 previous preventive treatments had failed". The drug has not been around long enough for there to be long term evidence. This is preposterous on its face. Indeed, this infers that all new drugs that have evidence of being effective for some in the short term cannot be introduced to the NHS until they are no longer new drugs. I'm sorry but this seems to be not only hindering comprehensive care options for people like me but also using a bludgeon where a surgical precision is required. Where a new medicine is proven safe and effective in the short term and where there is no or very few other options available and they offer lower chances of success, this medicine should be made available to patients on the NHS. I have not worked for 2 years because of chronic

migraine. I am lucky to have a relatively high earning partner so I do not depend on support from the state but I often think of people unlike me in my position and wonder what they could do.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I am writing in despair to ask you please, to reconsider allowing erenumab (aimovig) to be available on the NHS.

My life has been destroyed since the age of 20 by chronic migraine (15+ per month). I had to drop out of university in my second year and then spent 4 years at home. During a good patch when large doses of indometacin helped I got a full time job but had to give that up as the tablets had terrible side effects and had to be stopped. I have no boyfriend, children or any of the things I expected to have.

Since 2006 I have seen specialists in Liverpool, London and Stoke. All preventative medication has failed including botox, nerve blocks, TMS, and vagal nerve stimulation. In 2016 I even had an ONS implant which I was sure would work, but no.

I spend most afternoons in bed hoping that sleep might help.

In October 2018 my parents started paying for me to have aimovig injections privately. Initially 70mgs but now 140mgs, as there was only slight benefit with the 70mgs. I have felt so much better since this and am even smiling again. I long for normality and not to be so dependent on my Mum.

My parents are both retired and cannot afford aimovig in the long term.

Erenumab is my last hope and I ask you with all my heart to think again for those of us who never know what a "crystal clear head" is...

Thank you,

[redacted]

Name	[redacted]
Role	Patient
Other role	Housewife
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: As a chronic migraineur of 30 years who has tried several prophelactic options including botox. With no improvement. I am now in my 4th month of 140mg of erenumab, this has been a lifechanging treatment for me. My migraine attacks have reduced from most days being affected by an attack with 10/12 days a month. In a dark room vomiting. To a total in the last 4 months of 8 days mildly affected. I am asking nice to please reconsider this treatment to be available on the NHS.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I'm very disappointed to hear that Aimovig (erenumab) will not be recommended for use on the NHS. I have tried nearly all the preventatives, including pizotifin, beta blockers, anti-depressants and Botox. Only Aimovig has helped. Beta blockers have helped a little, but their effect was limited. Before Aimovig I suffered from 12-15 migraine days a month, which was too many to treat with sumatriptan. I started using Amiovig two months ago, and it has reduced my migraine days by two thirds. The remaining days can be treated with sumatriptan without exceeding the monthly dose limit. This has changed my life. I understand that it is expensive, and accept it should only be prescribed to people who have tried everything else, including Botox. I decided not to wait for the NICE approval, and to try Aimovig on private prescription, as I couldn't wait a full year thinking there was a potential treatment out there. I had to try it. Now I know it works I can't imagine going back to where I was a few months ago. But I can't afford it. Budgeting for one year's dose has hit my savings hard. I can't afford to do this year-in, year-out.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: It is really disappointing that Aimovig is not being approved for use by the NHS. It is an innovative new treatment, which as a long term migraine sufferer I was hoping to try. I have not so far found any other preventative which works for me, and Aimovig sounded like a good option, being specifically formulated for migraine. I do hope that there can be a reconsideration.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Aimovig is the first drug that has been designed specifically for migraine. The prevention of migraine from the current treatments is in actuality a side-effect. Many people suffer the true effects of these medications for months if not years trying to control their headaches, resulting in a substantial loss of quality of life and excess usage of sick leave. Also the dispensing of these unsuitable drugs for the required trail periods is a waste of NHS money. Aimovig, and similar drugs in development, could solve these problems in many cases. However, without support from the NHS the impact will be minimal, due to the limited number of patients able to afford private health care. I hope Aimovig will be recommended for NHS use in the future.	

Name	[redacted]
Role	I work for a Headache Charity, the National Migraine Centre, as a GP Headache Specialist
Other role	GP Headache Specialist
Organisation	National Migraine Centre
Location	England
Conflict	None
Notes	None

Comments on the ACD: In my role as a GP Headache Specialist working with patients with both episodic and chronic migraine, I feel that the role of Erenumab needs to be considered in those patients who have tried and failed oral medications but also failed Botox treatment. Botox is a very useful and sometimes very effective treatment but there are a number of very relevant differences between Botox and Erenumab.

Individual's experience of migraine is very variable and we already know there are at least 42 genes involved in the causation of migraine. We see on a weekly basis the variation in response that patients have to the headache treatment strategies currently available. Even within one group of drugs, eg the triptans, responses can range for an individual from being unable to tolerate one type to finding great benefit from another. One hat does not fit all!

Botox therapy fails in some but we have been prescribing Erenumab in the National Migraine Centre to patients who can afford to pay for it themselves and we have been impressed by the response in some patients who have failed many other treatments including Botox.

It may be reasonable to build into approval of Erenumab, a condition of having tried and failed Botox. I do however feel that there are also other considerations to be taken into account.

Botox is 31 injections, with an option to inject in 8 further sites. The injections are acidic and so sting and are quite uncomfortable. Side effects are rare but can include muscle weakness and asymmetrical facial drooping. It must be injected by a trained Healthcare Professional and so the patient must attend a specialist centre. Pressure on NHS Headache clinics is huge at the moment and, with scarce resources and few trained personnel, delays before treatment starts and also long gaps between courses can occur. I recently saw a patient who was eligible for Botox and had been referred to a local NHS clinic. The wait for an assessment appointment was 8 months. She was then seen and told that she would only get the injections every 4-6 months -this kind of breach of the injection protocol leads to wind up of the pain in the brain again and negates the beneficial effects of the previous dose. I know of another case who was told she would be put on the waiting list for Botox and that the wait would be a year before treatment could start.

Chronic Migraine sufferers are desperate people. The impact on their lives in terms of health, with co-morbidities of depression and anxiety being very high, work -with financial strains, and personal lives -family, relationships and social lives all suffer, is extreme. The prospect of a new treatment which is self-administered, very acceptable in terms of ease of use, low in side effects and also effective has been a glimmer of hope in an otherwise very

dark and miserable existence.

Erenumab can be administered easily by the patient once taught. It does not require special storage and seems very low in side effects. (Oral preventer medications are often very difficult to tolerate in the high doses needed for them to be effective and also with cautions of interactions with other conditions (eg asthma, depression) or medications a patient might be taking.

One further comment is about the impact of Erenumab and Botox on quality of life rather than headache days. Headache days are quantifiable easily and so are often the primary outcome measures in studies of efficacy. We know, however, from studies and from clinic experience that the drop in pain score on a day of headache from eg 9/10 to 7/10 may result in a patient having a quality of life improvement which enables them to get up out of bed, move around, care for their child and begin to be involved in life again. Headache days are not the whole story -quality of life improvements are so important but harder to measure. I urge the Committee to reconsider approval for this drug which can be life changing for these desperate sufferers.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Migraine is a debilitating condition which can have a huge impact on the lives of people who suffer from it. Reports from America suggest erenumab has been very successful in preventing migraine, and those who have used it (who, in many cases have tried many other preventatives) have described the positive impact it has had.

This is a huge breakthrough in the treatment of migraine, which has caused real - legitimate - excitement for patients in the UK, who look forward to a life free from migraine.

Many migraineurs have to miss work or social activities, or have reduced productivity, because of the severity of the condition.

One in seven people suffer from migraine, and any medication which can have such a marked impact on this awful condition should be available through the NHS. I hope NICE will reconsider its decision and allow erenumab to be prescribed to patients with migraine, to whom it offers a real hope for the future.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I have suffered migraine from the age of 4. Over the years it has become unbearably painful and life restricting. I have tried every prophylactic including Botox and all were unsuccessful. The pain has decreased but the frequency has increased often to 15 plus per month. I use Sumatriptan for pain relieve. I can understand the cost implications of Aimovig but surely the price will lower as more people use it. It's a shame that an effective drug for stopping migraine is being rejected. Migraine effects thousands of people and the WHO lists it just below paraplegia. I have lost a significant time through migraine as well as the pain levels involved. It's had a major effect on my home and social life. I was fortunate that when they were at their worst I had a supportive husband.	

Name	[redacted]
Role	Carer
Other role	Development Director
Organisation	None
Location	Wales
Conflict	None
Notes	None
Comments on the ACD: this drug has the possibility to change the lives of chronic migraine suffers who live in hell with the disabling pain - please reconsider not making it available. if you have never suffered or witnessed the side effects of migraine you cannot understand the terrible effects for the victims and their families	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	None
Conflict	None
Notes	None

Comments on the ACD: Has all of the relevant evidence been taken into account?

Prior to their decision to recommend the NHS does not make Aimovig available to patients, the committee stated that they considered the evidence submitted by the company, the views of non-company consultees and commentators, as well as clinical experts and patient experts. I note that even in their subsequent consultation document, the committee state they are wishing to invite views from the consultees and commentators for this appraisal and the public.

The committee has therefore failed to state that they wish to consider qualitative evidence of the lived experience of chronic migraine sufferers in any detail, aggregating them only to the views of the public in general. For this reason, I believe the committee has failed to take all of the relevant evidence into account at the appropriate time. I would further add that failure to do so puts the committee at risk of unlawfully discriminating against chronic migraineurs, which can be considered to be a disability under the Equality Act (2010).

I would therefore like to implore the committee to consider collecting and analysing detailed case studies from a representative sample of chronic migraine sufferers in the UK (the very people the committee continually state in their previous papers are the very people set to gain the most from the medication) and their experiences of being treated for the condition by the NHS. In anticipation of this, I have set out a brief account in comment 2 of my own experience and rationale for why the committee should reconsider their recent decision to advise the NHS against making Aimovig available to sufferers at a reasonable cost.

My Lived Experience

My name is [redacted], I am a 27-year-old female and was first diagnosed with migraines with aura at the age of 8. For the majority of my childhood and adolescence, my migraines remained episodic (< 15 headache days per month) however by the age of 22 they became chronic (>15 days per month) and in January 2018 I was forced to take long term sick leave from my employment in [redacted] as I could no longer function well enough to hold down a job. With little improvement in my condition by December 2018, I was left with no other choice but to resign. It is now January 2019 and I am no further to feeling better or finding a more migraine friendly job which, as you can imagine, is stressful. It is particularly difficult as I was a high performing employee up until the point that my migraines became so unmanageable, having first entered [redacted] as part of their [redacted] which identifies rising talent and candidates for senior leadership positions in Whitehall.

The standard of care I have received from the NHS thus far has been poor. In the past, I have been advised (and followed the advice!) of GPs to eat less cheese, have a mouth guard fitted at night to stop me grinding my teeth, to take less painkillers to prevent medication overuse headache and then in the same breath been told to take more painkillers and as early as possible to quash the headache. While I do not blame GPs as they only receive 4 hours of training on headache disorders, I was advised by a headache specialist in St Thomas hospital to avoid caffeine and ibuprofen altogether and then when I explained I tried to exercise to prevent migraines but experienced severe post-exercise headaches, to pop two nurofen and have a strong cup of coffee.

I became disillusioned with going to my own GP for help as it was an endless cycle of being told not to take too many painkillers as they would make my headaches chronic and then being given either an anti-epilepsy medication or antidepressant that did absolutely nothing to stop them coming in the first place. Finally, I decided to go private (whilst on sick pay) to The National Migraine Centre who have been incredibly sympathetic to my suffering but who have still be unable to provide me with anything that works in the long term. My last consultation ended in me being told I could have Aimovig if I could pay £400 each month for it, which, being currently unemployed, you can see how I just couldn't afford to do. I was therefore incredibly disappointed and disheartened to hear that I couldn't get it on the NHS when you rejected it a few weeks ago. While you have said it's because aimovig has not been deemed to be any more cost effective than botulinum toxin, I would like to point out several counter arguments to that in the next section.

Thank you for taking my comments into consideration.

[redacted]

Name	[redacted]
Role	Private Sector Professional
Other role	Headache Specialist Doctor
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I work as a headache specialist doctor for the [redacted]. We currently prescribe Erenumab privately to many patients. The documentation states that there are "already options for preventing migraine including beta-blockers, antidepressant and epilepsy medications". Unfortunately there is a 1 in 4 chance that these medications will work, they take at least 6 weeks to become effective and longer to up-titrate to an effective dose. They are laden with significant side-effects which can be just as disabling as migraine (particularly chronic migraine). The next point that Botox is already available is true but this is also not effective in all patients. It is also painful to administer as it is acidic in nature, and often becomes more painful as time goes by. The waiting times for Botox on the NHS are variable (largely because it requires training to administer and people have to fulfil certain criteria in order to get it).

None of the above treatments have been specifically formulated to manage migraine unlike Erenumab. It has a low side-effect profile and, in our experience, is very effective. It also only takes 2 weeks for the effect to be noticeable (as can be the case with Botox). Unlike Botox, it does not have to be administered by a healthcare professional, only requires one injection as opposed to 31+ and is not painful.

The disabling effect of migraine and its effect on the economy should also be considered. It costs the UK economy £10 billion per year largely due to inadequate management. Therefore the benefits of using erenumab and thus enabling people to return to normal lives should not be underestimated. Headache is only part of the picture with migraine. It is listed in the 7 WHO most disabling conditions. The ability to carry out normal activities, socialise and work need to be considered when deciding on the suitability of a medication. Finally, I will say that a number of my patients who have started erenumab report that it is "life-changing": one had been off work for 3 months with chronic migraine and was now starting to return to full-time work.

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I think it is important that this medication is available on the NHS, as there is no single drug available that gives relief to all migraine sufferers; it is therefore vital that there are alternatives available for chronic suffers to try. This medication has had promising results in the studies thus far, giving fresh hope to many who are still crippled by migraines on a daily basis despite having tried every 'solution' made available to them. Lots of sufferers are not able to afford to buy erenumab privately therefore, the NHS deciding against making it available would mean leaving these people stuck with a debilitating condition despite the fact that a potential cure exists.

Erenumab has been rejected on the grounds of not being cost effective, however, the chronic migraine sufferers who would use this medication are people who are unable to work, attend school, university etc because of being in constant pain. This would increase their likelihood of receiving benefits from the government in the future, which would cost a lot more annually than this medication. Furthermore, chronic migraine sufferers are not able to lead active lives, so are likely to be overweight and cost the NHS more in weight-related ill-health issues.

Migraines are incapacitating and chronic sufferers are not able to live life fully, so there is an increased risk of isolation and anxiety (especially among the young who are missing essential schooling, or adults needing to work). This leads to a higher risk of depression, which will then need to be treated with gp visits, consultations and probably medication further costing the government. Aside from the financial burden placed upon the government by allowing this group to go untreated, the decreased quality of life and consequent increased suicide risk must not be ignored - the effects of chronic migraines on the sufferer's mental health must not be under estimated. If even one life is improved through this medication, then erenumab's contribution to the NHS is invaluable. The reality is that this medicine has the potential to save lives.

My friend's daughter has suffered with daily migraines for 7 years now, the pain makes her vomit. She had to drop out of 6th form as her condition is disabling. She is a very intelligent girl who is anxious about what the future holds for her, and has become increasingly isolated as her friendship group has slowly disappeared - she is so frequently unable to leave her bed, that maintaining relationships outside of immediate family has become very difficult. She has tried every treatment that she has been offered including alternative therapies; none of which have provided long-term relief. It is important that this medication is available to all regardless of financial circumstances, as enjoying a basic quality of life and not dreading waking up in the morning when a potential cure is available should be a right available to everybody, especially in one of the largest economies in the world.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: In addition to work and social life there are other major impacts of migraine. My child was killed and I learned techniques to manage my grief. Having a migraine meant not being able to sleep, go for a walk, read, talk to people, paint or any other technique for coping and made the impact of grief much more unbearable.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Please reconsider this decision, as I am a migraine sufferer , having between 4 and 6 attacks month which are very debilitating: **DECISION** **erenumab) and NICE has concluded that they do not recommend Aimovig for use in the NHS.**	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Firstly, please excuse my poorly worded submission, chronic migraine has caused me to have permanent cognitive difficulties so thinking and expressing myself coherently is incredibly difficult for me these days.

To give some context about myself - I am a 37 year old chronic vestibular migraine sufferer. I have suffered every single day for the last 4 years with daily migraine, constant head and eye pain and 24/7 balance, distorted vision, memory, speech, derealisation, reduced intelligence and cognitive difficulties. I am highly disabled and housebound for a lot of the time. It started literally overnight. I have seen 3 neurologists on a regular basis throughout the last 4 years, tried 7 preventative medications (either with no effect or I couldn't reach a therapeutic dose due to intolerable side effects), tried Botox, 3 day-patient IV infusions, acupuncture course, psychologists and physiotherapists all via the NHS. I have tried all the triptans, neither these nor other pain relief medication has ever worked to lessen my daily pain. I get about an hour in total without too much head pain a day. I have not had one day off, or one day relief in the last 4 years.

I am been rendered disabled overnight by this condition and become a shell of my former self. I used to work as a head of department in well-established London based company, but lost my job and life as a result of this condition. It is like being in prison with no end in sight. Sadly, I am dependent now on Government disability benefits

For people like me and I am aware there are many for whom chronic migraine has taken their life away and current treatments have all been ineffective â€" having more treatment options available to us is the only thing giving us hope that we can get some of our life back. I realise cost-effectiveness is a big consideration, especially when NHS resources are so limited, but this is about giving us our lives back. This is as important as any cancer treatment because whilst we may not die from migraine, we do not live either.

I believe the cost-effectiveness evaluations do not take into account the following aspects:

Where results from Erenumab are successful, a patient will have a significant reduction in need and use of other medical care e.g. acute or preventative medicines (often taken alongside botox), GP and hospital clinic/consultant appointments, A&E or inpatient hospital use.

There is also no consideration for knock-on effects - other costs to the NHS caused by ill health stemming from migraine. Chronic migrainers can be almost permanently disabled by the severity of symptoms and so are unable to exercise, eat well, work etc. This gives rise to patients developing other physical and mental health conditions during their lifespan for which they

will need treatment from the NHS for.

There are also additional costs implications outside of medical sphere not considered. There will be many chronic migrainers who are literally made disabled by their migraine condition, cannot work and need support via Government benefits. This financial support thorough benefits adds up to considerable amount throughout a patients lifespan if they cannot access all possible treatments that could make them well enough to return to working life.

As I outlined earlier, over the last 4 years I have used a HUGE amount of NHS resource so far in trying to manage my migraine symptoms. If Erenumab had been available to me earlier and successful, I would not have needed a lot of this.

Thank you for considering my comments. I hope the committee will change their mind and take a chance on Erenumab for the sake of those of us chronic migraine suffers for whom it has destroyed our lives and if this is not made available to us there is little other treatment or hope available.

Name	[redacted]
Role	Carer
Other role	Retired from Management of Social and Health Care, Oxfordshire;
Organisation	None
Location	England
Conflict	None
Notes	I am presently retired but have worked in higher management in public service where resources were scarce but do feel that to do nothing at this time will be damaging and a positive way forward needs to be identified.

Comments on the ACD: When it comes to balancing benefits and costs, there will always be difficulties particularly when dealing with patients whose experiences of migraine and treatments are very different, will differ from month to month and from one health practitioner to another. However, I comment as the mother of a 46 year old daughter who has suffered from migraine since her teens. She has been diagnosed with chronic migraine; she has taken numerous prescribed medications none of which were effective; she has accepted any treatments offered including botox and a device implanted in her chest and head for pain relief, which was subsequently removed being ineffective as was all other treatment. She manages with great difficulty to work three days per week, relying on eletriptan and candasartin. She has the support of her GP and is fortunately able to attend a migraine clinic but the cost to her and our family both in terms of watching her suffer, financially, the impact on my granddaughter and the social isolation just cannot be counted. She cannot even take a holiday unless someone is able to go with her. Because of the constant migraines and medication, her physical and mental health continues to deteriorate. How could Nice begin to include multiples of this situation in its deliberations of cost/benefits? This is the first developed treatment for migraine and signals some hope for people such as my daughter. We accept, as we have with previous treatments, it may not work for everyone but to lose the opportunity to use it would be heart breaking particularly knowing that if personal finance was available it would be possible. Despite this, I can understand the need for Nice to ask for more clarity but at this stage I feel it would be impossible to identify lifetime outcomes, to make comparisons between dispirit groups of migraine sufferers or appropriate amounts of the medication to be given because each patient needs to be considered according to individual need but to add erenumab to the medications available under the NHS, particularly in migraine clinics, offers some hope to migraine sufferers and signal that progress is being made towards an eventual cure.

Name	[redacted]
Role	Patient
Other role	Self Employed
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I suffer from chronic migraine and have been attending the National Migraine Centre in London for a number of years. I have tried many preventative treatments (including Botox injections, which were funded by the NHS), none of which have been effective. When I heard about Erenumab (Aimovig injections) in the Media, I immediately spoke to the National Migraine Centre about it and they prescribed it to me recently. I'm currently in my first month of a three month, three injection trial and so far the results have been incredibly positive. The number of migraine days has reduced and on the days when I have had a migraine the pain intensity was greatly reduced, exactly what they told me would hopefully happen. This new treatment could potentially change my life. The drawback is obviously the price. I'm not sure I can keep paying for this monthly injection indefinitely at the current cost if the NHS fail to provide it. I feel this is a very promising new treatment for migraine sufferers such as myself and am upset that it will not be more easily available. This is the first treatment purely for migraine, that I have come across, and is the first preventative treatment I have tried that actually works! I hope the issues raised by NICE can be addressed so that this innovative treatment can be offered on the NHS in the near future.

Kind regards

[redacted] - Migraine sufferer.

Name	[redacted]
Role	Patient
Other role	Teacher
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: For someone who has suffered from migraine all their life and tried all available options, the news that there may be a new treatment gave me so much hope. I struggle through on preventative medicine; triptans and motilillium for my 2-3 migraines a week. I prioritise getting through the working week which means that I often have no options left to help by the end of the week. It's exhausting. My place of work is not terribly sympathetic and you live with the fear of capability procedures if you are not able to keep the pace going. A new option would change my life beyond words. (If it worked) on a part time teacher's salary, my only option would be NHS so this preliminary report is a huge blow. Why should those who make a real difference to the world, like public sector workers, be denied the right for a possible reduction in pain? I urge you to reconsider as it worries me that this may only be available privately when it affects such a huge proportion of people from all backgrounds. Thank you.

Name	[redacted]
Role	Patient
Other role	Specialist Support Mentor for Students with Autism
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Background

I am a 49 year old female migraine sufferer. I have episodic hormonal migraines on average 10 days a month. This has increased from 3 days a month during my 20's and 30's - the increase is believed to be caused by peri-menopausal hormone fluctuations. I use sumatriptan as rescue treatment during an attack; the efficacy of this is reducing with age as migraines become more frequent and severe. I cannot increase use of triptans due to risk of medication overuse (also known as rebound) migraine. I have tried 3 prophylactic medications: Propranalol, nortriptyline and pizotifen; none had any effect on migraine frequency or severity and all caused a range of side-effects that impacted significantly on my ability to work or carry out normal daily functions.

I am otherwise fit and well and have made considerable adjustments to my lifestyle to cope with my condition e.g. no late nights, no travel, no alcohol, no vigorous exercise such as aerobics classes. I make sure I eat a very healthy diet and regularly practice yoga and meditation to help me cope with this condition.

I am currently living with migraines which have the following impacts:

I cannot work every day due to migraine attacks so I work part-time

I don’t consider myself able to apply for or accept promotions at work

I have to take sick leave several days a month

Reduced ability to carry out family and domestic responsibilities

My relationship with my husband and children suffers

Extra domestic work for my husband (including childcare)

Husband’s career is affected as he has to take time off for childcare when I am unwell

Huge reduction in social life - I regularly have to cancel events and cannot commit to arrangements

I cannot travel further than 3-4 hours from home which severely limits family holidays. Flying has become a trigger in recent years.

Mild depression as a result of all of the above.

My migraine, in common with many women, has been inherited - my maternal grandmother, mother, aunt and two female cousins all have the

same condition.

It is necessary to consider different types of migraine that have different causes and likely different pathophysiology. For example, my type of inherited hormonal migraine is distinct from that caused by head injury, food intolerances, etc.

There is published scientific evidence that CGRP is influenced by oestrogen:

Labastida-Ramirez A, Rubio-Beltran E, Villalon CM, MaassenVanDenBrink A. Gender Aspects of CGRP in migraine. Cephalagia. 2017 Jan

Ibrahimi K, Danser AJH, Villalon CM, van den Meiracker AH MaassenVanDenBrink A. Influence of varying oestrogen levels on trigeminal CGRP release in healthy women. Journal of Headache Pain 2013;14 (Suppler 1): p123

Anecdotal evidence also indicates that CGRP blockers (or receptor blockers such as erenumab) are particularly effective in preventing hormonal migraine. Contributors to migraine support groups are increasingly reporting this effect from users of erenumab in USA and Europe as well as those receiving it privately in the UK or as part of a hospital trial.

As a sub-group, women with episodic hormonal migraine will not need erenumab (or other CGRP blockers) beyond menopause. The impact of their migraine is at its worst during the years when they are working and in many cases building careers. Therefore any calculations of cost-effectiveness should take this into consideration – i.e. their ability to earn more, pay more tax and take less sick leave that is allowed by use of erenumab during these years and then their need for the erenumab tailing off in their 50's.

Women have to contend with a medical model that is based on male experience. The migraine sub-group I belong too is exclusively female. It could be argued that it is discriminatory to deny an effective, purpose-built technology to this group based on a cost analysis and evidence which is based on the wider migraine community including men and those with different migraine pathophysiology.

Name	[redacted]
Role	Parent of chronic migraine sufferer who has undergone many treatments without result
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: The document continually compares the use of Erenumab with the use of botulism. No consideration is given to the possibility that it may be effective for patients for whom botulism is ineffective.

No consideration is given to the cost savings for chronic migraine sufferers in terms of ability to work and quality of life.

Because the majority of sufferers are women the findings raise the question of discrimination and perceived lack of worth of women.

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	I have removed left my name off the end of the comment in line with your comments on patient confidentiality. The details left in are important to the comment I would like to make!

Comments on the ACD: Sirs

I have followed the progress of Erenumab through clinical trials, availability in the USA, and this consultation process, and as such awaited the publication of your findings with interest. I have read the "Appraisal consultation document" and although I have a background in the sciences my comments are on the basis of being a chronic migraine sufferer rather than a scientific analysis.

I have suffered with chronic migraine for the best part of a decade, and have tried many (certainly >5) medications, including Botox, plus other non-clinical treatments such as acupuncture, mindfulness, CBT, yoga, time off work etc.

This illness has affected my quality of life to the level preventing me from starting a family, near break-up of my marriage, and significant suicidal ideation. My current medication plan enables me to work but only on a temporary basis but I cannot continue like this for the rest of my career, and being 33 I would otherwise expect to be in the workplace for another 35+ years. The symptoms of migraine impede my daily work and the side-effects of the medication cause significant cognitive impairment such that some days I cannot work effectively at all. I have managed to keep my job thus far but I cannot say how long that might last.

With all that in mind, reading the words "Erenumab is unlikely to be cost effective for..." was crushing. As you have stated there is a clinical benefit, but it is considered to be insufficient to make the drugs available to patients like me. With the treatments currently available I am at the end of the line with regards to medical options, and a drug such as Erenumab represents hope: it could offer a statistically significant improvement in my condition.

Thank you for taking the time to read my comments, and I hope you are able to reconsider this economic decision regarding such a life-changing condition.

Kind regards

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: It was very disappointing to hear that the drug had been rejected. I have been a migraine sufferer for over 15 days and have tried every drug presently available. I see the reason behind this drug being rejected, is that there is no evidence that erenumab is more effective than botulinum toxin type A, but what are the alternatives for people who cannot take botulinum toxin type A Like myself? I suffer chronically with migraines, which means I can suffer up to 25 a month. I feel that it is unfair that I will be denied the opportunity to try this new drug, which has been made specifically for this extremely debilitating illness.	

Name	[redacted]
Role	Regulation Officer
Other role	None
Organisation	None
Location	Scotland
Conflict	None
Notes	Despite the fact I reside in Scotland, my sister resides in England and I believe may benefit greatly from this treatment.

Comments on the ACD: I am writing this on behalf of my sister, who suffers from chronic migraine. I have not seen my sister in many years as we live a number of miles apart and visits require to be arranged. In the last 11 years, when I have arranged to visit, she has not been well enough to get out of bed. My sister has no quality of life, has had to give up work and spends around 99% of her time in bed in excruciating pain. She is unable to read the papers made available to the public regarding Erenumab, hence the reason I am writing this. It should be noted that I do not suffer from migraine, but as you will see from the above, it has a significant impact on my life (and those around my sister).

As a lay person/member of the public, I have reviewed the available papers to the extent possible and note the points from certain pages of the papers which I list in the following and commentary beneath the point taken from the papers. I believe I have taken a pragmatic a view as possible and urge NICE to consider the evidence in a similar vein.

It is my view that the following points (not exclusively) require further explanation and clarification together with the reason why Erenumab might not be available on the NHS to treat migraine, particularly chronic migraine.

Appraisal consultation paper

Page 3

There is no evidence comparing Erenumab with other oral preventative treatment in chronic migraine and there is uncertainty about whether the medication works long term.

The studies compared Erenumab with a placebo, taking this into account the above is therefore a moot point. Further studies require to be carried out in this respect. There will be uncertainty about whether the treatment works long term until it is actually utilised in the long term in a real world context.

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The costs are higher than NICE considers acceptable for substantial uncertainty.

There will always be a degree of uncertainty with new medication. This is the first medication of its kind, and as previously stated, requires to be utilised in a real world context in order to establish certainty or otherwise. It is unlikely that this will be established whilst the treatment is in its infancy.

Page 6

There was a clinically meaningful response (30%) for reduction in chronic migraine frequency and it would be tried with patients who had three previous preventative treatments that had failed.

Clinical significance was set at a level stating 30% reduction was a meaningful response. This therefore indicates that the effect of this medication in the treatment of chronic migraine is clinically significant and consequently cost effective.

Page 7

The evidence does not fully reflect the most relevant subgroup of people who may be eligible for Erenumab in clinical practice.

As the first medication of its kind, a limited number of studies have been carried out to date. Use in a real world context with this subgroup may be beneficial (and further studies could also be be carried out using participants from this subgroup).

The Committee is concerned that the people excluded from the trials were likely to represent the people most in need of treatment the most clinically important subgroup.

As above (it would be useful to understand why this subgroup was excluded from the study and what proposals exist to remedy this shortfall in the research).

140mg of Erenumab is clinically effective compared with best support care.

This statement indicates that the treatment is effective in the treatment of both episodic and chronic migraine, therefore would indeed be cost effective.

Page 8

All participants of study showed a reduction in occurrences of migraine.

As above.

Page 9

In an extension study improvement in monthly migraine was maintained at 12 weeks for up to 52 weeks, however the Committee state that there is no evidence to indicate that efficacy could be maintained in the long term.

As above.

Page 10

No more effective than Botulinum Toxin Type A.

The writer notes many of the studies compared Erenumab with a placebo, rather than another drug (not designed for treatment of episodic or chronic migraine). Erenumab cannot be reasonably compared to a treatment which

was not designed for the same purpose.

Page 11

Adverse events were low and the drug was well tolerated.

It is unlikely patients will experience any adverse side effects. This indicates that the majority of sufferers will be able to return to full time employment should they wish, contributing to the economy as they may have before they became ill.

Page 12

It is believed a 10 year time horizon is not long enough as patients could be taking the drug for longer.

As previously stated, as with any new treatment, the future cannot be predicted.

Page 13

The Committee considered that the treatment effect waned over a 5 year period and treatment effect was unlikely to be maintained indefinitely and so a constant treatment effect was implausible.

As above.

Page 14

Participants were given questionnaires on days they were attending appointments, so it can be assumed that patients were feeling well on those days.

The study data would be skewed by this method of data gathering.

Pages 15 to 20

Cost effectiveness.

A significant portion of the paper is concerned with this. Although I am aware this is a major consideration, in my view, it is not the most salient.

Conclusion

The Committee had not seen any evidence for the effectiveness of Erenumab for either chronic or episodic migraine when compared with other preventative treatment. There is no evidence of long term effectiveness.

On the face of it there DOES appear to be evidence, taken from a double-blind study that Erenumab is indeed effective in the treatment of chronic and episodic migraine in the correct dosage.

Committee papers

Page 9

Erenumab is the first migraine specific preventative treatment.

Taking into consideration the above statement, as a member of the public, an explanation as to why this treatment might not be trialled by the NHS would be welcome (other than cost).

Page 83

Study 295 is the pivotal trial for Erenumab in the chronic migraine population. Participants used an eDiary to record data.

Study 295 created some interesting findings, many of which point to Erenumab being the most effective treatment for chronic migraine available.

The study was a double-blind study funded by Amgen.

A study of this nature should point to the effectiveness of this treatment due to the fact there would be minimal external bias or influence on the results.

Name	[redacted]
Role	Patient
Other role	Project Manager
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have suffered from migraines for the past 20+ years, the last 5 of which have been chronic. As I got older it got progressively worse, to such an extent that in 2017 I had to give up a well-paid corporate career. I have tried all sorts of treatments but nothing seems to work consistently. Sumatriptan has given me a lifeline but as a chronic sufferer if I take too many of these I end up with a medication overuse headache and get into a downward spiral. I am resigned to never working full time again and am trying part time (around my migraines) property development, however, even this is difficult. My key issue is that my migraines have affected my earning potential, which is massively reduced, and then the tablets that may provide relief, and give me my life back, are only available privately and at such a cost that I cannot afford them. I ask that you reconsider your decision, especially for, and maybe only for, chronic sufferers like myself.

I have such a low quality of life at present, emotionally and physically, and am really disappointed that potential relief is out there but out of my grasp. Please help me and other chronic migraine sufferers.

Name	[redacted]
Role	Patient
Other role	Migraineur
Organisation	None
Location	Scotland
Conflict	None
Notes	None
Comments on the ACD: I can see that this drug is expensive. However, for those of us who have lived with chronic migraine for decades it could be life-changing. I know it may not work long-term, but after 30 years of daily migraines and the failure of numerous drugs and other alternatives the chance of even a few months' break would be wonderful. And then there are our poor frustrated GPs trying to work out how to help us!	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I am absolutely devastated that this drug cannot get past by NICE **I have suffered with migraines for almost 35years and cannot remember not having a headache** **I just want a chance of a pain free life.**	

Name	[redacted]
Role	Patient
Other role	Patient
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I am in the early stages of using Aimovig but after almost 2 months my migraines have reduced by more than 50%. I am very disappointed that NICE is not recommending this drug for NHS use. Your recommendation of Botulinum toxin type A is unacceptable for many - multiple painful injections on the head should not be a first line treatment when a relatively convenient and pain free drug is out there.If more trials are needed then get them done ASAP. Please reconsider this decision which means that only people with £5,000 a year to spend can have their migraine substantially reduced.	

Name	[redacted]
Role	Patient
Other role	Recruiter
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I suffer chronic daily migraine and this affects my day to day life severely. This includes personal and working life. I have tried all treatments on offer which are ALL by products made specifically for other conditions and still continue to suffer lots of pain daily. I was actually off work with migraine at the time I heard this treatment had not been approved for the NHS. This was exacerbated the pain further. I earn good money but I cannot afford to pay privately. Why is migraine, one of the most debilitating Neuro conditions not being taken more seriously ans when a treatment of its very own is produced it is declined. It may be costly but if it works and people are in less pain this may well decrease costs in other areas of the NHS such as mental health that we may also make use of as a result of the pain. I have had to seek CBT and talking therapy as a result of pain. These sorts of treatment could be avoided perhaps. I hope my comments are taken on board. Many thanks. [redacted]

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Migraine is a debilitating condition that desperately needs new treatments. Existing treatments have many side effects that reduce quality of life even if they are effective at preventing migraine. Further, patients with the same symptoms respond differently to the same treatments, indicating that migraine is a very heterogeneous disease.

Migraine has not been sufficiently studied to be able to predict which treatments will work for which patient subgroups, so it is unsurprising that studies that cannot properly segment patient populations see ambiguous results.

Since this treatment clearly works for a subset of patients, it should be approved. The alternative for these patients is chronic debilitating pain, or significant side effects from current treatments. There are patients in the NHS today who are not adequately treated by existing treatments, who would be able to live much better lives with Erenumab. It is obvious that Erenumab should be approved.

Name	[redacted]
Role	Patient
Other role	Creative Consultant
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: The NICE documents suggests that botox is a better solution however blocking pain, relaxing muscles or inhibiting nerves is not an answer. The only treatment that can be effective for migraine is one that treats the blood vessels in the head. Erenumab does work on the blood vessels in the head. Zolmitriptan is an excellent cure as it works on the blood vessels and also on the serotonin receptors however as zolmitriptan is a cure rather than a preventative drug. Any drug that works on the blood vessels in the head to prevent rather than cure a migraine is the only drug that will treat this debilitating disease.

Erenumab (Aimovig) belongs to a new class of drugs called calcitonin gene-related peptide receptor (CGRP-R) antagonist. CGRP-R is a chemical produced by the body that acts on blood vessels in the brain which are believed to be responsible for the development of migraines. Erenumab reduces the number of monthly migraine attacks by blocking CGRP-R receptors on blood vessels.

The project documents do not always clearly differentiate between migraine and headache and one paragraph compared migraine treatment of one drug to a headache treatment of another drug. Migraine is not a headache. Headache is just one of the migraine symptoms and more often than not the main symptoms include feeling flat; brain fog; sensitivity to light, noise and smell; nausea; vomiting; head and neck pressure. For example my migraines start with all of these symptoms several hours before a headache therefore drugs that just treat a headache are useless for most migraine sufferers. The documents do not mention what migraine symptoms the people who took part in the Erenumab tests had or what symptoms were helped.

Any drug that cures a headache is more than likely not going to treat a migraine. (continued below)

Since migraine affects mainly the female gender the decision not to make it available on the NHS, even for a few chronic sufferers to try, can be construed as discrimination. Studies have shown repeatedly that our medical system has an inherent bias against women and unconscious medical bias is a real phenomenon.

Some patients who have tried Erenumab have said that it is life changing. For example a patient on the London's Migraine Clinic said "they recommended I try Aimovig. I started at 70mg dose, which almost the same day I felt some relief and the minor headaches were gone. However the severe migraines were still there just a reduced pain. With the recommendation of the National Migraine Centre I increased to 140mg dose. This dose has worked for me and it is not an exaggeration to say it's been life changing. I am no longer in daily pain, I can make arrangements without

feeling anxious....."

In addition when considering the cost of Erenunab you should take into consideration the effect of lost working days on our economy, the on-going cost of other drugs such as zolmitriptan and the cost of hospital beds and ambulances.

I would like to suggest that the Erenumab drug is available on the NHS initially for chronic sufferers.

After reading about Erenumab I feel absolutely absolutely certain that without a doubt it is the only drug that will work for migraine. Based on my experience with zolmitriptan which treats the blood vessels and receptors (I actually feel it working like magic in my head) any preventative drug that works in a similar way will perhaps give me my life back. (I am now 54 and lost the best part of my life to this debilitating disease).

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: The nature of migraine is that one treatment doesn't fit all. Many patients have to try many different medications before finding one that works. Botox is referred to in this document as being as effective as Erenumab, but given that there's such a wide variance of cures for each patient, shouldn't as many as possible be made available to maximise the chance of curing a patient's chronic migraines? As a sufferer of chronic migraines, I've tried countless medications over the past five years, including botox, with limited success. The current decision not to deliver Erenumab has made me despair for my future options - anticipating its release on the NHS had previously been a lifeline of hope.

Name	[redacted]
Role	NHS Professional
Other role	Consultant neurologist
Organisation	None
Location	England
Conflict	Yes
Notes	Novartis have funded conference meetings and also attended paid advisory board meetings

Comments on the ACD: Dear NICE staff

Thank you for looking into this new treatment option for migraine which has great unmet needs.

1. Although erenumab has not been trialled against a comparator particularly the cheaper oral prophylactics, it's use can be reserved for those failing at least 3 preventives with evidence in migraine. Therefore lack of a comparator trial is not a problem in my opinion.

2. In addition to efficacy responses, one also has to take in account retention rates due to side effects mainly, which are quite poor for most oral prophylactics and which are quite high for erenumab at 1 year in a follow up study.

3. Although more expensive, use if erenumab can be restricted to high impact refractory migraine. This will include chronic migraine and some high frequency episodic migraine patients. These refractory patients having tried several oral options and Botox for chronic migraine are severely disabled , have poor quality of life and are active users of health resources which all adds up to costs. In this group, achieving a 40-50% likelihood of reducing migraine days by 50% should be cost effective.

I am grateful if these points can be considered.

Thank you

[redacted]

Name	[redacted]
Role	Carer
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: The decision to decline to offer erenumab on the NHS is extremely disappointing. At a time when chronic pain is often unexplained, leaving sufferers to continue through life unaided and with no possibility of a cure on the horizon, in my husband's case his chronic headaches are also linked to depression. He has suffered from both chronic headaches and depression for over 6 years now. It has prevented us from starting a much wanted family, and it has lead him to experience deep depressive periods, including phases where he has been suicidal. As you can imagine, being the partner of someone in such pain is also quite debilitating, and I have also had to seek support from the NHS and charities for both physical and mental health treatment myself.

I expect this decision to be seriously reconsidered.

Name	[redacted]
Role	Healthcare Other
Other role	CEO
Organisation	National Migraine Centre
Location	England
Conflict	Yes
Notes	We are a charity and have received an educational grant from the manufacturer to provide GP headache master-classes.

Comments on the ACD: Migraine is a complex condition and almost all of our patients at the NMC have struggled to find relief having tried numerous treatments. Some have accumulated well over 50 interactions with the NHS, a few claim 100+ appointments. This combined with the cost of their many medications is expensive and clearly ineffective.

No treatment is universally effective including Botox which although extremely useful in some cases does nevertheless require expertise to inject therefore creating cost, complexity and often delay in treatment.

Often patients are interested in their overall quality of life rather than simply headache days, although QoL is more difficult to define and measure it does not alter the fact that it is relevant to patients.

Approval of Erenumab would provide clinicians with another treatment option, typically for those (chronic) patients experiencing miserable lives whilst still costing the NHS (and the economy) considerable sums of money.

Name	[redacted]
Role	Public
Other role	PhD Student
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: For a certain amount of patients they super-responded to the anti-body after failing three or more other conventional treatments. This is cost effective when you consider the costs a standard chronic migraine patient incurs; preventative drugs, neurology referrals, A&E visits, psychiatric support and acute treatments such as triptans. This does not include the fact the majority of chronic migraine patients cannot work due to disability and so require disability living allowance. This anti-body should be considered for use in the NHS.	

Name	[redacted]
Role	Patient
Other role	Unemployed due to disability
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I am one of the chronic migraine sufferers desperate for treatment. My quality of life is poor and I'm unable to work due to the severity of my illness. I have tried all of the preventative options including botox, and haven't responded. If this drug could be made available for people like me I would be given an opportunity to life live again. I'm aware of the expense, but so many of us are unable to contribute to society whilst like this, and just want to try to rebuild our lives. Few of us can afford private treatment due to the lack of income caused by our disability. I would appreciate if you could reconsider this decision. Thank you.	

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	None
Location	None
Conflict	None
Notes	None
Comments on the ACD: Migraine has changed my life in the last 6 years, impacting on all areas of my life. I have tried half a dozen medications and botox unsuccessfully. I feel that I should be given the opportunity try Erenumab in order to regain my quality of life. **MIGRAINE AFFECTS A LOT OF PEOPLE AND SHOULD BE ECOGNISED AS A DISABILITY.**	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I feel you need to review decision as cost of botox is still high and the consultation cost on top and regular visits needed where aimovig will be self-administered so will be just as cost efficient. I had tried everything and if you take into account that I'm no longer able to work because of chronic migraine and the cost of drugs I have been prescribed over the last eight years I would think it would become cost effective if I could even consider returning to work. I hope you will consider the views of those who had their lives completely dismantled because of migraines. No other medication has previously been designed specifically for migraines we have always been an afterthought. **Regards** [redacted]	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	

Comments on the ACD: "The committee concluded that migraine, particularly chronic migraine, is a debilitating condition that significantly affects health-related quality of life."

Migraines are often misunderstood by health professionals (GPs), employers and often family members.

GPs will often feel they can 'cure' chronic migraine insisting on changing medication or trying preventatives (that have usually been tried before - but often there is insistence that I try it again) that lead to horrendous side effects and further days off work. They will also often block attempts to see specialists in headaches/migraines and on one occasion I have had a GP get really angry with me as I went to see a private practitioner (which I had to pay for).

Employers are obliged to conduct back to work assessments these days and the frequent question I am asked is "haven't you sorted/cured this yet - you've had XXX days off for the last XXX months"? Requests for dimmed lights or 'rest rooms' can often be ignored or denied as most workplaces are now 'open-plan'.

Chronic headaches and migraines are also not on the recognised disability list so long term career prospects are poor and often lead to different complications around mental health.

As a chronic headache and migraine sufferer for over 20 years I am still being offered the same treatments, the same preventatives (which were never specifically designed for migraine) and often than not the same walls! When I mentioned this drug to my GP before Christmas she though it highly unlikely that you would approve this drug so in part to me if feels like you had made a decision before fully consulting with the relevant people.

I am a migraine and headache sufferer with over 20 years of experience of said affliction!

Name	[redacted]
Role	NHS Professional
Other role	District Nurse
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: PLEASE let us try Erenumab - living with severe head pain is dreadful.

This is a personal plea.

Name	[redacted]
Role	Carer
Other role	Parent and carer of chronic migraine sufferer
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: It is good to see that the committee recognises that migraine, particularly chronic migraine, is a debilitating condition that substantially impacts on quality of life. This relates to personal, social and working life and can lead to isolation and dependency with no work prospects. Women are more likely to have migraine than men and this severely debilitating problem impacts disproportionately on young women. If erenumab is not approved, this decision will affect the life and employment chances of these women. This could be viewed as gender discrimination.

The report states that the cost effectiveness estimates are higher than what NICE normally considers acceptable when there is substantial uncertainty. I do not understand the uncertainty since the previous paragraph states For people who have had at least three treatments, the clinical trial evidence shows that erenumab 140mg works better than best supportive care for preventing chronic migraine (and 70mg also works better than best supportive care). In Section 3.6 the report confirms that improvement with erenumab (both 70mg and 140mg) was statistically significant.

My 26 year old daughter has a 2:1 from the University of Bath and wanted to be a special needs primary school teacher. She managed this by taking opioid painkillers as well as her oral medications. She no longer takes any painkillers, on the advice of her Neurologist, and is unable to work due to chronic refractory migraine. She has had chronic migraine since her early teenage years and has tried many oral medications (many of which have had serious side effects) as well as nerve blocks and several trials of botulinum toxin without improvement. We have paid for four injections of erenumab so far and she has experienced substantial improvement. This is the first time in 15 years that she has had migraine-free days. Erenumab has given her real hope of a working and social life but it may not be possible for me to finance this indefinitely. For low income sufferers, who cannot gain access to this drug privately, the Committee's decision not to recommend erenumab perpetuates the rich/poor divide in both work and social life. This could be viewed as class discrimination.

I see that the Committee concluded that erenumab's long term effectiveness is uncertain, although trials showed that at 52 weeks chronic migraine improvement was sustained. This drug has very few side effects (none in my daughter) and it seems wrong to make young people wait in pain for another 10 years whilst more data is gathered. The NHS always prides itself, especially for cancer patients, on people not being left in pain this is not true at all for the migraine population. If erenumab is prescribed only by Consultant Neurologists then, where it is not being effective, it can be stopped.

I note that the Committee felt that the evidence in favour of erenumab, rather than botulinum toxin, was not sufficiently robust. However, the odds ratio favoured erenumab, although the results were not statistically significant. For patients who have already tried botulinum toxin with no effect, erenumab could be another hope. Could erenumab be classified as a 5th line treatment and be specialist-prescribed only?

I do not understand the Committee's view that additional resources would be needed to provide erenumab in specialist clinics. Unlike botulinum toxin, erenumab is self-administered after initial injection and training by a nurse. Surely specialist clinics are already needed for botulinum toxin administration and this needs to be done by specially trained consultant neurologists.

I note that the Committee concluded that the ICER for erenumab was likely to be higher than around £20,000 per QALY gained (the actual figure seems to be missing) compared to botulinum toxin. Section 3.17 states £20,000 is acceptable. The Work Foundation's Society's Headache: The socioeconomic impact of migraine report of 2018 estimates that £8.8 billion is lost in productivity in the UK every year due to migraine. Compare this to the £8 million lost in the UK due to rheumatoid arthritis (National Rheumatoid Arthritis Society 2010). The NICE consultation on the biologic drugs for rheumatoid arthritis (TA195) published in 2010 noted QALY of £21,100 for rituximab and £24,000 for infliximab, both above £20,000 nine years ago. Women with migraine, who have not been helped by oral medications and botulinum toxin, need to get back to work and erenumab offers this chance.

SLIDE 5: This slide shows the cost of erenumab to be £386.50 plus £40.04 for administration (total £426.54) versus botulinum toxin £276.40 plus Â£116 administration (total £392.40). My daughter who cannot work because of her debilitating migraines receives £443 per month in benefits. This is not enough to live on and I have to support her from my small NHS pension. If she could work and earn £25,000 per annum, as a graduate might expect, she would pay around £4,500 in taxes plus repayment of her student grant and would not need to claim £5316 per annum in benefits. She would therefore be benefiting the UK economy in excess of £10,000 in return for the NHS money spent on her erenumab treatment. If my daughter is never able to work due to her chronic migraine and I am no longer around to support her, her cost to the NHS and social services is likely to rise substantially.

CONCLUSIONS: I consider that the recommendations are NOT a sound and suitable basis for guidance in the NHS due to the points made above. I do not believe that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. This report appears to be saying that erenumab works but that it costs too much and yet the enormous cost to society, let alone personal cost in terms of pain and isolation, seems not to be taken into account.

Name	[redacted]
Role	Patient
Other role	None
Organisation	England
Location	England
Conflict	None
Notes	None
Comments on the ACD: I feel strongly that this drug should be available on the NHS. Migraines have affected both my life and the lives of family and friends, and believe that this drug will be life-changing for sufferers.	

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: I am a patient who has lived with chronic migraine for 11 years. I am in constant pain. I have tried many different medications, a nerve block and Botox. Almost all the treatments had no effect and those that did did not work very well or stopped working long term. People like me need all the treatment options available. I have been unable to work full time since the migraines began which puts me at significant financial and career disadvantage. I have been unable to return to university for a masters because of the resulting light sensitivity and disrupting nature of the illness. I have had to limit my family size because the burden of dealing with this illness. People like me need options for when the existing treatments don't work, and they don't work for everyone. Please make alvomig available on the NHS and give patients like me another chance at life.	

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	None
Conflict	None
Notes	None
Comments on the ACD: As a migraine sufferer I am very concerned and disappointed about this decision, I strongly urge you to reconsider. So many lives are ruined due to migraine and it costs the UK billions of pounds in lost earnings every year. Please reconsider.	

Name	[redacted]
Role	NHS Professional
Other role	GP
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: Re Erenumab.

I am a GP in East Sussex.

I would like the following comments to be put to the review committee.

The use of this drug would be for those migraine sufferers who are deemed to be in the severe intractable category .Their lives are ruled by their unpredictable pain and associated symptoms. Their quality of life and ability to work is clearly affected.We run the risk of letting these patients down at a time when they have generally exhausted all other avenues of treatment. These are patients who are very often, by nature of the severity of their illness, being looked after by secondary care as well as primary care. This gives the opportunity to limit the prescribing to only the severe cases.

These patients have limited treatment options and we must remember that potentially their lives are in danger because of the impact of untreated severe pain and the effect that this can have on their health and well-being. Suicide is a known outcome for some patients with this condition.

Erenumab has been discussed and documented in the national media and in medical journals. For some, therefore, this treatment has been eagerly awaited as a lifeline that may help their migraine.

The use of Erenumab would be initiated and controlled by secondary care specialists (neurologists). Monitoring of efficacy in individual cases would be essential and the drug could easily be stopped if no benefits were achieved.

This is a relatively small group of patients nationally and we must act as their advocates to try to achieve some sort of possible help for this disabling condition.

I feel that we run the risk of ignoring this small group of patients who have a disability albeit a silent one which is rarely spoken about.

Yours faithfully

[redacted]

[redacted]

Name	[redacted]
Role	Public
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: My daughter suffers 24/7 chrnoic migraine pain. She received top A* and A scores on all her GCSEs, and now she is locked in a darkened room due to chronic migraine. She was on track to go to Cambridge. Now, through chronic migraine, she is dependent on society and cannot contribute her many gifts. Shame on those who would deny her a chance at ending a life of extreme pain and becoming a productive member of society again.

I would ask the committee to reconsider their decision based upon several factors. Firstly, the cost impact of migraine was not sufficient; the cost to the UK is estimated at £2.25 billion per year (Steiner, 2003). This makes the cost of erenumab pale in comparison to the lost productivity of our citizens who suffer migraines.

You also cite that no studies have compared the effectiveness of Botox vs erenumab in chronic migraine patients. But this is a false question. At least 2% of the population suffer from chronic migraine (Natoli, et al 2010) and for a great many of them, even Botox does not provide relief. So it is not a question of deciding whether Botox is more efficacious for migraine than erenumab; at a bare minimum you could look at providing erenumab for those poor souls for whom nothing-- even botox-- works. This is the first migraine-specific preventative medication ever designed, and it is frankly shocking that you would dismiss its potential to help chronic migraineurs who are locked in their rooms in unimaginable pain, day after day after day. Limit its initial release if you must, but do not deny it to at least those for who all else is failed. You could end up with many more productive people earning money and paying national insurance to pay for these medications!

References:

Steiner TJ et al. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia. 2003;23(7):519-527

Natoli JL et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010 May;30(5):599-609

Name	[redacted]
Role	Public
Other role	Director
Organisation	None
Location	Wales
Conflict	None
Notes	None

Comments on the ACD: NICE should absolutely give this treatment approval! Shocking if approval is denied!

Name	[redacted]
Role	Patient
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I have suffered from chronic migraine since 2011. I've tried all the recommended prophylactic migraine medication which caused side effects and no positive response. Starting Botox in 2015 at the National Migraine Centre in London helped initially and meant I could get off atenolol, which was severely impacting my quality of life and many days off work. The first three rounds of Botox made some positive steps however it quickly became less effective. I have been surviving on taking triptans or domperidone and aspirin for my migraines in the past 6 months, and spent about 7-10 days a month off sick and completely debilated. Since starting aimovig in December - January (3 months/ 3 injections) I've had reduced levels of migraine days per month and migraines have been shorter in duration. I would like to see NICE consider this drug on the NHS for chronic migraine sufferers where Botox and other drugs haven't been effective. Just over £400 a month for a pain reduced/and sometime pain free quality of life seems worth it but not everyone can afford this. Please re-consider. Aimovig has been created to fight chronic migraine as its primary purpose but Botox was another accidental migraine drug, found to reduce migraine in some, but it has only a 50% success rate. The first drug to be specifically designed to combat and reduce migraine needs more consideration to fight the whole picture of how migraine effects not only the individual patient but the UK economy as a whole.

Name	[redacted]
Role	Carer
Other role	None
Organisation	None
Location	England
Conflict	None
Notes	None
Comments on the ACD: Migraine is a hugely debilitating condition which, due its invisibility, is not taking seriously by many employers and even much of the medical profession. It blights people's lives, is a major cause of loss of working days and particularly for chronic or continuous sufferers, prevents them working or socialising at all, causing knock on effects such as loss of confidence, depression and anxiety, not to mention the huge stress it places on family and other carers. Erenumab is at last a drug developed specifically to treat migraine. For the many migraine sufferers who have tried a number of different treatments - preventive drugs of various sorts, occipital nerve injections, botox etc. - but without ant relief, erenumab offers a real hope, as a migraine specific drug, of some relief after years of misery. Trials over the past three years in the US have had very positive results. It also has the major advantage of few, and those minor, side effects. To deny the opportunity to try this treatment, specifically researched and developed for migraines, to the many thousands of sufferers who have tried a raft of the present, non-migraine specific, medicines currently on offer, would be little short of immoral. It would also be extremely short sighted given the evidence that could accrue as a result of a roll out through NICE, and also in terms of the deleterious effects on the economy of this county through loss of working days as result of migraine, and the expense to the NHS through dealing with the knock on effects of chronic migraine such as depression.	

Name	[redacted]
Role	Patient
Other role	Retired PA and Office Manager for The Co-op
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: I cannot stress strongly enough how disappointed I am at your decision to reject Erenumab. It's my 61st birthday tomorrow and I have suffered with severe migraine all my life. I have visited some of the top neurologists in the UK, have tried every type of available medication via the NHS, but nothing has helped. incidentally, all at great expense to the NHS no doubt - and whilst quality of life is a major factor to consider surely cost-benefit should be as well, given the NHS treatment and consultations over my lifetime, the cost will have run into hundreds of thousands of pounds. As all these previous medications were developed for the treatment of other conditions, I had to suffer all the side effects too. I have also, at my own expense, tried various alternative treatments. I had to take early retirement, again at my own expense, in my mid-fifties as the quantity of painkilling medication I was taking just to get to work every day was putting me at risk of a stroke. Millions of workdays are lost every year by those with migraine, think of the cost to the economy! Not to mention the suffering. I spend more than half of every month with migraine, which involves lying in a darkened room, sometimes accompanied with vomiting. Yes, I have Triptans and painkillers but I'm restricted to a small amount of Triptans per month, far less than the number of migraine attacks. Painkillers are ineffective against this debilitating condition, and many sufferers have become addicted to painkillers with codeine to try and carry on with their lives.

Erenumab is a real hope for us, being the first drug targeted at migraine specifically, please, please don't deny us the chance of some relief! I just want to enjoy a normal life, being able to plan for events without the frequent cancellation necessary because of migraine attacks. I don't want to spend half my life in bed feeling more dreadful than non-migraine sufferers can possibly imagine. Please give me and all those other suffers a chance of life without pain and misery. I beg you to reconsider!

Name	[redacted]
Role	Patient
Other role	Unemployed, on disability benefits due to chronic refractory migraine
Organisation	None
Location	England
Conflict	None
Notes	None

Comments on the ACD: The committee has made their recommendations based on the fact that botulinum toxin type A and other oral preventive treatments are available. This means those who have tried multiple medicines and botulinum toxin type A with unsuccessful results are left with nowhere to turn. I believe erenumab should be proposed as the next stage in the treatment pathway, in the fifth line, after having had an inadequate response from botulinum toxin type A. This appraisal consultation reads as an either/or situation between erenumab and botulinum toxin type A, however, it should be based on the best available medicine to allow the best quality of life. Botulinum toxin type A has improved the lives of some migraineurs; however, as the migraine disease is so individual it is clear that not everyone will have benefit from the same treatment. Since the age of 11 I have tried 14 different oral preventive drugs, had 5 different triptans and 8 different types of therapies including 3 sessions of botulinum toxin type A with no improvement. I have also tried lots of alternative therapies and lifestyles; I even had heart surgery as there was a small possibility of migraine improvement. I am now 26 years old and have only got progressively worse as I have aged. My consultant neurologists have been running out of options. To be a young woman with no future prospects in either work or socially due to my chronic migraines it had left me feeling helpless until I heard that medicines were being designed specifically for my disease. I had no expectations as one doesn't after so many failed treatments for so many years. As I was desperate to get my life back I started erenumab privately with the support and finance of my parents for the time being. So far I have had 4 monthly injections of 70mg and I am now hopeful that my migraines won't dictate my life and my future. This is the first time in over ten years that I have had migraine free time. However, since I will not be able to permanently self-fund, if NICE doesn't approve erenumab for NHS use my migraines will eventually return to devastate my life.

The committee has stated that the cost-effectiveness is too high, however, I don't believe that the committee has fully reflected on the cost migraine has on the economy each year. In 2010 the House of Commons paper Headache Disorders not respected, not resourced stated that each year migraine costs the UK economy Â£3.42 billion in lost productivity compared to the £150 million per year cost of NHS resources treating migraine. This shows that it is in the best interest of the UK economy to try to provide the best care and treatment for migraine sufferers. My case provides evidence that improperly treated migraine costs the UK more than the cost of the correct medication. I am currently unable to work due to my migraines and therefore claim disability benefits. Each year I am costing the government £5,316 in benefits alone. If I was able to continue improving due to erenumab and therefore join the workforce I would no longer be receiving money from the government but would be contributing instead. Being unable to find the correct treatment for chronic migraine does not only cost the NHS money for multiple doctor consultations and trial and error with medications but it also costs them

further money on other health conditions. Migraine influences other conditions, such as depression, and often these conditions improve when migraine improves. Not to mention the long term effect on physical and mental health which results in more consultations and therapies. For example, chronic migraine restricts the amount of exercise that a person can do which can lead to illnesses and diseases such as cardiovascular disease, which would then result in even more NHS funds needed to treat these additional conditions.

The committee seems worried about the cost of set up for erenumab within the NHS and have decided additional resources are needed. I don't understand why further resources would be needed as those who would be prescribed this medicine would already be referred to a consultant neurologist; in fact it would need less time and money to prescribe than botulinum toxin type A. Erenumab seems like the simpler and cheaper option. Botulinum toxin type A needs a trained consultant neurologist to perform the procedure each time whereas erenumab can be administered at home by the patient. The patient would have to attend the very first session with a nurse to be instructed on how to administer the injection but it is an easier and more migraine friendly option than having to attend an appointment each time. It also helps make the patient more autonomous and take responsibility for their disease. It is unrealistic to expect migraine sufferers to be able to attend each appointment as planned due to the unpredictable nature of the disease. This means that often appointments are missed, resulting in delayed treatment and consequently missed time at work or social activities. As is the policy at most hospitals a last minute cancellation more than once results in a discharge. This in turn results in further missed treatment and time and money trying to rectify the problem. Comparing this problematic setup to an at home administered injection which allows migraine sufferers to continue their treatment even if they are unable to get out of bed seems like a simple choice. Having at home treatment stops the patient missing work for an appointment or missing treatment. It also results in less time and money being spent in the NHS.

The Committee has also stated that there is no long-term evidence of effectiveness. But it was also stated that there is evidence of 52 weeks of improvement for those with chronic migraine and 64 weeks for episodic migraineurs. In that year of improvement a migraine sufferer can enjoy their lives, work and reduce their other health issues related to migraine. It is also a year where they will not need constant neurologist appointments, multiple oral drug preventatives and trips to A&E. Furthermore, these effects could last longer than a year, resulting in a much higher quality of life for each patient. If the effects wore off after a year then the patient would not continue the drug, as is the case with every drug they would have tried previously.

The World Health Organisation classifies severe migraine as one of the four most disabling conditions, alongside quadriplegia, dementia and active psychosis. It could therefore be argued that for NICE to reject the first medicine specifically designed to improve the lives of these disabled people, it is discrimination. As most migraine sufferers are young women it could be argued that withholding approval for erenumab is helping to keep these women out of work and therefore is discriminatory. Furthermore, as this drug has been approved for use in the UK via the European Medicines Agency, not recommending it for NHS use discriminates against lower income sufferers as they will not be able to access this drug which could

improve their lives. The House of Commons has stated in Headache Disorders not respected, not resourced that The Department of Health should recognise that migraine and other headache disorders are a major public-health issue.

Please take a moment to think about how you would feel if you were me, or I was your daughter/sister/wife/friend, and help me and others like me live a pain free life.

Comments on the ACD received from the public through emails

Name	[redacted]

Comments on the ACD: To Whom It May Concern

I understand Erenumab (ID 1188), for prevention of migraine, consultation ends 31/1/19 and that this drug is not being recommended for use in the NHS.

As a chronic migraine sufferer since the age of 10 years (now 67 years) I have spent most of my life not knowing from one day to the next how I am going to be. A few years ago my pattern changed dramatically for no known reason and I now have periods of getting cluster migraine with the visual disturbances one after another in the same day and have been prescribed several different preventatives, from beta blockers to Topiramate (anti-epileptic drug). Unfortunately, I am still suffering on a regular basis.

I would really like to see this Erenumab available on the NHS as it is very distressing not knowing what the future holds for me and I speak for many others who suffer like me.

As a decision not to approve for the NHS has been recommended I sincerely hope that you can reconsider this decision and change it to one of approval.

To have a new preventative for migraine could change the rest of my life. How exciting would that be? To have a 'normal' life should at least be available to everyone if possible.

I so look forward to being free of this debilitating condition one day. It seems it could, with the right decision and mindset, happen soon. Please help!

Yours sincerely
[redacted]

Name	[redacted]

Comments on the ACD: Dear Sirs

Re: Aimovig® (erenumab) and NICE's conclusion: they do not recommend Aimovig for preventing migraine.

I'm unsure where I can make comment about this but feel I need to:

I've suffered with migraine all my adult life and feel it's the curse of the devil and have felt suicidal at times.

I have experienced some horrendous times in my life and in work, it is difficult to recall them all but I've sobbed uncontrollably as I've had to yet again drag myself home in the car (a one-hour's drive) and take yet more time off work feeling so low, so guilty and in pain. I think I've been made to feel guilty so often, even by some friends as if I've brought it on myself, "and what did you do this time to bring it on?" I've always felt somewhat guilty and made to feel worse by others who think I'm letting them down because I

cannot now attend a function or event, drive them somewhere as previously planned or similar. I've missed many events, such as a family wedding, short breaks, trips to the theatre and nights out with friends and family. Holidays have been ruined and hundreds of days of my life spent in pain, in bed with the curtains drawn praying the migraine will lift soon.

I've spent a long time putting myself through an assortment of tests, avoiding certain foods and alcohol and tried a huge array of alternative medicine and other things that I thought might 'cure me'. I went through food intolerance testing, Acapuncture (which is a story by itself as I was finally offered ten free sessions by the acupuncturist as he was so convinced he would cure me…and didn't); Homeopothy, stress-relieving treatments like Reflexology, seeing an Osteopath & Chiropractor, trying aromatherapy massage, Yoga & Tai Chi classes. Vitamin B and Magnesium supplements, went to my Dentist to be fitted with a dental brace (in case my teeth grind), herbal remedies, tried a light-mask, a Sea-Band around my wrist and naturally etc. However, nothing really works except prescribed preventative medication, for a while but nothing is a cure-all. I started getting migraines really badly lasting for three days, most of which was spent flat out in bed feeling dreadful trying to look after myself as I lived alone.

I feel that I've tried most relevant medications over the years: migraleve, Beta blockers (Propanolol), Sanomigran each night (was taking 15mg but I put half a stone in weight on so compromised and reduced it), Progesterone only pill (POP), Mefenemic acid for a short while and Naproxin. I've tried most triptans but never felt they had a profound effect stopping my migraines (Almotriptan, Naramig, Frovatriptan, Rizotriptan, sumatriptan etc.…), I was using soluble Paramol but then they stopped making it. Tried Ibruprofen or paracetamol in the hope it might slow down or stop an attack but didn't. One of the best prophylactics for me at the time was Amitriptylene (anti-depressant) until the efficacy wore off a few years later. I've been on Venlafaxine, Gabapentin and Topirimate (which made my migraines disappeared for ONE-WHOLE year, then returned as bad as ever), etc....

I think more media attention and awareness of it has helped and people are more supportive now than they ever were in the past. However, you can still get people who think a migraine is 'just a headache'. I've experienced the worse in people and the best. However, even those who show sympathy have no real knowledge of what it's like to suffer a bad migraine attack, how it feels, how it leaves you feeling and what the impact is. I think there is always more room for more education.

Managers in work and other staff members have not always seen migraine as something dreadful to suffer, more an excuse to take more time off or leave work early etc. I had one senior manager who suggested I might want to think about giving up work and letting someone else (more-healthy) take my job. I was once made to drive around 70 miles each day for two-days during a conference which I'd organised and the 'academic' manager told me that he 'very much expected' me to be there even though he knew I'd got a migraine. He seemed to view my migraines as something a 'weak woman' might have, "Oh [redacted], not again". I could mention many awful instances but on the whole things over the past few years seem to have improved slightly. I think the main positive aspect is when you are paid sick-leave by your organisation for taking time off (whilst flat out in bed suffering), not

being told you will have to use your annual leave days (again) or come into work.

Migraine is a horrendous debilitating condition which makes us feel lonely and isolated, anything that can be done to help, such as 'effective' preventative medication can make people feel more human and not such a social outcast.

I ask you to reconsider the decision.

With best regards

[redacted]

Name	[redacted]
Notes	[redacted]

Comments on the ACD:

[redacted]: As a person who lives with Chronic Migraine, I cannot make plans as I cannot predict how ill I am going to be from one day to the next. My migraines leave me completed debilitated, I cannot function effectively and I cannot hold down a job, I do not lead a normal family life and I have no friends, not because I never had a any friends but because people move on without you while your migraine has consigned you to your dark, cool bedroom yet again.
I am reliant on family members coming in to cook or clean or me or I live on takeaways. My household chores just build up until a family member says I'll hoover round or I'll do some washing for you.
Every day I have headache symptoms, in the last year alone I have had over 230 migraine days, the remaining days are postdrome days. 2018 was 100% lost to migraines!
I do not have a life, I am a prisoner inside my own body, caused by a medical condition that is widely out of control and has not responded to the routine medication / treatments.
The prospect of a drug that could change this, is the holy grail for people with Chronic migraine. The chance to be prescribed Erenumab on the NHS was cruelly snatched away by NICE last month, please, please do give those of us with the most need, the chance to try this wonder drug!

There are very few effective treatments out there, the most effective treatments for one person often do nothing for the next person.
I have been taking medication for my migraines and receiving other treatments such as Botox, Acupuncture, Osteopathy, Chiropractic Treatment, following diet and lifestyle advice and nothing helps.

Currently, I am using a gammaCore Sapphire vagal nerve stimulator, this has been provided on a free trial by Electrocore.

Before migraines, I had a life, a portfolio carer which included teaching Master's students in Strategic Leadership and Management as well as running my own business, now I cannot function without aides, adaptions and assistance.

There are currently no migraine specific drugs that work for people with chronic migraines, we take medication that was developed to lower blood pressure, to treat depression, to manage epilepsy and much more.
We need a drug or a series of drugs that are designed for the uniqueness of migraine!
Migraine is not just a headache, it is a serious physiological condition with affects so much more than just the head.

Migraine Buddy (an app for recording details of your migraines) describes migraine as:

"Migraine is a neurological condition, which affects about 15% of the population. On top of the extreme throbbing pain, migraines can be accompanied by symptoms such as nausea, extreme sensitivity to light/sound or even vomiting in some cases."

"Although there are countless medical and non-medical reliefs available for migraines, it can be extremely tricky for a migraineur to find the one that will work best for them. This is why recording all your attacks with Migraine Buddy will help you keep track of the reliefs and their effectiveness which will be useful information for you and your doctor!"

The Health Needs Assessment for people living with neurological conditions in Lincolnshire report published in July 2018 states that many people in Lincolnshire feel that primary care staff (GPs, nurses, etc) do not have a detailed knowledge of neurological conditions, this is clearly backed up by the lack of knowledge that the HCP has on serious Neurological conditions.

George, T., Toze, M., Sisson, K., and Ray, M. (2018, 6), state:

"Service users and carers expressed frustration with a perceived lack of knowledge and understanding of neurological conditions by primary and urgent care health professionals, which leads to delays in referral, diagnosis and the onset of treatment. They also felt that there was a lack of information about services available to support them in living with neurological conditions. They highlighted problems associated with transfer from one service, or part of a service, to another because of organisations not communicating effectively and using different policies and processes. This is particularly problematic for those who have to travel out of the county for treatment."

The National Institute for Health and Care Excellence (NICE) Final scope for the appraisal of Erenumab for preventing migraine document issued in March 2018 describes migraines as:

"Migraine is on a continuum, and it is possible for people to move between episodic and chronic migraine:

Episodic migraine is defined as the occurrence of headaches on less than 15 days per month.

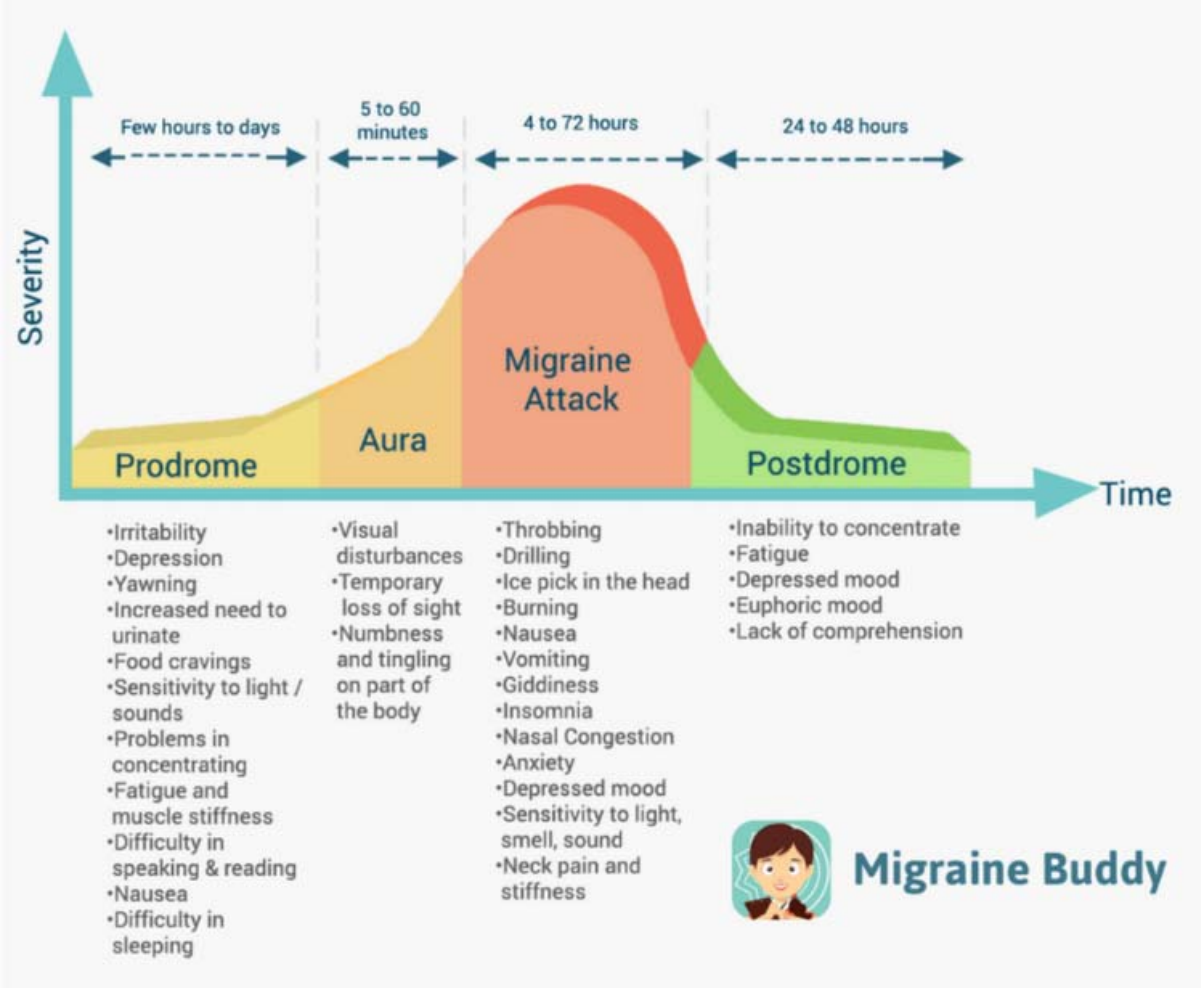
Chronic migraine is defined by the International Headache Society as the occurrence of headaches on 15 days or more per month for at least 3 months where the attacks fulfil criteria for pain and associated symptoms of migraine without aura on at least 8 days per month for at least 3 months, where there is no medication overuse, and where the headaches are not attributable to another causative

disorder. A person must previously have had at least 5 attacks fulfilling the International Headache Society's criteria for migraine with or without aura.

It is estimated that there are 190,000 migraine attacks experienced every day in England.

Prevalence has been reported to be 5–25% in women and 2– 10% in men."

As detailed in the graphic below Migraines can come in four stages.



Patients living with migraines need to be able to access a migraine specific drug that has a proven (official and unofficial) track record.

A life!
Erenumab has positive reviews and positive feedback on social media where people are the most critical. It works, the evidence in the clinical trials should of course be looked at, but so should the testimony of those who use the drug.

If Erenumab was to be made available this year on the NHS, it is likely that I would be in one of the first cohorts of patients and it is also likely that I would have some kind of life style that I have not had during the last six years.

Constipation, this is one of the most widely reported side effects, to me this would be more of an issue than having to inject myself, developing hardened skin at the inject sites or even not having as much of a response as I would like.

Patients who have chronic migraines and who have not responded to Botox, Nerve Blocks or Acupuncture as well as table / suspension medication.

Not providing Erenumab on the NHS is a fundamental dereliction of duties by NICE, it goes against the founding principle of a free healthcare system available for all at the point of use.

It also infringes the human rights of patients who are severely debilitated by migraines. Refusing this drug / technology will deny me a right to lead a life free from degrading and inhumane treatment, it denies me the right to a private family life and the right to not be discriminated against.

That Erenumab is a fundamental treatment in the next generation of migraine drugs, denying it will cost the UK economy more in lost work days and sickness / disability benefits than it saves the NHS.

• Erenumab is the first migraine specific drug in more than 20 years, it has very good results.
• Migraine is much more than just a headache, it is a series of physiological symptoms that affect the entire body.
• Denying Erenumab on cost grounds is a false economy as much more will be spent on lost work days, sickness and disability benefits over the rest of my lifetime than will be spend on Erenumab.
• Denying Erenumab is in breach of the Human Rights of people who live with migraines.
• That NICE has looked specifically at the cost implications, ignoring the official and unofficial evidence of the benefits of Erenumab, and that this flawed decision was made by a panel that does not include a headache specialist nor a neurosurgeon.

Thank you for your time.

[redacted]: Imagine being in constant pain every waking moment of every single day. Picture waking up to a beautiful morning where the sun is bright and the birds are tweeting and your head feels like it is being crushed in a vice and you can't look at the sun because it hurts your eyes and any noises drive you insane. You've tried 11 different drugs that are made for epilepsy, depression or other diseases that aren't what you have and none of them do anything except cause horrible side effects. It's been 10 years now that you have been in constant pain, with no crystal clear days and you can't remember how many different alternative treatments you've tried - from botox to DHE. This is my reality.

But then one day you are given an injection which gives you the relief you have been longing to have for the past ten years. The injection that brings your daily pain down from an 8/10 to a 3/10 within days. The injection that means you can go to work and do your job properly without having to sit in a dark room and leave work early to just sleep.

Please re-evaluate the decision you have made that is taking away the opportunity for so many people to feel the relief that I have finally found after the long and painful journey I have had.

Name	[redacted]
Role	Consultant Neurologist and Headache Specialist at [redacted]

Comments on the ACD: I am writing with regard to the above NICE recommendation.

A few points to my contribution to the appraisal which I would be grateful to be taken on board:

If health and social care were to be amalgamated it is highly likely that Erenumab would has significant cost savings. This is because the drug is addressing an unmet need in a population which is largely of working age. Although the current end points used is a 30% and 50% improvement it is the HIT-6 and other standardised disability assessments which will allow assessment of what proportion of individuals you get back to work and reduce days off work.

There has only ever been one study comparing combination oral preventatives and no good RCT on head to head studies.

It is not going to be something a drug company would pursue if the drug has been found effective vs placebo as this risks involved in showing inferiority of the drug.

There is no funding within the NHS for such projects

The best case scenario will be a meta-analysis

Migraine is a lifelong disorder. It is unlikely that any company will obtain e.g. 5-10 year data to assess long term response.

Even if they did there is unlikely to be a worthy comparison, thus this criterion provided as one of the reasons not to support use of the drug is an unrealistic expectation. This sort of data is likely only to be available after the drug has been in use for some years.

Patients do not like taking daily oral medication

The greater the frequency at treatment the poorer the long term response and then more complicated then neuropsychological morbidity which further feeds the disorder. Thus to offer this drug late does not allow the opportunity to make an impact in those patients with frequent migraine and hence allow the possibility of preventing the evolution to chronic migraine

This cannot be done with Botox as the RCTs in episodic migraine were negative

This is only the second time in the history of migraine that there is an effective drug specifically targeting the actual disease processes. Triptans revolutionised the acute treatment of migraine. The CGRP MAbs work as preventative for which we have limited option. The burden of disability in migraine is mainly from the more severely affected patients.

From the perspective of cost it seems reasonable that patients try at least 3 preventatives. However I would not advocate a fourth and Botox prior to the CGRP Mabs as by this time the patient has evolved into a more intractable disease process.

Medication overuse – the CGRP Mabs seem to work in this group, while other preventatives do not reach the 50% reduction neither does Botox. Medication overuse is one of the key indicators for longer term intractability We do not yet have adequate mental health services to support these patients as much of the of the disability is behaviourally driven.

[redacted]

Name	[redacted]

Comments on the ACD: I have been a migraineur since the age of 16 when I started my first job, suffering migraine without aura. In those early days I had limited medication and I was generally told that the migraines would perhaps stop when a. I had children b. went through the menopause c. reached the grand old age of 50. Well, I have given birth to two sons, gone through the menopause and have reached the age of 55 yet still I suffer this often debilitating condition.

I have many triggers, including stress, lack of sleep, long journeys, heat, flashing lights, strong smells like paint or certain perfumes, long periods between meals, dehydration, anxiety, over exertion.

A typical attack is a throbbing/ pulsating pain on the left hand side of the head - I am left handed. If not caught in time the migraine can be accompanied by nausea, vomiting, diarrhoea, sensitivity to light and sound, fatigue, yawning and muscle stiffness in the neck and shoulders. The migraine can last 12-24 hours.

In the hours following the migraine I feel tired, my body aches, I find it difficult to concentrate, I feel 'hungover' and delicate. My mind also feels muddled and my brain crowded. I find general conversation difficult to process and I have difficulty word finding.

This has had a massive impact on my life. I had migraines during pregnancy and was unable to take medication. When my children were small I regularly had to rely on good friends to help ferry the children back and forth to school. I have missed celebratory events including a graduation, a retirement, several days of a holiday, had ruined weekends away and have lay on countless medical bays on days out. This has obviously also impacted heavily on my family. They have watched me writhing around in pain and have had to look after themselves during the hours of the pain phase and the latter phase until I return to normal.

Over the years I have taken preventative medication every day. Currently I manage my migraine with daily Amitriptyline and take Sumitriptan in the form of a tablet or an injection pen and Zolmitriptan in the form of a nasal spray on the onset of a migraine. I currently suffer 4 – 8 migraine headaches a month by no means a chronic sufferer yet in managing my migraines it is necessary for me to take large amounts of medication. This despite

maintaining good health due to a healthy diet, eating plenty of fresh fruit and vegetables. I also exercise regularly through walking, swimming, working out in the gym, yoga and am a keen skier.

I have attended a number of sessions run by the Migraine Trust and was excited to learn that a new drug specifically for migraine prevention was nearing becoming a reality. It was great to hear that this new drug erenumab had been rolled out in the States and the next step was to so present it to NICE in the UK. How utterly disappointing to learn that it had been rejected mainly on the grounds of cost. I didn't expect this to be a cure nor did I expect to be prescribed this monthly injection pen as a non-chronic sufferer. However I am totally devastated for those chronic sufferers whose lives must be extremely miserable. That tiny glimour of light, the hope of normality free of pain taken away.

Name	[redacted]

Comments on the ACD: Dear Sir or Madam,

I am extremely disappointed that Nice have found that Erenumab should not be available on the NHS. As someone whose life is severely affected by migraine I hope that this decision might be reconsidered.

Best wishes
[redacted]

Name	[redacted]

Comments on the ACD: Dear Sir or Madam

I am pleading with you to PLEASE authorise the use of Erenumab on the NHS in the UK.

My daughter's life has been severely blighted by the curse of migraine since the age of 7 years (she was 29 in Nov). We have tried so very many of the standard medications as well as homeopathy and acupuncture but nothing has worked for her.

For a brief period she had a job in a secondary school art department that she loved, however she was victimised because of all the days off she needed due to her chronic migraines, and eventually they did away with her job (they couldn't directly fire her as that would have been considered medical prejudice)

If you would allow her the opportunity to take Erenumab you would effectively be giving her, her life back!
Thank you for your time and consideration.

Yours most sincerely
[redacted]

Name	[redacted]

Comments on the ACD: 1.I have been trying as a migrainer to work out how to provide feedback on this trial. It is not straight forward by any means. I declare an interest. I am a 3+ Chronic Migrainer.
2. On the questions the committee was interested in receiving comments:
***arguably the review of this treatment took a selective view of the evidence**
***again, arguably the review is not entirely reasonable for the following reasons**
a) The uncertainty point on cost is one that could be made on any trial that doesn't last a lifetime. And of course the value put on migraine relief may not be well served by dismissing a 'promising' treatment without saying how long the trial would need to last to be convincing?
b) The Botox comparison is only relevant up to a point. It works for some and provides maybe an alternative comparison, but not a definitive test of this treatment, which had other controls.
c) On the exclusion of chronic 3+migrainers the data on those subjects should be viewed in the overall picture of the migraine data. The medicine clearly works for chronic migraine, and the study appears well powered.The treatment also works for episodic migraine, so potentially huge benefit there. The distinction made is anyway somewhat artificial.
***The proposed guidance is not a suitable basis for guidance to the NHS because it ignores the benefits of this first preventive treatment for migraine. Not having availability of this treatment within the NHS is the worst decision that might be made.**

***I cannot see any bias in the guidance, but the bar it sets for 'success 'is very high for migrainers as a class.**

[redacted]

Name	[redacted]

Comments on the ACD: To Whom it May Concern

I would like to comment on the recent draft guidance that Erenumab is unlikely to be available on the NHS.

I am a severe migraine sufferer - I get migraines 24 days out of 28, and I was forced to retire from General Practice when I was 45 as a result of them. Subsequently I was tried on every oral preventive drug available, as well as trying Botox, and heaving several surgical procedures including neck facet joint injections and sub occipital nerve blocks. None of these treatments worked, and eventually I was able to enrol in a trial testing one of the other CGRP inhibitors (fremenezumab).

Fremenezumab helped my migraines significantly, and I became optimistic about the idea the once these drugs were licensed, I might be able to look forward to some kind of relief from my pain, and that I might possibly be able to return to work.

However, I hear now that this is possibly not to be. I am therefore writing to ask, whether the committee would consider making these drugs available to selected individuals, who have shown to gain significant improvement from them, in the face of other failed treatments.

I believe, as an individual and as a doctor, that this compassionate approach, would be a valid and acceptable policy, that would help select people who suffer from chronic, intractable pain on an almost daily basis.

Yours sincerely

[redacted]

Name	[redacted]

Comments on the ACD: To whom it may concern,

I have been a migraineur for over 25 years. The prospect of Erenumab was a glimmer of hope for me.

I am a chronic migraine sufferer, debilitated for at least 20 days per month. I've tried beta blockers, antidepressants, anti-convulsants, angiotensin blockers, the Cephaly device, CBD oil, acupuncture, reflexology, osteopathy, homeopathy, aromatherapy, oxygen, meditation & yoga. None have helped & the only light on the horizon was this drug. I hate the term "headache" it is SO much more than a headache. My pain is excruciating, torturous pain that goes on for hours/days on end, confining me to a dark quiet room but unable to sleep, then the hangover symptoms afterwards & then another attack just when I'm trying to get back on my feet again. At times I've felt suicidal as I just don't know how to cope with the pain anymore. I have had to give up my job & social life, lean heavily on my husband for childcare & now as a result he's struggling to cope with his work/life balance. We have no help & we have no spare money. This is such a cruel disease & now the NHS are being cruel not helping us. I worked for the NHS for 24 years & felt proud of it but am now so angry, frustrated & disappointed in them. This is so very depressing.

I have, over the last 25 years, had innumerate visits to the GP, neuroscience and Migraine Clinics. I've tried varied, dangerous and expensive drugs which have had long term impact on my condition, leaving me with intractable transformed migraine. I am now being referred to tertiary care. What I am saying is that a simple deployment of an effective drug would have cost the NHS far less and personally cost me far less in the long run than the list price of Erenumab. The report makes a comparison to botox as a remedy; this seems to be a flawed premise. The botox treatments are impractical to manage (requiring for me a regular and frequent drive of over 120 miles as a round trip - impossible for a chronic Susanmigraine sufferer) whereas erenumab can be self-administered. I understand that costs vs effect are important considerations for NICE but this report seems to be blinkered to the reality of migraine treatment and the personal, economical and social effects of a chronic illness.

Kind regards

[redacted]

Name	[redacted]

Comments on the ACD: TO whom it may concern,

I would like to state that the following should be taken into consideration:

1) There is no need to request 4 oral preventatives to have failed before considering Erenumab. The standard practice currently is the failure of 3 oral preventatives before trialling the injectable thereapies.

2) The advantage of Erenumab compared to Botox on a practical level is that this would release capacity to see other patients in clinic as Erenumab can be self-administered at home.

3) 70mg should be the starting dose and if they receive a partial response then this can be increased to 140mg as opposed to starting 140mg at the onset.

Thanks,

[redacted]

Name	[redacted]

Comments on the ACD: Hello

Re: Erenumab for preventing migraine [ID1188] - my comments on the current outcome

I am a 29yo migraine and headache sufferer for the past 5 years. I have tried so many methods of pain management and preventatives to manage this, however my neurologist has now ran out of options that are available.

I had 1.5yrs of the botulinum toxin type A treatment (every quarter) with unfortunately no luck as hopeful as we were. I have read a lot about amorvig and seen the use of it by fellow migraine sufferers over social media how it is helping prevent the quantity of migraine and severity of them.

As a migraine sufferer your days aren't always measured by how many migraines a month you have had, but the severity makes a massive difference too. It is possible to continue with my daily tasks? Or is it so unbearable that I can't move from the spot and lay in darkness.

My migraines have had a massive impact on my life and literally hit my like a wall out of nowhere one day, and never left. The possibility of the new treatment has given me hope the past 9months whilst I've been left with no treatment plan or pain relief.

We need to have access to such medicines as no two peoples migraines are the same. I hope that the outcome of the NHS declining the use of this medicine is reviewed and hopefully changed as I know that I am not the only one who has been waiting a long time for a new medicine to help improve the management of these daily rehabilitating migraines.

If there are any other questions I could answer please let me know.

Kind regards

[redacted]

Name	[redacted]

My daughter is 18 years old and has had migraines since she was 11. During this time the severity, frequency and duration of her migraine has increased. She has been prescribed 6+ medications all of which have not worked and some which have produced horrible side effects. She is now having Botox (provided by our private health insurance) as there is woeful access to us for it to be provided on the NHS. This is also not working for her. My daughter always planned to go to University. She achieved excellent GCSE results and started studying for her A levels when her migraine took over her life. She has had to stop school and for the past 2 years has been struggling with the pain and isolation having this disease causes. She's now not only dealing with chronic pain but also depression. I am extremely worried about what the future holds for her. What do we as parents say to her? There's nothing more we can do? I am urging you to please reconsider making Erenumab available on the NHS as this appears to be the only option left for her. Thank you.

Name	[redacted]

Thank you for accepting my comments in relation to Erenumab.

Firstly, I cannot state clearly enough how important it is for a chronic migraine sufferer to have the opportunity to try Erenumab.

Over the last four years I have tried, without success, all of the treatment options listed in your consolation document including beta-blockers, antidepressants and epilepsy medications. Please do not underestimate the side effects of these drugs – fatigue, lack of clarity in thinking, one gave me a feeling of a loss of control.

I am currently on my third round of botulinum toxin type A which has provided marginal improvement (I have more clear days).

I suffer from 11-15 days migraine per month – with headache on many of the other days. I can only manage life with the support of Zolmitriptan.

When weighing up the cost of the medication it is important to consider
The loss to the economy – my ability to work is severely affected by suffering migraine
The cost/side effects of triptans

I am a full time carer to my husband who has a brain injury – he is extremely distressed when he sees me constantly vomiting.

If I am unable to look after him because of the severity of the migraines there would also be a cost as he would potentially require full time care.

Knowing that Erenumab was on the horizon has given me (and I am sure many chronic migraine sufferers) hope.

Could Erenumab be considered as an alternative to botulinum toxin type A?

Thank you for considering my comments.

Best wishes

[redacted]

Name	[redacted]

Good evening

I wonder if you can help?

I'm a chronic migraine sufferer, in pain most days, having a totally debilitating affect on my life.

I currently hold down a job but this is getting more difficult month by month.

I take a significant number of Rizatriptans at a great cost to the NHS. If I become too ill to work, this again would have a negative impact on the public purse as I would hopefully be entitled to support.

I was part of the fremanuzamab trial through University Hospitals of North Midlands (Stoke), [redacted], and this helped greatly. In fact the cold turkey impact of trial end has been particularly difficult and I have very little quality of life.

I have worked hard since the age of 17 (now 51) and paid my taxes to help support this country and the NHS.

[redacted] tells me that fremanuzamab has not yet been approved in the UK but erenumab has and he can prescribe for £380pm. I'm afraid that this is out of my reach but I could find 50%. I also took far, far fewer expensive triptans on fremanuzamab so I believe there would be no negative financial impact to the NHS if you were to agree to help work with me to fund the other 50%.

I am desperate for some help and would very much appreciate your thoughts on my fair proposal. I would also be interested in when / if you believe erenumab or fremanuzamab may become NICE approved.

[redacted]

Name	[redacted]

I would like the following put forward please,

I am a 35 year old mum of two, supported through every migraine, by my loving husband I've suffered with hemiplegic migraine from the age of 13. In short terms I have basically stroke like symptoms every time I have a migraine. It's beyond terrifying, as I get older the migraines take longer and

longer to recover from. I have on a number of occasions been taken by ambulance to hospital due to the severity of my migraines. I am under [redacted] Neurologist and see a headache specialist nurse in between appointments. The pain is unbearable and the effects on my mental health have been vast. I live in constant fear of the attacks, worried about time off work, Uni, will they happen on special days like weddings, parties, on holiday. How do my boys feel seeing me during a migraine? They must be scared too. I've tried topiramate, propranolol, gabapentin, amitriptyline, tolfenamic acid, many many Triptans, large doses of aspirin, candestartan, nortriptyline, duloxetine, magnesium, riboflavin, tramadol and over the counter pain relief. Currently my migraines are between 3/4 a month with what has been describe by the neurologist as a constant migrainous state on every other day, meaning a headache and numbness which do not subside. I am currently waiting for Botox but the NHs trust I use can give initial appointments but are not able to maintain the rounds of Botox meaning after 16 weeks they have been unable to facilitate further injections. Patients go back onto medication until an appointment is available. And who can say if it will work. Erenumab was to me a possible light at the end of a long dark tunnel which now seem beyond my reach. I am currently a mental health nursing student and have worked as an auxiliary nurse for a number of years in NHS hospitals. I understand the financial strain on the NHS and am proud to work as a student within it. I have sought Erenumab privately but considering I may need two injections 140mg an approximate cost of £382 per injection is beyond the realms of my financial possibilities. This injection I'm sure has given hope to many who live with this debilitating condition, hope of a normal life with less pain and anguish. Consider the multiple medications we currently take I take 6 tablets before bed along with pain killers daily. I have chronic side effects but the little relief from migraine they create is outweighed. I ask you to reconsider the decision look at the money I cost the NHS in emergency care, ambulances, medication, neurology consultations, MRI scans, lumbar punctures, specialist nurse consultations not to mention days off sick as an auxiliary and from placement as a student nurse. This really feels like the first time in 20+ years I/we have a chance at a better life. I ask you to consider my position and that of many of thousands of others in your decisions to reject this medication.

Name	[redacted]

Comments on the ACD: It is totally unbelievable that you even remotely consider Botulin injections to have remotely the same efficacy of CGRP or chance of some kind of relief .

Having witnessed the total hell of extremely severe migraine triggered and suffered for so many days on the 3 occasions after botulin injections were given by a high profile member of your commitee which did zero to resolve the day in day out hell of what is actually Intractable post traumatic chronic migraine that is utterly destroying the life of a supremely talented young girl.

Every single available medication and treatment has already been tried ....nothing whatever relieves the hell this girl has genuinely suffered for over 5 yrs since the injury and your decision robs her and every other intractable migraine sufferer a chance of life without pain .

There are thousands of areas and situations right across the entire NHS where fortunes could be saved but nothing whatever is done about them . Yet the loss of incomes and associated tax revenues , reliance on benefits and all the other restrictions that are forced on Migraine sufferers which will totally dwarf the cost of providing CGRP meds and freedom from horrific pain .....the total figures involved simply do not stack up to proper scrutiny .

It is this lack of joined up thinking which is wrecking lives and for which NICE are now wholly responsible .

I can but suggest NICE members are forced to actually suffer Intractable migraine for years on end because then they might have a glimmer of what its truly like and see things in a different light.

[redacted]

Name	[redacted]

Hello ,
I
My name is [redacted] **. I suffer chronic migraines . I know that the new drug is now not going to be released on the nhs . This is so devastating . I work part time and financially struggle .**
Is there any hope for the future ? I cannot afford to have this drug due to this disability . Any hope or suggestions ?
Desparatley,
[redacted]

Erenumab for preventing migraine [ID1188]

NICE is asking for clinical expert input following the release of the preliminary guidance on erenumab for preventing migraine. During consultation we received comments from stakeholders which disputed some of the conclusions made by the committee. In addition, the company (Novartis) has provided some additional evidence for erenumab which includes a redefinition of high frequency episodic migraine, long term treatment effectiveness evidence and treatment discontinuation rules.

We are planning to use your responses to the following questions to help inform the committee on the most appropriate analyses to consider at the next appraisal committee meeting.

You can return your responses via email to [redacted] or alternatively I could call you to talk through the questions over the phone ([redacted]). Please let me know your preference.

1) **High frequency episodic migraine (HFEM):**

   a. Is HFEM a clinically distinct subgroup of patients in migraine?

   b. In the appraisal consultation document (ACD) HFEM is defined as 10-14 monthly headache days (MHD). Is this correct?

      In the company's new evidence, they focus on people with chronic migraine and HFEM only, the latter being defined as those with 10-14 monthly **headache** days. This is different to their original submission because their trials for episodic migraine (STRIVE and LIBERTY[1]) defined HFEM as 8-14 monthly **migraine** days. The company note that this reflects a patient cohort with the highest unmet need who are treated by headache specialists, for whom erenumab is particularly appropriate. The evidence review group (ERG) have expressed concern in the company's redefinition of the HFEM subgroup because neither trial provides effectiveness data for erenumab using 10-14 MHD.

   c. Can the trial data from STRIVE and LIBERTY using 8-14 MMD adequately inform the effectiveness of erenumab in HFEM?

[1] ARISE also examined the effectiveness of erenumab 70mg in the episodic migraine population however the company have now excluded the 70mg dose from their evidence.

d. Do you agree that patients who experience 10-14 MHD (ie HFEM) have a similar burden on quality of life as those who experience chronic migraines?

2) **Comparators**:

Prior prophylactic treatment' is defined as any recognised migraine-preventative treatment, including beta-blockers, tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, calcium-channel blockers, ACE inhibitors or angiotensin receptor blockers, and valproate. 'Failure' is defined as treatment cessation due to inadequate response or intolerability.

a. What treatment would you currently offer to a patient with **episodic migraine** for whom 3 prior prophylactic treatments have failed?

b. What treatment would you currently offer to a patient with **chronic migraine** for whom 3 prior prophylactic treatments have failed?

c. What treatment would you currently offer to a patient with chronic migraine for whom 3 prior prophylactic treatments *and* botulinum toxin type A have failed?

3) **Erenumab compared with botulinum toxin type A:**

a. Following an indirect treatment comparison, the committee concluded that there was no robust evidence that erenumab is more clinically effective than botulinum toxin for treating chronic migraine. Given the potential for bias in the analysis, the lack of statistically significant results and the wide confidence intervals, the committee suggested a scenario in the economic modelling in which erenumab and botulinum toxin are considered to have similar effectiveness. Do you think such a scenario is clinically plausible?

b. The company and stakeholders have suggested that erenumab might reduce the burden in terms of mode of administration compared with botulinum toxin. To address this difference, they have conducted a scenario analysis which applies a small disutility (a reduction in the quality of life) for people receiving botulinum toxin relative to erenumab. Do you agree that patients treated with erenumab may have a reduced burden, in terms of the mode of administration, compared with patients who receive botulinum toxin?

4) **Positive discontinuation**:

a. The company have included a 'positive discontinuation' scenario in their new evidence submission. This assumes that patients who continue to benefit from treatment will remain on erenumab for a maximum of 64.5

weeks. At this point, these patients will be re-evaluated over 12 weeks and it is estimated that 20% would stop erenumab ('positive discontinuation'). Those patients who do not maintain a treatment response during the re-evaluation period would return to treatment with erenumab and would be reassessed at 76.5 week intervals thereafter.

Further, the company cites newly published guidelines from the European Headache Federation that anti-CGRP monoclonal antibodies be stopped after 6-12 months of treatment. The expectation is that some patients will need to return to treatment.

i. Would clinicians reliably apply a positive stopping rule to stop erenumab?

ii. At what point would you reassess a patient for treatment effectiveness? Would this be between 6 to 12 months or other?

iii. Do you think, as the company have presumed, that 20% of patients stopping treatment after 1 year is a clinically plausible assumption?

iv. For those patients who stop treatment how long would the benefit of erenumab last? The company have assumed that the benefits last for 12 weeks and then MMD return to those levels seen in the placebo arm of the trial. Is this a clinically plausible assumption?

v. Are there likely to be patients who remain on erenumab indefinitely?

vi. Would erenumab treatment be stopped in patients when their chronic migraine converts to episodic migraine following a response to treatment?

5) **Waning of erenumab treatment effect while people *remain* on treatment**:

The appraisal committee considered that there was no evidence to suggest erenumab would maintain constant effectiveness over the period of treatment. In the absence of evidence, they accepted scenarios whereby treatment effectiveness would start to decline linearly at 5 or 10 years until the effectiveness of erenumab matched best supportive care.

a. Do you agree with the committee's approach to consider treatment waning at 5 or 10 years, given the absence of any long-term data?

b. Do you have any evidence/clinical experience to suggest erenumab effectiveness would be maintained at a constant level over time, for example from other monoclonal antibodies used in other disease areas?

6) The effects of comorbid psychiatric illness

a. To what extent does comorbid psychiatric illness (e.g. depression) affect response to treatment in migraine?

b. How prevalent is psychiatric illness in patients with migraine?

7) **Service costs:**

a. Would treatment with erenumab be initiated in specialist headache clinics?

b. Do you envisage erenumab being administered in specialist headache clinics **only** in order to monitor for adverse side effects?

c. At any point, could erenumab be administered at home by the patient or in a primary care setting?

d. If erenumab was administered at home or in primary care, how frequently would the patient need to return for specialist assessment?

e. Would all patient follow up involve a clinician appointment or could it include a nurse appointment?

f. Do you envisage an increase in referrals to specialist clinics if erenumab is available? If so, what additional resources would be needed to meet the this demand?

g. Are there any other costs or savings related the administration of erenumab that have not yet been accounted for?

Questions	[redacted]	[redacted]	[redacted]
Is HFEM a clinically distinct subgroup of patients in migraine?	No – best seen as a continuous spectrum	HFEM has only been recognised as a subgroup in the last 10 years. There is currently no distinct classification in the diagnostic manual.	In my clinical practice at the Oxford Headache Centre, I typically see patients with infrequent episodic migraine, frequent episodic migraine and chronic migraine. The frequent episodic migraine group often transition into chronic migraine and vice versa. I would therefore regard the frequent episodic migraine as a continuum with chronic migraine but behave in a clinically distinct manner from infrequent episodic migraine.
In the appraisal consultation document (ACD) HFEM is defined as 10-14 monthly headache days (MHD). Is this correct?	This is not a formal criterion in the international Headache society classification and arbitary	The prospective study on Botox propose that treatment should continue until the frequency of headaches come down to single figures. There is no double blind randomised controlled data on that. There is no real evidence to support either 10-14 or 8-14 MHD as high frequency. However, consensus from experts would suggest HFEM is 8-14 MHD.	The question then is how many headaches does a patient need to have to be in the frequent episodic migraine group I.e. HFEM. The literature has used 10-14 monthly headache days in epidemiological studies. The clinical trials have used 8-14 days. As with chronic migraine, 15 days – the cut-off is arbitrary as there are no mechanistic studies to suggest that subjects experiencing at least 8 days or 10 days or 14 days are a distinct group. My own opinion is that this a continuum.
Can the trial data from STRIVE and LIBERTY using 8-14 MMD adequately inform the effectiveness of erenumab in HFEM?	Within the context of the limited accuracy that the whole are admits - yes	'Migraines' are more severe than 'headaches'. For prophylaxis, the work by Richard Lipton indicates that people with less than 4 MHD do not require treatment, 4-6 MHD would consider treatment and 8+ MHD should be on treatment. People with 8-14 MHD or MMD are normally on preventive treatment so erenumab can be used with either.	I think this is not a reasonable criticism because the therapy has efficacy in 8-14 days and efficacy in 15 days+ migraine…so there is little plausibility to argue the 10-14 MHD is not going to respond since (1) erenumab is effective in the broader 8-14 group and (2) efficacy is retained even as headache days increase.
Do you agree that patients who experience 10-14 MHD (ie HFEM) have a similar burden on quality of	It can be much higher	Experts would agree that people with 10-14 MHD experience a similar burden to those with chronic migraine.	I believe they do – this group are usually getting a headache on average 3 days of every week. Very often these individuals

life as those who experience chronic migraines?			will transition into the defined chronic migraine state. Intervention at this earlier stage could lead to prevention of significant disability.
What treatment would you currently offer to a patient with **episodic migraine** for whom 3 prior prophylactic treatments have failed	NICE recommendations first. Then candesarten, Valproate, Flunarazine. Possible pizotifen. Then occipital nerve inj	Those with low frequency episodic migraine (<8 MHD) would receive beta-blockers, candesartan, topiramate, or venlafaxine. Usually one of these drugs would be effective and it is uncommon for someone to have failed all of them. For HFEM (8-14 MHD) the treatment would be similar to chronic migraine with the following used: amitriptyline, topiramate, candesartan, venlafaxine, or botox. To a lesser extent, greater occipital nerve block. It would be expected that 50% would respond to the initial treatments and the remaining 50% to try botox. Around half of those on botox would respond and for the remainder we struggle and often recommend the less desirable options such as valproate, Flunarazine etc.	Practically from the classes listed valproate is not used due to risk of fetal harm; serotonin-noradrenaline reuptake inhibitors and calcium channel blockers (except flunarizine which is difficult to source in my area) have weak evidence – hence I typically have a selection of 4 drugs (amitriptyline, propranolol, topiramate and candersartan) So after 3 drugs I have one further drug that I will use and then I have to try drugs with little evidence of efficacy
What treatment would you currently offer to a patient with **chronic migraine** for whom 3 prior prophylactic treatments have failed?	As above then Botox		As above – one further drug and then Botulinum toxin and then occipital nerve stimulation. Due to waiting lists, I would trial other drugs with less evidence base for efficacy
What treatment would you currently offer to a patient with chronic migraine for whom 3 prior prophylactic treatments and botulinum toxin type A have failed?	As above		Occipital nerve stimulation
The committee suggested a scenario in the economic modelling in which erenumab and botulinum toxin are considered to have similar	Yes – I think a cost minimisation exercise would be appropriate	The data suggests that erenumab is slightly better than botox with an increase in therapeutic gain. Could argue that both are equal in clinical effectiveness as suggested by the committee but when including the	Yes. But there is also an issue that Botulinum toxin in many areas can be difficult to access and has very long waiting lists making headache treatment access inequitable across geographies. Hence the provision of CGRP monoclonal antibodies

effectiveness. Do you think such a scenario is clinically plausible?		burden of clinic visits, number of injections, adverse events and treatment burden for administration of botox there is better option in the form of erenumab.	would result in better addressing the needs of migraine sufferers than Botulinum toxin.
Do you agree that patients treated with erenumab may have a reduced burden, in terms of the mode of administration, compared with patients who receive botulinum toxin?	No response given	As above, there is an increase in resource use and burden associated with botox. It is only available in highly specialised centres and requires multiple injections in the head and neck which are performed by a specialist. However, erenumab can be self-administered following initial training by a specialist.	Yes significantly less burden on the patient and please also see comment above on equity of access
Would clinicians reliably apply a positive stopping rule to stop erenumab	Yes – if clear guidelines given	Nobody really knows the answer to this. Experience of providing botox treatment shows that treatment is stopped due to a positive response in 50% of people at 2 years and 75% of people at 5 years (only 25% are still on treatment at year 5).	Yes – I think both clinicians and patients would always seek to ensure a therapy was still required.
At what point would you reassess a patient for treatment effectiveness? Would this be between 6 to 12 months or other?	6 mths and one year	We can make some assumptions of the treatment process for erenumab. After starting treatment, patients will be assessed at 3 months and those who do not show a response will stop treatment (negative stopping rule). Those who do show a response will be reassessed after a further 12 months. During this time, those who seem to lose response to treatment could be reassessed before 12 months.	In the CM group, I would suggest 12 months.
Do you think, as the company have presumed, that 20% of patients stopping treatment after 1 year is a clinically plausible assumption?	I think it could be higher	It is plausible that about 20% of those on erenumab who are experiencing benefit will stop treatment each year - based on experience from treating migraine patients with Botox.	I have no means to judge whether this is plausible.

For those patients who stop treatment how long would the benefit of erenumab last? The company have assumed that the benefits last for 12 weeks and then MMD return to those levels seen in the placebo arm of the trial. Is this a clinically plausible assumption?	Not known	No, there is a 50% chance of relapse if treatment is stopped (experience from Botox is that around half of the patients would relapse and come back to restart the treatment within 6-12 months while the remaining half remain in remission. It is likely that those experiencing benefit at 6-12 months will sustain that benefit. It is possible that the benefit could last much longer than the 12 weeks assumed by the company.	This seems plausible as (1) the drug is required to be administed monthly and then (2) the efficacy is evident at 3 months…so it is plausible that if the underlying drivers of migraine are still present, the loss of benefit will mirror the onset.
Are there likely to be patients who remain on erenumab indefinitely?	Yes	One could recommend other treatments to those 25% who remain on one treatment for 5 years or more. This is based on the experience with Botox where 25% were still on treatment at year 5.	Yes
Would erenumab treatment be stopped in patients when their chronic migraine converts to episodic migraine following a response to treatment?	No. I don't think the diagnosis of chronic migraine is a helpful one	Could carry on giving erenumab as per the license. I would suggest continuing treatment until headache frequency is <10 days/month then stop. This would also be the most economically viable option.	Good question! – I think the treatment should continue for 12 months to allow the changes in the migraine brain / peripheral nervous system to normalise so that there is a good chance the subject is in true remission. The danger of stopping too early is that the migraine rebounds.
Do you agree with the committee's approach to consider treatment waning at 5 or 10 years, given the absence of any long-term data?	I don't think it is appropriate to model this far into the future	From experience of treating migraine patients with Botox, around 10% patient stop responding to treatment inspite of a very good response at the start. We consider that these patients have developed resistance to treatment and may even happen with Erenumab.	In the absence of evidence I am not sure how one can assume a linear decline in effectiveness if this has not been seen in the 12 month period. Chronic migraine patients have often been suffering for many years so the duration of the disease does not impact the effectiveness. Is there then a plausible reason to think blockade of CGRP/CGRP receptor will become tolerized in the long term? – again if this is not observed over 12 months, I see no rational reason to assume this will occur over several years.
Do you have any evidence/clinical experience to suggest erenumab effectiveness would be maintained at a constant level over time, for example from other monoclonal	Not known		

antibodies used in other disease areas			
To what extent does comorbid psychiatric illness (e.g. depression) affect response to treatment in migraine?	significant	Unless the treatment itself is a contributing factor to the development of psychiatric illness, there will be no effect.	In my clinical experience surprisingly little impact – my impression when starting headache practice was that anxiolytics and antidepressants would play a role in adjunctive therapy but I have not really observed any appreciable effect of treating anxiety/depression on migraine frequency…nor the reponse to migraine treatment.
How prevalent is psychiatric illness in patients with migraine?	Chronic migraine 70%+ have anxiety or depression	There is no major prevalence of psychiatric illness. It is expected that some people will experience low mood or depression as migraine is a debilitating illness. It is more likely that other coexisting physical health conditions will be prevalent with chronic migraine.	Anxiety is very common. Depression is also a comorbidity
Would treatment with erenumab be initiated in specialist headache clinics	It certainly shoud be and not by “headache specialist”	Yes, it must be monitored which is not possible in Primary Care. Guidelines would need to be implemented at initiation.	Yes – initiation in hospital or community
Do you envisage erenumab being administered in specialist headache clinics **only** in order to monitor for adverse side effects?	No. patient selection is the key issue	No, it will be initiated in specialist headache clinics and the patient will have contact with a nurse to monitor effects.	No
At any point, could erenumab be administered at home by the patient or in a primary care setting?	Yes	Yes, following initiation at a specialist clinic the patient can be trained to self-administer at home.	Yes

If erenumab was administered at home or in primary care, how frequently would the patient need to return for specialist assessment?	At least annual	First assessment at 3 months then again at 12 months.	At 3 months ater initiation and then every 12 months
Would all patient follow up involve a clinician appointment or could it include a nurse appointment?	Specialist nurse ok	Yes, it could be a nurse appointment, does not necessarily have to be a clinician. Repeat prescriptions could be initiated in tertiary care and after 3 months the GP could prescribe.	Could be a nurse
Do you envisage an increase in referrals to specialist clinics if erenumab is available? If so, what additional resources would be needed to meet this demand?	Difficult to say. May not have a large impact	The same was considered for botox when it became available but the increase in referrals never really happened. It is likely that 20% of those eligible for erenumab will be referred so no additional resources required.	This patient group already are being seen in specialist clinics – and typically need repeated follow-up as their headaches are poorly managed. So its likely burden on specialist clinics (and A/E and general neuro clinics) might reduce
Are there any other costs or savings related the administration of erenumab that have not yet been accounted for?	No	At initiation, there will be a requirement to train patients who will self-administer erenumab. The company have been providing support for nurses to carry out this training. This support should continue to come from the company not the NHS.	Reduced A/E and general neuro attendance

Appendix: Additional Cost-Effectiveness Analyses (Using ERG Update to Novartis Model)

This document should only be considered in conjunction with our ACD response dated 31st January 2019. Please note that information highlighted in turquoise in this document is Commercial-in-Confidence.

1 Background

Novartis discussed the key topics raised in the ACD with the NICE technical team by telephone on Tuesday 15th January 2019 to seek further clarity. Based on this conversation, our understanding is as follows:-

- *Comparison with botulinum toxin:* The committee would like to see a scenario assuming no difference in efficacy between erenumab and botulinum toxin. However, as this represents an extreme scenario the NICE technical team agreed that it would be reasonable for Novartis to provide analysis in its response based on 'mid-point' odds ratio to illustrate how the cost-effectiveness changes in response to a less extreme assumption. There was also discussion that other benefits of erenumab compared to botulinum toxin such as mode of administration were not discussed at the committee meeting, and Novartis confirmed they would re-present the scenario analysis incorporating this assumption that was included in its submission.
- *Treatment waning:* Novartis agreed to provide further justification as to why treatment waning was not applicable for erenumab (please see point 3 in the ACD response template document). Additionally, it was discussed that it would be reasonable for Novartis to provide analysis looking at alternative treatment waning assumptions, as an illustrative scenario analysis, in which treatment effect was waned at a later point than immediately after the 12-week response assessment.
- *Service costs:* Novartis and the NICE technical team both discussed that incorporation of service costs into the cost-effectiveness model would be difficult, with Novartis expressing a view that it was at odds with reality and feedback from experts. Novartis confirmed it would not be including service costs in the cost-effectiveness model and would provide justifications for why it believed they are not applicable to this appraisal (please see point 6 in the ACD response template document). Additionally, Novartis discussed that it was important that headache specialists' insights on this topic are considered by the committee.
- *Dose:* The NICE technical team confirmed that, based on its assessment of clinical effectiveness an incremental cost-effectiveness, the committee would be comfortable making a recommendation based on the 140 mg erenumab dose only. Therefore, the analyses that follow are provided are based on the 140 mg dose of erenumab only. This means that the pairwise cost-effectiveness analysis has been presented vs. the relevant comparators (botulinum toxin in chronic migraine (CM) and BSC in high frequency episodic migraine (HFEM)), as fully incremental analysis is no longer relevant when considering a single erenumab dose.

- *Comparators:* Novartis confirmed it would not provide analysis comparing erenumab to a fourth oral comparator, as it did not believe that such a comparison was appropriate or justifiable. The NICE technical team agreed that it would be reasonable for Novartis to provide further rationale on why erenumab should not be compared to a fourth oral comparator (please see point 5 in the ACD response template document).

2 New Analyses using the ERG-amended model

2.1 *Version of model used for analyses*

The model version used for these analyses is the version supplied to Novartis by NICE on October 2018 with the file name *"ID1188 erenumab ERG analyses 08112018RB (ACIC)"*. Novartis has amended the error identified at ERG clarification stage in relation to the conversion between weekly and annual results.

[redacted]

2.3 *Assumptions used in 'new' analyses*

Assumptions used for the revised analysis of cost-effectiveness are presented in Table 1.

Table 1: Model assumptions

Variable	Novartis Base Case Assumptions (September 2019 submission)	NICE Appraisal Committee Assumptions	Novartis Revised Base Case Assumptions
Population	Adults with migraine for whom ≥3 prior prophylactic treatments have failed:-	Adults with migraine for whom ≥3 prior prophylactic treatments have failed:-	Adults with migraine for whom ≥3 prior prophylactic treatments have failed:-

	• Whole population • Chronic migraine • Episodic migraine	• Chronic migraine • Episodic migraine	• Chronic migraine • High-frequency episodic migraine (10–14 MHDs)
Analysis	• Pairwise	• Incremental • Pairwise	• Pairwise
Dose	• Blended dose • 70mg • 140mg	• 70mg • 140mg	• 140mg
Time horizon	10 years	Lifetime	Lifetime
Comparators	• *Chronic migraine:* BSC and botulinum toxin • *High-frequency episodic migraine (10–14 MHDs):* BSC	• *Chronic migraine:* Botulinum toxin • *High-frequency episodic migraine (10–14 MHDs):* BSC	• *Chronic migraine:* Botulinum toxin • *High-frequency episodic migraine (10–14 MHDs):* BSC
Treatment effect	• Maintained over time	• Maintained over time • Wanes over 5 years • Wanes over 10 years	*Base case:* • Maintained over time *Scenarios:* • Wanes over 10 years after 12 weeks (ACD scenario) • Wanes over 10 years after 5 years – revised waning assumption (alternative to ACD scenario)
Stopping treatment	Revert to baseline monthly migraine days except non-responders who maintain any benefit seen at 12 weeks	Revert to non-responder monthly migraine days at 12 weeks	Revert to non-responder monthly migraine days at 12 weeks
Drug acquisition costs (per dose)	• Erenumab 70 mg: [redacted] (with confidential PAS) • Erenumab 140 mg: [redacted] (with confidential PAS)	N/A	• Erenumab 70 mg: [redacted] (with confidential PAS) • Erenumab 140 mg: [redacted] (with confidential PAS)

Triptan costs	Triptan injection price reflects the price of oral triptan	Triptan injection price reflects the price of triptan injections	Triptan injection price reflects the price of triptan injections

Abbreviations: BSC: best supportive care; MHD: monthly headache day; N/A: not applicable' NICE: National Institute for Health and Care Excellence; PAS: Patient Access Scheme.

2.4 *Revised Base case results*

2.4.1 ***Revised Base case incremental cost-effectiveness results***

As described in our response to the ACD, we have refocussed the requested population to patients with 10+MHDs (CM and HFEM).

We believe the cost-effectiveness case for erenumab is strong. In the revised base case analyses below, the deterministic and probabilistic ICERs for erenumab vs. botulinum toxin in CM are below £20,000 per QALY. Even in scenario analysis with less extreme assumptions around waning or incorporation of a more conservative 'mid-point' relative effectiveness assumption (odds ratio) for erenumab vs. botulinum toxin, many ICERs remain close to £20,000 per QALY. Additionally, it is important to note that incorporating a mode of administration utility decrement for botulinum toxin significantly improves the cost-effectiveness of erenumab, leading to ICERs of less than £10,000 per QALY irrespective of assumptions around relative effectiveness vs. botulinum toxin and treatment waning.

We acknowledge that the revised ICERs in HFEM are above those usually considered acceptable to NICE and are above the threshold of £20,000 per QALY that the Committee specifically states in the ACD as the acceptable threshold for this appraisal. However, as outlined in our submission, and acknowledged in the ACD, patients with HFEM have a similar migraine burden to those with CM and, in clinical practice, are likely to benefit from treatment to a similar extent as patients with CM, and are also likely to be managed by headache specialists.

Additionally, incorporating a positive discontinuation rule, which is how clinicians anticipate using erenumab, improves the cost-effectiveness of erenumab leading to ICERs of less than £20,000 per QALY in CM and HFEM.

Chronic Migraine

The summary deterministic results for the revised base case for the chronic migraine population are presented in Table 2.

Table 2: Summary deterministic results in the chronic migraine population only versus botulinum toxin, erenumab 140 mg – no waning, full treatment effect vs. botulinum toxin

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

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

High-frequency episodic migraine (HFEM)

The summary deterministic results for the revised base case for the HFEM population are presented in Table 3.

Table 3: Summary deterministic results in the high frequency episodic migraine population i.e. 10-14 MHDs, erenumab 140mg – no waning

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

Abbreviations: BSC: best supportive care; HFEM: high-frequency episodic migraine; ICER: incremental cost-effectiveness ratio; PAS: QALY: quality-adjusted life year.

Whole migraine population (≥ 10 MHDs (HFEM+CM))

The summary deterministic results for the revised base case for the whole population (HFEM+CM) is presented in Table 4. This analysis has been conducted by running the CM and HFEM populations separately as per the base case settings in Table 1 and calculating weighted average total costs and total QALYs by assuming 66% of the population are CM and 34% of the population are HFEM.

Table 4: Summary deterministic results in the whole migraine (HFEM (vs BSC) and chronic migraine (vs botulinum toxin) i.e.≥ 10 MHDs), erenumab 140mg – no waning

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC vs CM and BSC vs botulinum toxin	[redacted]	[redacted]			
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; HFEM: high-frequency episodic migraine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

2.5 *Sensitivity analyses*

2.5.1 ***Probabilistic sensitivity analysis***

Chronic Migraine

In order to avoid an excessive volume of 'new' analysis, probabilistic sensitivity analysis (PSA) has only been run for the chronic migraine population. The probabilistic results for the revised base case for the chronic migraine population are presented in Table 5. The probabilistic results are similar to those estimated in the deterministic base case analysis. Scatter plots of incremental costs and QALYs for erenumab versus botulinum toxin are presented in Figure 1

and the cost-effectiveness acceptability curve for this analysis is shown in Figure 2. When considering a cost-effectiveness threshold of £20,000 per QALY and including the PAS, erenumab 140 mg has a probability of cost-effectiveness of [redacted] against botulinum toxin in the chronic migraine population. When considering a cost-effectiveness threshold of £30,000 per QALY and including the PAS, erenumab 140 mg has a probability of cost-effectiveness of [redacted] against botulinum toxin in the chronic migraine population.

Table 5: Summary probabilistic results in the chronic migraine population only versus botulinum toxin, erenumab 140 mg – no waning, full treatment effect vs. botulinum toxin

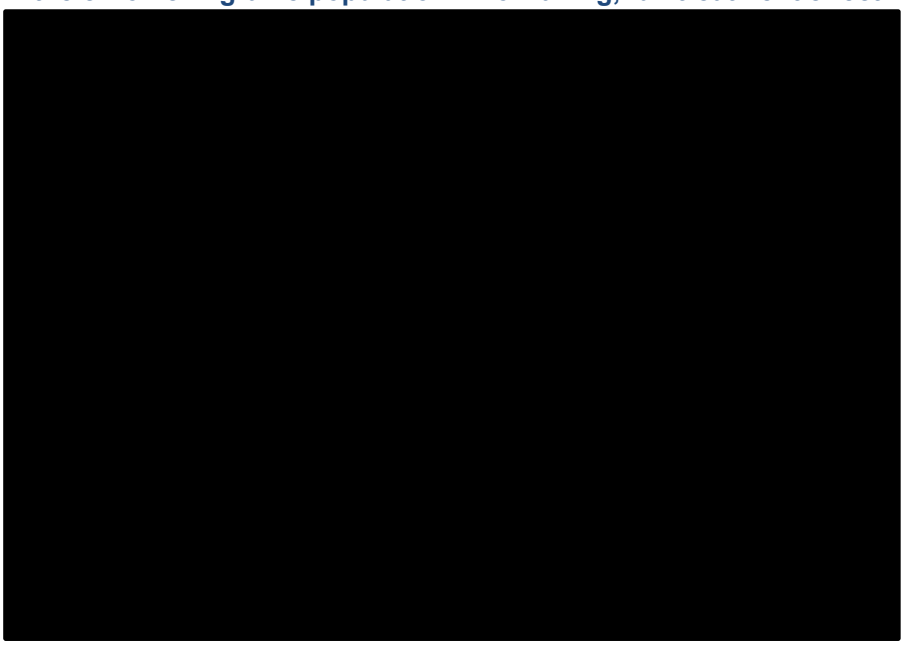
	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
No waning	**Botulinum toxin**	[redacted]	[redacted]			
	Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Figure 1: Cost-effectiveness plane for erenumab 140 mg versus botulinum toxin in the chronic migraine population - no waning, full treatment effect vs botulinum toxin

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 2: Cost-effectiveness acceptability curve for erenumab 140 mg versus botulinum toxin in the chronic migraine population – no waning, full treatment effect vs. botulinum toxin



2.5.1 ***Scenario analyses***

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analyses.

Comparison with botulinum toxin in CM

As requested by the Committee, deterministic results of the scenario assuming no difference in efficacy between erenumab and botulinum toxin in the chronic migraine population are presented in Table 6. This scenario can be selected by using cell D52 on the 'Settings and Summary' Tab to OR=1 in the cost effectiveness model. As highlighted in our main response document, we believe that this is an extreme scenario analysis and these results represent an unrealistic and highly conservative estimate of the incremental cost-effectiveness of erenumab versus botulinum toxin. It is presented solely to illustrate the sensitivity of changes to the odds ratio assumption.

Additionally, as mentioned in Section 1 following a discussion with the NICE technical team we have also presented analysis looking at 'mid-point' odds ratios of erenumab versus botulinum toxin to provide further context. Deterministic and probabilistic results of the scenarios are presented in

Table 7 and Table 8 respectively. This scenario can be selected by using cell D52 on the 'Settings and Summary' Tab to 'Mid-Point' in the cost effectiveness model. These analyses are also presented combined with alternative waning assumption scenarios as described below, to illustrate the combined impact of simultaneously varying these assumptions.

Additionally, as discussed with the NICE technical team (Section 1), in the original submission we provided scenario analysis incorporating a utility decrement associated with the mode of administration of botulinum toxin [see Section B.3.8.3 and Appendix U.2 of the original submission]. A vignette-based time trade off (TTO) utility valuation study was conducted in the UK to derive mode of administration (MoA) decrements for migraine prophylaxis treatments relative to erenumab. In this scenario, the utility decrements represent the average decrease in utility associated with adding each treatment mode to an otherwise identical health state, experienced by a patient. The MoA decrements are applied (additively) to each MMD-specific utility value. The MoA related utility decrement applied to botulinum toxin relative to erenumab is -0.059.

Table 7 of this response summarises the deterministic ICERs when combining the treatment waning and comparison with botulinum toxin assumptions as described above, alongside the administration utility decrement associated with botulinum toxin.

Treatment waning

In response to short-notice clarification questions Novartis provided a scenario analysis exploring long-term effectiveness by adjusting linearly over time the health state costs and health state utilities for erenumab and botulinum toxin to reflect the health state costs and health state utilities associated with BSC non-responders. Treatment waning, in this scenario, was applied from 12 weeks. However, with more time to reflect on this issue given that Novartis has provided longer-term data which shows that treatment benefit of erenumab is maintained over 1 year in open-label studies (52/64 weeks; see ACD response document point 3) applying treatment waning from 12 weeks does not, in hindsight, accurately reflect the available evidence base. Therefore, we have provided alternative waning scenarios applying the treatment waning beginning from year 5 (cycle 22), to further explore alternative treatment waning assumptions. This is in line with appraisals in the progressive disease multiple sclerosis where waning was applied after 5 years treatment[1]. The waning effect is applied from the selected starting time for the waning period of interest to the committee (i.e. 5 or 10 years). For this scenario, the start time of the waning period is selected using the format control at cell D50 in the 'Settings and

Summary Results' tab by selecting either 'No delay' for waning to begin at 12 weeks and 5-years. The duration of waning from this starting time point is then selected using cell F11 in the 'ERG' tab, with '1' for 5 year waning duration and '0' for 10 year waning duration. Deterministic and probabilistic results are presented in

Table 7 and Table 8 for chronic migraine, respectively.

As stated in our main response, we disagree with the application of treatment effect waning in the economic model and do not support use of ICERs based on this assumption for decision-making. This scenario is only relevant as an alternative to the ERG waning scenarios in the ACD and simply illustrates that the ICER is much less impacted if waning is implemented differently.

Positive discontinuation

Continued stakeholder feedback and UK advisory boards have indicated that, in the UK, clinicians would expect to also apply a positive stopping rule to the use of erenumab. Additionally, clinical experts at the committee meeting explained that in practice treatment breaks would be trialled in people responding to treatment. Under such practice, patients who are continuing to benefit from erenumab would not continue to receive erenumab indefinitely, but would undergo "positive discontinuation". Newly published guidelines from the European Headache Foundation support this, citing an expert opinion-level recommendation that anti-CGRP monoclonal antibodies be stopped after 6-12 months of treatment. The expectation is that some people will need to return to erenumab treatment. Incorporation of a positive stopping rule was presented as a scenario analysis in the company submission (scenario 6; further described in Section B.2.2.2 (page 129) and Appendix X to the company submission). In these scenarios at 64.5 weeks, patients entered a "re-evaluation period" health state, in which they remained for 12 weeks, representing a period of assessment. A proportion of patients were assumed to positively discontinue from this health state, whilst the remaining patients returned to an "on treatment" state, from which they re-entered the "re-evaluation period" health state at a later assessment time point. In this scenario re-evaluations occurred periodically, every 76.5 weeks (64.5 weeks + 12 week re-evaluation period between each re-evaluation). This continued throughout the time horizon, with a decreasing number of patients undergoing re-evaluation each time due to movement of some patients to the positive discontinuation state during each re-evaluation. Deterministic results of scenarios including a positive discontinuation scenarios are presented again in Table 9, this time using the revised base case assumptions outlined in Table 1 of this document. In these scenarios MMDs for people who positively discontinue are assumed to be maintained or changed to 12 week placebo MMDs. In the context of application

of a positive stopping rule in UK clinical practice, waning is no longer a relevant consideration as patients would not be expected to receive continuous erenumab treatment in the long-term.

Table 6: Summary deterministic results in the chronic migraine population only versus botulinum toxin, erenumab 140 mg – No benefit over botulinum toxin, no waning

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

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

As stated above, we believe that this is an extreme scenario analysis and these results represent an unrealistic and highly conservative estimate of the incremental cost-effectiveness of erenumab versus botulinum toxin. It is presented (deterministically only) solely to illustrate the sensitivity of changes to the odds ratio assumption.

Table 7: Scenario results for chronic migraine incorporating different efficacy vs. botulinum toxin, treatment waning and utility decrement associated with mode of botulinum toxin administration – deterministic results

	Without applying mode of action utility decrement		Applying mode of action utility decrement	
	Comparison with Botulinum toxin assumption		Comparison with Botulinum toxin assumption	
Treatment waning assumption	Base case ITC	Mid-point ITC	Base case ITC	Mid-point ITC
No waning (Novartis submission assumption)	[redacted]	[redacted]	[redacted]	[redacted]
10 years of waning after 12 weeks (ACD scenario)	[redacted]	[redacted]	[redacted]	[redacted]

10 years of waning after 5 years (revised ACD scenario)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
Further information on how the utility decrement is applied can be found in Section B.3.8.3 of the original submission and Appendix U.2 of the original submission

Table 8: Scenario analysis results in chronic migraine incorporating different efficacy vs. botulinum toxin, treatment waning and utility decrement associated with mode of botulinum toxin administration – probabilistic results

	Without applying mode of action utility decrement		**Applying mode of action utility decrement**	
	Comparison with Botulinum toxin assumption		**Comparison with Botulinum toxin assumption**	
Treatment waning assumption	**Base case ITC**	**Mid-point ITC**	**Base case ITC**	**Mid-point ITC**
No waning (Novartis submission assumption)	[redacted]	[redacted]	[redacted]	[redacted]
10 years of waning after 12 weeks (ACD scenario)	[redacted]	[redacted]	[redacted]	[redacted]
10 years of waning after 5 years (revised ACD scenario)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Table 9: Scenario analysis results for incorporating positive discontinuation – deterministic results

	CM		**HFEM**	
	Maintain MMD improvement	**Change to 12 week placebo MMDs**	**Maintain MMD improvement**	**Change to 12 week placebo MMDs**
Including positive discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; MMD: monthly migraine days; QALY: quality-adjusted life year
Information on how the positive discontinuation is applied is further described in Section B.2.2.2 (page 129) of the company submission and Appendix X to the company submission

Summary

We believe the cost-effectiveness case for erenumab is strong. In the revised base case analyses below, the deterministic and probabilistic ICERs for erenumab vs. botulinum toxin in CM are below £20,000 per QALY. Even in scenario analysis with less extreme assumptions around waning or incorporation of a more conservative 'mid-point' relative effectiveness assumption (odds ratio) for erenumab vs. botulinum toxin, many ICERs remain close to £20,000 per QALY. Additionally, it is important to note that incorporating a mode of administration utility decrement for botulinum toxin significantly improves the cost-effectiveness of erenumab, leading to ICERs of less than £10,000 per QALY irrespective of assumptions around relative effectiveness vs. botulinum toxin and treatment waning.

We acknowledge that the revised ICERs in HFEM are above those usually considered acceptable to NICE and are above the threshold of £20,000 per QALY that the Committee specifically states in the ACD as the acceptable threshold for this appraisal. However, as outlined in our submission, and acknowledged in the ACD, patients with HFEM have a similar migraine burden to those with CM and, in clinical practice, are likely to benefit from treatment to a similar extent as patients with CM, and are also likely to be managed by headache specialists.

Additionally, incorporating a positive discontinuation rule, which is how clinicians anticipate using erenumab, improves the cost-effectiveness of erenumab leading to ICERs of less than £20,000 per QALY in HFEM and CM.

References

1. NICE Technology Appraisal Guidance. Ocrelizumab for treating relapsing–remitting multiple sclerosis TA533. July 2018. https://www.nice.org.uk/guidance/ta533/resources/ocrelizumab-for-treating-relapsingremitting-multiple-sclerosis-pdf-82606899260869

in collaboration with:

Erasmus School of Health Policy & Management

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Erenumab for preventing migraine (addendum 3)

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

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ERG's comments on the Company's response to the ACD

NICE has requested (mail on February 11th, 2019) the ERG to comment on the Company's response to the ACD and their updated analyses. More specifically the following issues were mentioned:

1. The Company's revised base-case and scenarios in relation to the updated PAS price
2. The impact of the assumptions used
3. Is the refocused population (HFEM = 10-14 monthly headache days) sufficiently accounted for in the trial data
4. The incorporation of treatment waning parameters within the analyses
5. The use of a 'mid-point' odds ratio
6. Is the utility decrement applied to Botox within the new analyses reasonable

1. The Company's revised base-case and scenarios in relation to the updated PAS price

In the Company's revised base-case, the following adjustments were implemented (compared to their original base-case):

[redacted]

- Populations considered: chronic migraine and high-frequency episodic migraine (HFFEM) subgroup (10–14 MHDs).
  Originally, the episodic migraine population was also considered and the HFEM subgroup definition was slightly different (8–14 MHDs).
- Comparators: botulinum toxin was considered as comparator for chronic migraine.
  Originally both BSC and botulinum toxin were considered as comparators for chronic migraine.
- Treatment effect extrapolation: assuming the treatment effect is maintained over time.
  This is similar as in the original base-case. However, the impact is increased due to the increased time horizon.
- Erenumab dose: 140mg *(removing the blended dose is consistent with ERG analysis 4)*.
  Originally 70mg as well as the blended dose were also considered.
- Time horizon: lifetime *(consistent with ERG analysis 5)*.
  Originally the time horizon was 10 year.
- Triptan injection price: was assumed to be reflected by the triptan injection price *(consistent with ERG analysis 6)*.
  Originally this was assumed to be reflected by the triptan oral price.
- MMD frequency after treatment discontinuation: all treatment discontinuers are assumed to have the week 12 non-responder MMD frequency *(consistent with ERG analysis 9)*.
  Originally, the MMD frequency for discontinuers was dependent on the nature of treatment discontinuation.

Additional change not mentioned in Table 2 of the document *"ID1188 Erenumab ACD comment appendix Novartis v0.1 310119 SC [ACIC].docx"*:

- Fixing errors (ERG analyses 1-3) adjustments by the ERG (amending the error identified at ERG clarification stage in relation to the conversion between weekly and annual results)

Based on the overview above, it becomes clear that the new base-case proposed by company is consistent with most of the ERG adjustments. However, important differences between the new base-case proposed by company and the ERG base-case, as presented in the ERG report, are:

- The exclusion of BSC as comparator for chronic migraine
- Assuming the treatment effect is maintained over time.

The ERG believes these adjustments are appropriate (as applied in the ERG base-case). Table 1 presents the deterministic results when incorporating these additional adjustments.

Table 1: Deterministic ERG base-case for the chronic migraine population (revised PAS)

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]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To inform the committee regard[redacted] ratio (OR) of erenumab versus botulinum toxin used in the model, the[redacted] analyses as provided above while assuming an OR of 1.0. (see Table 2).

Table 2: Deter[redacted]r the chronic migraine population (revised PAS) + OR = 1.0

Technologies	To[redacted] costs	[redacted]QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effectiveness) + OR = 1.0						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year) + OR = 1.0						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

One of the adjustments made by the company was to change the HFEM subgroup definition. In the original CS and in the included trials, this subgroup was defined as 8-14 MHD. In the Company's response to the ACD this subgroup was defined as 10-14 MHDs. Tables 3 and 4 provide the estimated results using the 10-14 and 8-14 MHD subgroup definitions respectively.

Table 3: Deterministic ERG base-case for the HFEM population (10-14 MHDs; revised PAS)

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]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Superseded see erratum

Table 4: Deterministic ERG base-case for the HF[redacted]s; revised PAS)

Technologies	Total costs	Total QALYs	[redacted]	[redacted]	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming c[redacted]eness)						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (tr[redacted]g over five-year)						
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2. The impact of the assumptions used

In Tables 7-10 of the document *"ID1188 Erenumab ACD comment appendix Novartis v0.1 310119 SC [ACIC].docx"*, the company explored additional scenarios/assumptions. Related to:

- Waning of treatment effect
- OR obtained from the indirect treatment comparison
- Mode of action utility decrement (-0.059 of botulinum toxin relative to erenumab)
- Positive discontinuation

See original ERG report for the ERG's comments regarding the mode of action utility decrement and the positive discontinuation scenario. In short, the evidence to underpin these analyses is considered weak (i.e. an unpublished vignette-based study including mostly general population respondents for the mode of action utility decrement and no evidence for the positive discontinuation). Hence, the plausibility of these scenarios is difficult to determine, making them challenging to interpret.

The ERG acknowledges the substantial uncertainty in the indirect comparison (that is not captured in the 95% confidence interval) due to two main reasons: 1) the different outcome (MHD vs MMD) and; 2) the different time point used for botulinum toxin (compared to Erenumab and BSC). However, whether using the midpoint OR, the original OR or an OR of 1.0 is most plausible to reflect this uncertainty is difficult to determine; no justification was provided for the choice of 'midpoint'. To inform the robustness of the presented results to this uncertainty, the ERG presented analyses using the original OR and an OR of 1.0 in Tables 1 and 2 respectively.

The additional treatment waning scenarios presented by the company were:

- Treatment waning from week 12; treatment waning period of 10 year (similar as scenario analyses 4 presented in the original ERG report).
- Treatment waning from 5 year; treatment waning period of 10 year.

Long-term effectiveness is considered by the ERG as a key uncertainty in this appraisal. After 12 weeks there is no comparative effectiveness evidence and after one year (52 weeks for chronic migraine and after 64 weeks for episodic migraine) there is a complete lack of effectiveness evidence. In addition, the longer-term data from the open label studies are presented for the whole study populations (not those with 3 or more prior treatments or those with HFEM). As argued in the original ERG report (see section 5.2.6 for more details), the ERG believes that, given the absence of evidence related to the long-term effectiveness, it is uncertain whether and to what extent there is waning of the treatment effect. Again, as mentioned above, the plausibility of the presented scenarios is difficult to determine, making them challenging to interpret. To inform the robustness of the presented results to this uncertainty related to the extrapolation of treatment effectiveness, the ERG presented (as in the original ERG report) analyses using 1) constant treatment effectiveness and; 2) treatment waning with a 5-year period (see Table 1).

Please note that other uncertainties (e.g. definition of response to treatment) than those explored by the company have been discussed in the original ERG report.

3. Is the refocused population (HFEM = 10-14 monthly headache days) sufficiently accounted for in the trial data

This 'refocussing', along with limiting the submission to the 140 mg dose only, means that the available data are even fewer (n=36 from STRIVE and n=148 from LIBERTY). All of the available results for the HFEM population can be found in Table 4.11 in the ERG report (only change in MMD and response rate for 50% reduction in MMD are reported). It should be noted that the CS defined the HFEM group, for both the STRIVE and LIBERTY studies, as 8-14 MMD, rather than the 10-14 MHD specified in for the 'refocussed' population, i.e. neither the CS nor the study reports for STRIVE and LIBERTY provide any effectiveness data for a HFEM population defined as 10-14 MHD. Consequently, as mentioned in the original ERG report, for the HFEM population it is assumed that data from patients with MMDs can be used to inform outcomes in patients with MHDs in the economic model. Given that MMDs and MHDs are separate outcomes, this assumption may be invalid. The potential bias caused by this assumption is unclear.

4. The incorporation of treatment waning parameters within the analyses

See sections 1 and 2 as well as the original ERG report.

5. The use of a 'mid-point' odds ratio

See sections 1 and 2.

6. Is the utility decrement applied to Botox within the new analyses reasonable

See sections 2 and the original ERG report.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

ERRATUM to Erenumab for preventing migraine (addendum 3)

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

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Based on the overview above, it becomes clear that the new base-case proposed by company is consistent with most of the ERG adjustments. However, important differences between the new base-case proposed by company and the ERG base-case, as presented in the ERG report, are:

- The exclusion of BSC as comparator for chronic migraine
- Assuming the treatment effect is maintained over time.

The ERG believes these adjustments are appropriate (as applied in the ERG base-case). Table 1 presents the deterministic results when incorporating these additional adjustments.

Table 1: Deterministic ERG base-case for the chronic migraine population (revised PAS)

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]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To inform the committee regarding the impact of the odds ratio (OR) of erenumab versus botulinum toxin used in the model, the ERG performed the same analyses as provided above while assuming an OR of 1.0. (see Table 2).

Table 2: Deterministic ERG base-case for the chronic migraine population (revised PAS) + OR = 1.0

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effectiveness) + OR = 1.0						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year) + OR = 1.0						
BSC	[redacted]	[redacted]				

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

One of the adjustments made by the company was to change the HFEM subgroup definition. In the original CS and in the included trials, this subgroup was defined as 8-14 MHD. In the Company's response to the ACD this subgroup was defined as 10-14 MHDs. Tables 3 and 4 provide the estimated results using the 10-14 and 8-14 MHD subgroup definitions respectively.

Table 3: Deterministic ERG base-case for the HFEM population (10-14 MHDs; revised PAS)

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 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Deterministic ERG base-case for the HFEM population (8-14 MHDs; revised PAS)

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 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2. The impact of the assumptions used

In Tables 7-10 of the document *"ID1188 Erenumab ACD comment appendix Novartis v0.1 310119 SC [ACIC].docx"*, the company explored additional scenarios/assumptions. Related to:

- Waning of treatment effect
- OR obtained from the indirect treatment comparison

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Erenumab for preventing migraine (addendum 3)

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ERG's comments on the Company's response to the ACD

NICE has requested (mail on February 11th, 2019) the ERG to comment on the Company's response to the ACD and their updated analyses. More specifically the following issues were mentioned:

1. The Company's revised base-case and scenarios in relation to the updated PAS price
2. The impact of the assumptions used
3. Is the refocused population (HFEM = 10-14 monthly headache days) sufficiently accounted for in the trial data
4. The incorporation of treatment waning parameters within the analyses
5. The use of a 'mid-point' odds ratio
6. Is the utility decrement applied to Botox within the new analyses reasonable

1. The Company's revised base-case and scenarios in relation to the updated PAS price

In the Company's revised base-case, the following adjustments were implemented (compared to their original base-case):

[redacted]

- Populations considered: chronic migraine and high-frequency episodic migraine (HFFEM) subgroup (10–14 MHDs).
  Originally, the episodic migraine population was also considered and the HFEM subgroup definition was slightly different (8–14 MHDs).
- Comparators: botulinum toxin was considered as comparator for chronic migraine.
  Originally both BSC and botulinum toxin were considered as comparators for chronic migraine.
- Treatment effect extrapolation: assuming the treatment effect is maintained over time.
  This is similar as in the original base-case. However, the impact is increased due to the increased time horizon.
- Erenumab dose: 140mg *(removing the blended dose is consistent with ERG analysis 4)*.
  Originally 70mg as well as the blended dose were also considered.
- Time horizon: lifetime *(consistent with ERG analysis 5)*.
  Originally the time horizon was 10 year.
- Triptan injection price: was assumed to be reflected by the triptan injection price *(consistent with ERG analysis 6)*.
  Originally this was assumed to be reflected by the triptan oral price.
- MMD frequency after treatment discontinuation: all treatment discontinuers are assumed to have the week 12 non-responder MMD frequency *(consistent with ERG analysis 9)*.
  Originally, the MMD frequency for discontinuers was dependent on the nature of treatment discontinuation.

Additional change not mentioned in Table 2 of the document *"ID1188 Erenumab ACD comment appendix Novartis v0.1 310119 SC [ACIC].docx"*:

- Fixing errors (ERG analyses 1-3) adjustments by the ERG (amending the error identified at ERG clarification stage in relation to the conversion between weekly and annual results)

Based on the overview above, it becomes clear that the new base-case proposed by company is consistent with most of the ERG adjustments. However, important differences between the new base-case proposed by company and the ERG base-case, as presented in the ERG report, are:

- The exclusion of BSC as comparator for chronic migraine
- Assuming the treatment effect is maintained over time.

The ERG believes these adjustments are appropriate (as applied in the ERG base-case). Table 1 presents the deterministic results when incorporating these additional adjustments.

Table 1: Deterministic ERG base-case for the chronic migraine population (revised PAS)

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]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To inform the committee regarding the impact of the odds ratio (OR) erenumab versus botulinum toxin used in the model, the ERG performed the same analyses as provided above while assuming an OR of 1.0. (see Table 2).

Table 2: Deterministic ERG base-case for the chronic migraine population (revised PAS) + OR = 1.0

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY) full incremental	ICER (£/QALY) vs BSC
ERG base-case (assuming constant treatment effectiveness) + OR = 1.0						
BSC	[redacted]	[redacted]				
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year) + OR = 1.0						
BSC	[redacted]	[redacted]				

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

One of the adjustments made by the company was to change the HFEM subgroup definition. In the original CS and in the included trials, this subgroup was defined as 8-14 MHD. In the Company's response to the ACD this subgroup was defined as 10-14 MHDs. Tables 3 and 4 provide the estimated results using the 10-14 and 8-14 MHD subgroup definitions respectively.

Table 3: Deterministic ERG base-case for the HFEM population (10-14 MHDs; revised PAS)

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 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Deterministic ERG base-case for the HFEM population (8-14 MHDs; revised PAS)

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 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case (treatment effect waning over five-year)						
BSC	[redacted]	[redacted]				
Erenumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2. The impact of the assumptions used

In Tables 7-10 of the document *"ID1188 Erenumab ACD comment appendix Novartis v0.1 310119 SC [ACIC].docx"*, the company explored additional scenarios/assumptions. Related to:

- Waning of treatment effect
- OR obtained from the indirect treatment comparison

- Mode of action utility decrement (-0.059 of botulinum toxin relative to erenumab)
- Positive discontinuation

See original ERG report for the ERG's comments regarding the mode of action utility decrement and the positive discontinuation scenario. In short, the evidence to underpin these analyses is considered weak (i.e. an unpublished vignette-based study including mostly general population respondents for the mode of action utility decrement and no evidence for the positive discontinuation). Hence, the plausibility of these scenarios is difficult to determine, making them challenging to interpret.

The ERG acknowledges the substantial uncertainty in the indirect comparison (that is not captured in the 95% confidence interval) due to two main reasons: 1) the different outcome (MHD vs MMD) and; 2) the different time point used for botulinum toxin (compared to Erenumab and BSC). However, whether using the midpoint OR, the original OR or an OR of 1.0 is most plausible to reflect this uncertainty is difficult to determine; no justification was provided for the choice of 'midpoint'. To inform the robustness of the presented results to this uncertainty, the ERG presented analyses using the original OR and an OR of 1.0 in Tables 1 and 2 respectively.

The additional treatment waning scenarios presented by the company were:

- Treatment waning from week 12; treatment waning period of 10 year (similar as scenario analyses 4 presented in the original ERG report).
- Treatment waning from 5 year; treatment waning period of 10 year.

Long-term effectiveness is considered by the ERG as a key uncertainty in this appraisal. After 12 weeks there is no comparative effectiveness evidence and after one year (52 weeks for chronic migraine and after 64 weeks for episodic migraine) there is a complete lack of effectiveness evidence. In addition, the longer term data from the open label studies year are presented for the whole study populations (not those with 3 or more prior treatments or those with HFEM). As argued in the original ERG report (see section 5.2.6 for more details), the ERG believes that, given the absence of evidence related to the long-term effectiveness, it is uncertain whether and to what extent there is waning of the treatment effect. Again, as mentioned above, the plausibility of the presented scenarios is difficult to determine, making them challenging to interpret. To inform the robustness of the presented results to this uncertainty related to the extrapolation of treatment effectiveness, the ERG presented (as in the original ERG report) analyses using 1) constant treatment effectiveness and; 2) treatment waning with a 5-year period (see Table 1).

Please note that other uncertainties (e.g. definition of response to treatment) than those explored by the company have been discussed in the original ERG report.

3. Is the refocused population (HFEM = 10-14 monthly headache days) sufficiently accounted for in the trial data

This 'refocussing', along with limiting the submission to the 140 mg dose only, means that the available data are even fewer (n=36 from STRIVE and n=148 from LIBERTY). All of the available results for the HFEM population can be found in Table 4.11 in the ERG report (only change in MMD and response rate for 50% reduction in MMD are reported). It should be noted that the CS defined the HFEM group, for both the STRIVE and LIBERTY studies, as 8-14 MMD, rather than the 10-14 MHD specified in for the 'refocussed' population, i.e. neither the CS nor the study reports for STRIVE and LIBERTY provide any effectiveness data for a HFEM population defined as 10-14 MHD. Consequently, as mentioned in the original ERG report, for the HFEM population it is assumed that data from patients with MMDs can be used to inform outcomes in patients with MHDs in the economic model.

Given that MMDs and MHDs are separate outcomes, this assumption may be invalid. The potential bias caused by this assumption is unclear.

4. The incorporation of treatment waning parameters within the analyses

See sections 1 and 2 as well as the original ERG report.

5. The use of a 'mid-point' odds ratio

See sections 1 and 2.

6. Is the utility decrement applied to Botox within the new analyses reasonable

See sections 2 and the original ERG report.

Further analyses from ERG request

ERG base-case for chronic migraine (deterministic)

ERG deterministic results (erenumab 140 mg)	ICER (£/QALY)*
1. Constant treatment effectiveness (no waning)	[redacted]
2. Constant treatment effectiveness and equivalent effectiveness with botox (OR = 1)	[redacted]
3. Treatment waning over 5 years	[redacted]
4. Treatment waning over 5 years and equivalent effectiveness with botox (OR = 1)	[redacted]
5. Treatment waning over 10 years	[redacted]
6. Treatment waning over 10 years and equivalent effectiveness with botox (OR = 1)	[redacted]

* Fully incremental ICERs

** ICER compared with botox

ERG base-case for HFEM (deterministic)

ERG deterministic results (erenumab 140 mg)	ICER (£/QALY)*
1. HFEM = 10-14 MHDs, constant treatment effectiveness (no waning)	[redacted]
2. HFEM = 10-14 MHDs, waning over 5 years	[redacted]
3. HFEM = 10-14 MHDs, waning over 10 years	[redacted]
4. HFEM = 8-14 MHDs, constant treatment effectiveness (no waning)	[redacted]
5. HFEM = 8-14 MHDs, waning over 5 years	[redacted]
6. HFEM = 8-14 MHDs, waning over 10 years	[redacted]

* ICERs compared with BSC

ERG base-case for chronic migraine (probabilistic)

ERG probabilistic results (erenumab 140 mg)	ICER (£/QALY)*
1. Constant treatment effectiveness (no waning)	[redacted]
2. Constant treatment effectiveness and equivalent effectiveness with botox (OR = 1)	[redacted]
3. Treatment waning over 5 years	[redacted]
4. Treatment waning over 5 years and equivalent effectiveness with botox (OR = 1)	[redacted]
5. Treatment waning over 10 years	[redacted]
6. Treatment waning over 10 years and equivalent effectiveness with botox (OR = 1)	[redacted]

* Fully incremental ICERs
** ICER compared with botox

ERG base-case for HFEM (probabilistic)

ERG probabilistic results (erenumab 140 mg)	ICER (£/QALY)*
1. HFEM = 10-14 MHDs, constant treatment effectiveness (no waning)	[redacted]
2. HFEM = 10-14 MHDs, waning over 5 years	[redacted]
3. HFEM = 10-14 MHDs, waning over 10 years	[redacted]
4. HFEM = 8-14 MHDs, constant treatment effectiveness (no waning)	[redacted]
5. HFEM = 8-14 MHDs, waning over 5 years	[redacted]
6. HFEM = 8-14 MHDs, waning over 10 years	[redacted]

* ICERs compared with BSC

As discussed previously, given the difference between the deterministic and probabilistic results for the HFEM subgroup, the ERG would not be comfortable to present the probabilistic results for the HFEM subgroup.

Scenario analyses based on 30% response definition

ERG base-case for chronic migraine (deterministic)

ERG deterministic results (erenumab 140 mg)	ICER (£/QALY)*
1. Constant treatment effectiveness (no waning; 30% response definition)	[redacted]
2. Treatment waning over 5 years (30% response definition)	[redacted]
3. Treatment waning over 10 years (30% response definition)	[redacted]

* Fully incremental ICERs
*** ICER compared with BSC

ERG base-case for chronic migraine (probabilistic)

ERG probabilistic results (erenumab 140 mg)	ICER (£/QALY)*
1. Constant treatment effectiveness (no waning; 30% response definition)	[redacted]
2. Treatment waning over 5 years (30% response definition)	[redacted]
3. Treatment waning over 10 years (30% response definition)	[redacted]

* Fully incremental ICERs
** ICER compared with botox
*** ICER compared with BSC

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

Pro-forma Response

ERG report

Erenumab for preventing migraine [ID1188]

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

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 8 April** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inaccurate description of evidence provided

Description of problem	Description of proposed amendment	Justification for amendment
Addendum 3, page 2 and heading 3, page 5 Inaccurate description of the "refocussed" Novartis population	We suggest the following amends to clarify that the "refocussing" only applies to the episodic component of the migraine population. The chronic migraine component remains unchanged. Page 2: 3. Is the refocused episodic migraine population (HFEM = 10-14 monthly headache days) sufficiently accounted for in the trial data Page 5: **3. Is the refocused episodic migraine population (HFEM = 10-14 monthly headache days) sufficiently accounted for in the trial data**	Accurate description of the "refocussed" population to provide clarity.
Inaccurate description of available evidence. Addendum 3, page 5, 1st paragraph: *In short, the evidence to underpin these analyses is considered weak (i.e. an **unpublished** vignette-based study including **mostly general population respondents** for the mode of action utility decrement and **no evidence for the positive discontinuation**).*	Please remove or amend this statement: ~~*In short, the evidence top underpin these analyses is considered weak (i.e. an **unpublished** vignette-based study including **mostly general population respondents** for the mode of action utility decrement and **no evidence for the positive discontinuation**).*~~	The utility study was published in abstract/poster format at ISPOR 2018. It has now been published: Matza, et al. Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences Quality of Life Research; 2019 Mar 28. Additionally, the study was conducted with 400 participants of which 50% were general population participants and 50% were migraine population participants and

		therefore did not include 'mostly' general population respondents[1]. As detailed in the ACD response, there is evidence for positive discontinuation: • Please see: o ACD response template point, page 5 o ACD response appendix page 9-10 • Using positive discontinuation is how clinical experts at the 1st Appraisal Committee (AC) meeting described how they would treat people with erenumab • It is supported by European Guidelines from the European Headache Foundation citing an expert opinion-level recommendation that anti-CGRP monoclonal antibodies be stopped after 6-12 months of treatment[2] Additionally, UK BASH guidelines recommends the withdrawal of effective treatment to establish continued need in migraine prophylaxis management[3]. Similarly, NICE Clinical Guidelines recommend reviewing the need to continue migraine prophylaxis[4]. The Aimovig SmPC also states[5]; *Clinical studies have demonstrated that the majority of patients responding to therapy*

		showed clinical benefit within 3 months. Consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter. 1. Matza, LS et al. Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. Qual Life Res; 2019;Mar28. 2. Sacco S, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain. 2019 Jan 16;20(1):6. 3. British Association for the Study of Headache. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type Headache, Cluster Headache and Medication-Overuse Headache (3rd Edition). United Kingdom: British Association for the Study of Headache, 2010. 4. National Institute for Health and Care Excellence. CG150: Headaches in over 12s: diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg150. Last accessed: 06/04/18 5. Aimovig Summary of Product Characteristics
A justification for the choice of midpoint OR was provided. Addendum 3, page 5, 2nd paragraph: *However, whether using the midpoint OR, the original OR or an OR of 1.0 is most*	Please amend as follows: *However, whether using the midpoint OR, the original OR or an OR of 1.0 is most plausible to reflect this uncertainty is difficult to determine; ~~no justification was provided for the choice of 'midpoint'~~.*	A justification for the midpoint was provided in the pg 7 ACD response template and the appendix document: *ACD response template:* Novartis also present results in the Appendix whereby the difference between the two treatments represents a midpoint between the

*plausible to reflect this uncertainty is difficult to determine**; no justification was provided for the choice of 'midpoint'.***		odds ratio of the ITC (Section B.2.8.2 of the company submission), and an odds ratio of 1 (an assumption of equal efficacy, as per the Committee-requested scenario analysis). *Appendix document:* However, as this [an OR of 1.0] represents an extreme scenario the NICE technical team agreed that it would be reasonable for Novartis to provide analysis in its response based on 'mid-point' odds ratio to illustrate how the cost-effectiveness changes in response to a less extreme assumption.
Addendum 3, page 5. The plausibility of the alternative treatment waning scenarios provided by Novartis in the ACD response appendix is no different to the plausibility of other waning scenarios proposed by the ERG. There appears to be no consideration for the additional information provided by Novartis in the ACD response documents as to why treatment waning may not be applicable.	Please update this section: *As argued in the original ERG report (see section 5.2.6 for more details), the ERG believes that, given the absence of evidence related to the long-term effectiveness, it is uncertain whether and to what extent there is waning of the treatment effect. Again, as mentioned above, the plausibility of ~~the~~ <u>all</u> presented scenarios is difficult to determine, making them challenging to interpret. To inform the robustness of the presented results to this uncertainty related to the extrapolation of treatment effectiveness, the ERG presented (as in the original ERG report) analyses using 1) constant treatment effectiveness and; 2) treatment waning with a 5-year period (see Table 1).* The plausibility of the Novartis alternative waning scenarios should be considered, as they are no more challenging to interpret than existing waning scenarios. Consideration of the additional evidence provided in ACD response document on reasons why treatment waning is not	The plausibility of the scenarios provided by Novartis in the ACD response appendix is no different to the plausibility of other waning scenarios proposed by the ERG where waning starts at 12 weeks: as the ERG states "it is uncertain **whether** and **to what extent** there is waning of treatment effect". Indeed, there may be greater plausibility for the Novartis alternative waning scenarios as there is evidence that the efficacy of erenumab is maintained for 52 weeks in CM and 64 weeks in EM. Additionally, a clinical expert at the AC meeting stated there was no reason to believe treatment effect would wane over time. Therefore, the alternative suggestions from Novartis should be presented and discussed.

	applicable and alternative waning scenarios should also be included.	at the 2nd AC meeting is considered to ensure all relevant evidence and clinical expert opinion is sought on this issue. This will enable the committee have all relevant information at their disposal to inform decision-making.
Inaccurate description of scenarios presented Addendum 3, page 5: *Please note that other uncertainties **(e.g. definition of response to treatment)** than those explored by the company have been discussed in the original ERG report.*	This sentence should be amended: *Please note that ~~other~~ uncertainties ~~(e.g. definition of response to treatment)~~ other than those explored by the company have been discussed in the original ERG report.*	The response rates the committee concluded on at the 1st AC meeting (ACD, page 6) have been used in the revised analyses: 30% in reduction in MMDs for chronic migraine and 50% reduction in MMDs in the episodic migraine population.
Inaccurate description of available efficacy data Addendum 3, page 5: *Long-term effectiveness is considered by the ERG as a key uncertainty in this appraisal. After **12** weeks there is no comparative effectiveness evidence and after one year (52 weeks for chronic migraine and after 64 weeks for episodic migraine) there is a complete lack of effectiveness evidence.*	This sentence should be amended: *Long-term effectiveness is considered by the ERG as a key uncertainty in this appraisal. After ~~12~~ 24 weeks there is no comparative effectiveness evidence and after one year (52 weeks for chronic migraine and after 64 weeks for episodic migraine) there is a complete lack of effectiveness evidence.*	In the STRIVE study the double-blind treatment phase was 24 weeks[1]. 1. Goadsby, PJ etal. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017 Nov 30;377(22):2123-2132.

Issue 2 Description of ICERs and clarity regarding comparator

Description of problem	Description of proposed amendment	Justification for amendment
Table 1 in Addendum 3, page 3 and Table 1 and 3 in Addendum 4 page 1. In revised analyses in the CM population, Novartis conducted the comparison of erenumab 140mg vs botulinum toxin only as the ACD stated: *The committee concluded that botulinum toxin type A or another oral preventive treatment were the relevant comparators in chronic migraine* Since the ACD did not state BSC was an appropriate comparator for CM fully incremental analysis including BSC and botulinum toxin was not provided. Some ICERs e.g. ICERs for constant treatment effectiveness (no waning) and treatment effect waning over 5 years in Table 1 of addendum 4 are vs botulinum toxin and some are vs BSC. This makes the tabulated results unclear for decision makers.	In addendum 4 clarity should be provided for the committee stating which ICERs are ICERs for erenumab vs BSC and which are for erenumab vs botulinum toxin. Novartis recommends that all ICERs versus botulinum toxin are presented based on the committee's conclusion.	If ICERs are reported without clarity regarding the comparison on which they are based, this will create confusion for the appraisal committee and stakeholders in the process. Novartis recommends that all ICERs versus botulinum toxin are presented based on the committee's conclusion on comparators in the ACD.

Issue 3 Incorrect ICERS reported

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr><td>Incorrect results reported in Addendum 3, Table 3, page 4,</td><td>Changes required in Table 3 marked below:
<table>
<tr><th>Technologies</th><th>Total costs</th><th>Total QALYs</th><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (£/QALY) full incremental</th><th>ICER (£/QALY) vs BSC</th></tr>
<tr><td colspan="7">ERG base-case (assuming constant treatment effectiveness)</td></tr>
<tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Erenumab 140mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="7">ERG base-case (treatment effect waning over five-year)</td></tr>
<tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Erenumab 140mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>Correction of incorrectly reported results.</td></tr>
<tr><td>Incorrect results reported in Addendum 3, Table 4, page 4,</td><td>Changes required in Table 4 marked below:

Table 4: Deterministic ERG base-case for the HFEM population (8-14 MHDs; revised PAS)
<table>
<tr><th>Technologies</th><th>Total costs</th><th>Total QALYs</th><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (£/QALY) full incremental</th><th>ICER (£/QALY) vs BSC</th></tr>
<tr><td colspan="7">ERG base-case (assuming constant treatment effectiveness)</td></tr>
</table></td><td>Correction of incorrectly reported results. It appears that the results presented are based on a ≥30% MMD reduction response rule, rather than the ≥50 MMD response rule as preferred by the appraisal committee for episodic migraine.</td></tr>
</table>

	<table><tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr><tr><td>Erenumab 140mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td colspan="7">ERG base-case (treatment effect waning over five-year)</td></tr><tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr><tr><td>Erenumab 140mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>	
Incorrect results reported in Addendum 4, Table 2, page 1 and 2	1. Please provide the ICERs for sections 3 and 6 in the table below: **ERG base-case for HFEM** Deterministic results incorporating the company's adjustments <table><tr><th>ERG deterministic results (erenumab 140 mg)</th><th>ICER (£/QALY)*</th></tr><tr><td>1. HFEM = 10-14 MHDs, constant treatment effectiveness (no waning)</td><td>[redacted]</td></tr><tr><td>2. HFEM = 10-14 MHDs, waning over 5 years</td><td>[redacted]</td></tr><tr><td>3. HFEM = 10-14 MHDs, waning over 10 years</td><td>[redacted]</td></tr><tr><td>4. HFEM = 8-14 MHDs, constant treatment effectiveness (no waning)</td><td>[redacted]</td></tr></table>	Correction of incorrectly reported results. It appears that the results presented are based on a >30% MMD reduction response rule, rather than the >50% MMD response rule as preferred by the appraisal committee for episodic migraine

	5. HFEM = 8-14 MHDs, waning over 5 years	[redacted]	
	6. HFEM = 8-14 MHDs, waning over 10 years	[redacted]	
	* ICERs compared with BSC		

Issue 4 Lack of inclusion of all relevant data for discussion at the 2nd AC meeting

Description of problem	Description of proposed amendment	Justification for amendment
Addendum 4 does not include all relevant and reasonable evidence for discussion at the 2nd AC Meeting.	Addendum 3 and 4 should include ICERs for the following scenarios: • Positive discontinuation • Alternative treatment waning • Utility decrement associated with mode of botulinum toxin administration • Mid-point odds ratio scenarios for comparison with botulinum toxin We suggest the ICERs in the tables below would be informative to present in addendum 4. **ERG base-case for chronic migraine**	Novartis has concerns that by omitting these scenarios the Committee will not be presented with the full body of reasonable evidence that characterises the uncertainty, and that this would prevent the appraisal process and decision-making from being conducted fairly.

Deterministic results incorporating the company's adjustments	ICER (£/QALY)* vs Botox
1. Constant treatment effectiveness (no waning)	[redacted]
2. Constant treatment effectiveness and equivalent effectiveness with botox (OR = 1)	[redacted]
3. Constant treatment effectiveness and mid-point effectiveness with botox (OR = midpoint)	[redacted]
4. Treatment waning starting at 5 years and waning over 10 years	[redacted]
5. Positive discontinuation	[redacted]
6. Utility decrement	[redacted]

ERG base-case for HFEM
Deterministic results incorporating the company's

adjustments

ERG deterministic results (erenumab 140 mg)	ICER (£/QALY) vs BSC
1. HFEM = 10-14 MHDs, constant treatment effectiveness (no waning)	[redacted]
2. HFEM = 10-14 MHDs, waning starting at 5 years and waning over 10 years	[redacted]
3. HFEM = 10-14 MHDs, positive discontinuation	[redacted]
4. HFEM = 8-14 MHDs, constant treatment effectiveness (no waning)	[redacted]
5. HFEM = 8-14 MHDs, waning starting at 5 years and waning over 10 years	[redacted]
6. HFEM = 8-14 MHDs, positive discontinuation	[redacted]

Issue 5 Inaccurate description of company adjustments in addendum 4

Description of problem	Description of proposed amendment	Justification for amendment
The title of tables in addendum 4 states that the results are incorporating the company adjustments. However, many of the scenarios presented e.g. OR of 1 in the comparison with botulinum toxin and ERG preferred treatment waning are not those adjustments proposed by the company.	The title of tables should be updated and the company proposed scenarios should be included See also “Issue 4” for suggestions on amendments	Inaccurate description of the scenarios being presented in Addendum 4. Company scenarios provided by Novartis should be included in addendum 4 to ensure that the process is conducted fairly and there is full discussion of all reasonable evidence at the 2nd AC Meeting.

Further deterministic analyses requested by NICE 2

All analyses are deterministic and conditional on the ERG base-case (see original ERG report)
+ new PAS
+ effectiveness response criteria set to 30%
+ assumptions highlighted in the Tables

ICER*	Without mode of administration related utility decrement			
	Without positive discontinuation assumption		With positive discontinuation assumption	
	Botox OR based on ITC	Botox OR = 1	Botox OR based on ITC	Botox OR = 1
No treatment waning	[redacted]	[redacted]	[redacted]	[redacted]
5 year treatment waning	[redacted]	[redacted]	[redacted]	[redacted]
10 year treatment waning	[redacted]	[redacted]	[redacted]	[redacted]

* Fully incremental ICERs
** ICER for erenumab 140mg compared with botox
*** ICER for erenumab 140mg compared with BSC

ICER*	With mode of administration related utility decrement			
	Without positive discontinuation assumption		With positive discontinuation assumption	
	Botox OR based on ITC	Botox OR = 1	Botox OR based on ITC	Botox OR = 1
No treatment waning	[redacted]	[redacted]	[redacted]	[redacted]
5 year treatment waning	[redacted]	[redacted]	[redacted]	[redacted]
10 year treatment waning	[redacted]	[redacted]	[redacted]	[redacted]

* Fully incremental ICERs
** ICER for erenumab 140mg compared with botox
*** ICER for erenumab 140mg compared with BSC

Additional Cost-Effectiveness Analyses

1.1 *Introduction*

Following agreement from the NICE team, new evidence is being submitted by Novartis for committee consideration, as follows:-

1. Cost-effectiveness analyses incorporating a revised discontinuation-based approach to account for the theoretical loss of efficacy/waning of treatment effect that is currently preferred by the appraisal committee (see section 1.2 for methodology & 1.6 for results)
2. New 4.5 year clinical data that supports the long-term maintenance of treatment effect of erenumab (see section 1.3)

This document provides a concise summary of this new evidence. If any further information or clarity is required, we are happy to provide this.

1.2 *Loss of Efficacy/Waning of Treatment Effect*

In the waning scenarios considered in the erenumab appraisal to date (e.g. the ERG 5 and 10 year waning scenarios), health state costs and health state utilities were waned for responder patients. However, treatment was not discontinued as efficacy waned; therefore, **treatment costs continued to accrue over the long term**. Novartis believes this is an extreme scenario as clinical expert feedback in the NICE process to date is that treatment should be discontinued if patients no longer experience a clinically meaningful benefit. Additionally, waning of treatment effect was applied from 12 weeks, whereas emerging evidence supports the maintenance of erenumab efficacy in open-label studies for up to 4.5 years (see section 1.3).

Following a discussion with the NICE technical team on 4th July 2019, it was agreed that it would be reasonable for Novartis to provide an alternative scenario in which patients experiencing loss of efficacy **discontinue treatment and therefore no longer accumulate treatment costs**.

Implementation of this **scenario** in the model is described as follows:-

Original model version (all-cause discontinuation rate already accounts for patient withdrawal from treatment for any reason, including a small proportion due to loss of efficacy):

- In the original model, patients discontinue erenumab if they no longer experience a clinically meaningful response to treatment (i.e. negative discontinuation).
- This is reflected by modelling discontinuation of non-responders at the assessment time point (at 12 weeks), and modelling a further **2.38% all-cause discontinuation rate every 12 weeks which reflects withdrawal of responder patients from treatment over the long-term for any cause, including a small proportion for loss of efficacy**.
- These patients experience negative discontinuation and thereby lose both the benefits and costs of erenumab treatment.

- Therefore, the cost-effectiveness analysis already accounts for the potential for loss of efficacy in a small number of patients over the long-term, and appropriately addresses this by modelling in line with SmPC requirements to assess treatment benefit on an ongoing basis.

Updated model version to address committee concerns about treatment waning (as per original model version, plus additional discontinuation rate applied to illustrate the cost-effectiveness impact of more patients discontinuing treatment due to loss of efficacy):

- The model version we adapted for these analyses is the version supplied to Novartis by NICE on 25th July 2019 with the file name "ID1188 erenumab ERG analyses 08112018_NOVARTIS_Response 250719 AIC CIC".
- It is important to note that beyond the assessment period there is no way for the erenumab model to track individual patient MMDs. Therefore, it is not possible in the current model structure to track individual patient changes in MMDs and discontinue individual patients when they experience loss of response.
- Therefore, **the approach taken to account for additional discontinuation due to loss of efficacy was to implement an additional discontinuation rule solely to assess the impact of a higher treatment discontinuation rate (i.e. in addition to the 2.38% all-cause discontinuation rate described above).**
- A percentage of responder patients who experience loss of efficacy move from the "responders" health state to the "long-term negative discontinuation health state".
- There is no empirical evidence for a loss of efficacy to inform a model input value for the probability of this transition. Therefore, loss of efficacy is applied to responders at an assumed annual rate of 10% to account for the potential loss of efficacy in the absence of evidence. Similar rates were used in previous NICE HTAs for other lifetime chronic conditions (asthma TA431, psoriasis TA521, ankylosing spondyloarthritis TA383, multiple sclerosis TA535).
- The annual rate is adjusted to accommodate the model cycle length of 12 weeks. **Discontinuation due to loss of efficacy is applied at discrete intervals of 48 weeks (the closest to 52 weeks that can be achieved with a 12 week cycle length) at a rate of 9.24% (equivalent to an annual rate of 10%)** (This setting isturned on using cell D55 in "Settings and summary results" tab; annual discontinuation rate is in cell D32 in the "Long-term transitions" tab)
- Applying loss of efficacy continuously per cycle (every 12 weeks) was considered. However, based on clinical expert feedback that patients will be reviewed annually, application at discrete intervals of 48 weeks is more closely reflective of clinical practice.
- Loss of efficacy is applied to all treatment arms. The time loss of efficacy starts may be varied by from 48, 96, 144, 196 or 240 weeks (This setting is changed using cell D58 in "Settings and summary results" tab).
- These assumptions used to reflect discontinuation due to loss of efficacy have been validated through discussions with 3 headache specialists in England.

1.3 *Clinical Evidence of Long-Term Treatment Effect*

Since the last Appraisal Committee (AC) meeting, further evidence on the long-term benefit of erenumab has been published. These data are from 3 and 4.5 year interim analyses of a 5 year episodic migraine (EM) open-label extension of study NCT01952574 (cited on p112 of the Novartis submission Document B). These data provide further evidence, in addition to that previously provided in Novartis' response documents to NICE post-submission, that there is **maintenance of erenumab treatment effect in the long-term and no evidence of loss of treatment efficacy**. The longest-term data considered by the AC to date are 52 weeks of open-label data in CM and 64 weeks in EM; these new data provide open-label data up to 4.5 years. A summary of the 3 and 4.5 year data is provided below.

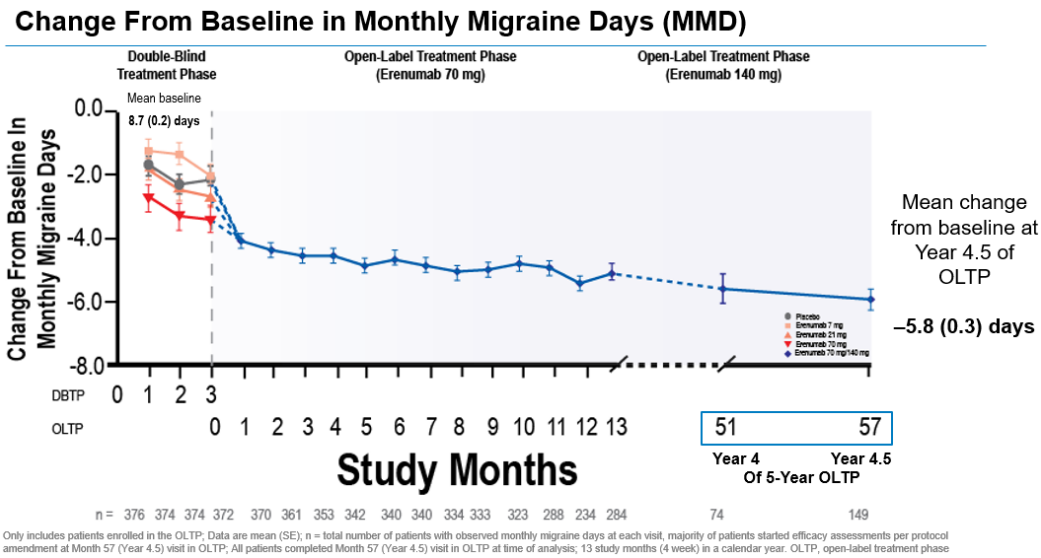
- **3 year data:** Ashina, M. et al. Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. Cephalalgia. 2019 May 30; Epub ahead of print[1]

  383 people entered the open-label treatment phase on erenumab 70mg, all those remaining on treatment after a median of 2 years (n=250) were switched to erenumab 140mg. Of the 250 patients on erenumab 140mg, 236 patients remained on treatment at the time of the 3 year interim safety analysis. 5.6% of people discontinued from 140mg dose, 0% due to lack of efficacy[2].

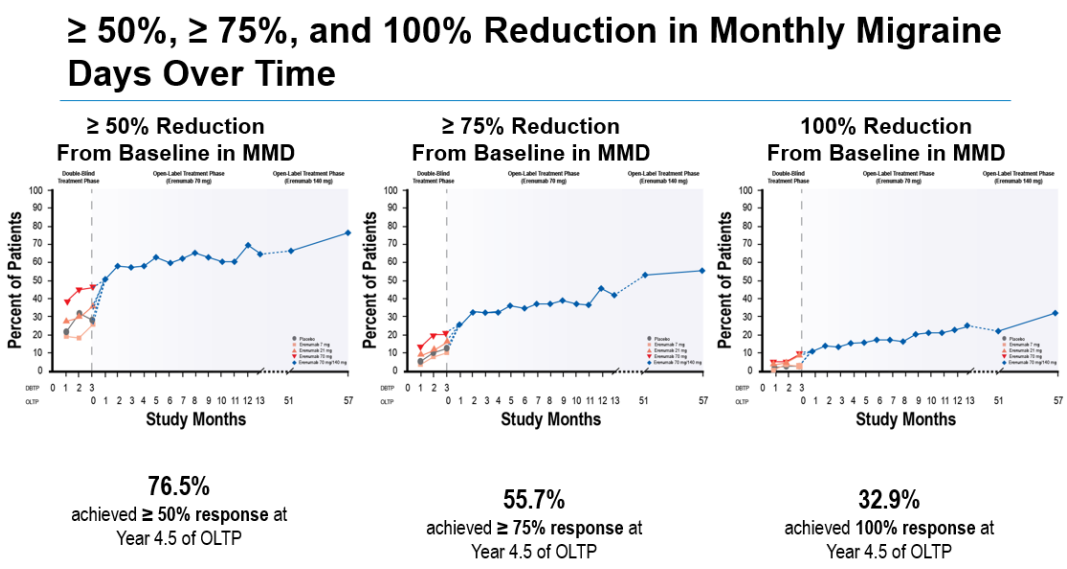
- **4.5 year data:** Ashina, M. et al. Sustained Efficacy and Long-Term Safety of Erenumab in Patients With Episodic Migraine: 4+-Year Results of a 5-Year, Open-Label Treatment Period. Presentation at American Headache Society, 61st Annual Meeting; Philadelphia, PA; July 11–14, 2019[2]

  250 people received erenumab 140mg during the open-label treatment phase and 221 patients remained on treatment at the time of the 4.5 year pre-planned analysis. 7.6% of people discontinued from 140mg dose treatment in 4.5 year the open-label treatment phase, 0% due to lack of efficacy[2].

The reduction in MMDs is at least maintained and potentially continues to increase, during the open-label treatment phase, as presented in the graphs below. This provides long-term data over a number of years in support of a lack of waning with erenumab:



Abbreviations: OLTP, open-label treatment phase



Abbreviations: OLTP, open-label treatment phase

1.4 *Base Case Model Assumptions*

Base case assumptions applied in the model are:

- **Population:** Adults with chronic migraine for whom ≥3 prior prophylactic treatments have failed
- **Analysis:** Incremental
- **Comparators:** BSC and botulinum toxin
- **Erenumab Dose:** 140mg
- **Time horizon:** Lifetime
- **Relative efficacy vs. botulinum toxin:** ITC, mid-point, OR=1

- **Response assessment:** 30% reduction in monthly migraine days (MMDs)
- **Additional treatment discontinuation due to loss of efficacy (applies to row 2 in results table only):** 9.24% discontinuation rate applied every 4 cycles (every 48 weeks) (discontinuation rates are equivalent to an annual discontinuation of 10%) starting at week 48

1.5 *Results*

As requested by the NICE technical team, analyses are provided for the CM population only.

Table 1: Summary base case deterministic results in the chronic migraine population only, erenumab 140 mg

	Scenario Type	Loss of Efficacy/Waning Assumption	Relative efficacy versus Botulinum toxin assumption		
			ITC	Mid-point	No benefit
1	All-cause discontinuation (small proportion due to loss of efficacy)	2.38% all-cause discontinuation per 12 week cycle already included **Novartis base case**	[redacted]	[redacted]	[redacted]
2	As per scenario 1 plus additional discontinuation of treatment due to loss of efficacy	2.38% all-cause discontinuation per 12 week cycle already included AND Additional discontinuation every 4 cycles (based on 10% annual rate) (see section 1.2) **New Novartis scenario**	[redacted]	[redacted]	[redacted]
3	As per scenario 1 plus treatment waning i.e. loss of efficacy and no additional discontinuation	5 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]
		10 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]

		10 years of waning after 5 years **Novartis variant of ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]

** ICER for erenumab 140mg compared with Botox

*** ICER for erenumab 140mg compared with BSC

1.6 *Other Scenarios/Sensitivity Analyses (See Appendices for Completeness)*

- **Pairwise analyses:** As requested by the NICE technical team, pairwise cost-effectiveness analyses are provided in Appendix A.
- **Varying additional rate of treatment discontinuation due to loss of efficacy:** Scenarios analysis using alterative discontinuation rates of 5% and 20% annually are provided in Appendix B and C.
- **Delayed onset of loss of efficacy:** Delaying the application of the additional discontinuation rate due to loss of efficacy from 48 weeks to 192 weeks based on the available evidence from open-label extension studies demonstrating treatment benefit is maintained over 4.5 years. Scenarios are presented in Appendix D.

1.7 *Conclusions*

Novartis does not support inclusion of waning assumptions in the economic model for erenumab in which treatment costs continue to accrue over the long-term. We believe that loss of efficacy is already appropriately accounted for in the modelling by incorporation of a 2.38% all-cause discontinuation rate every 12 week cycle, which includes a small proportion of patients discontinuing due to loss of efficacy.

However, we recognise that the committee has concerns about the uncertainty regarding long-term effectiveness of erenumab and hope that the new 4.5 year open-label extension data provided in this response helps to address some of these concerns. These data provide evidence that supports the maintenance of the treatment effect of erenumab up to 4.5 years, with no discontinuations due to loss of efficacy in the open-label phase of this study up to this time-point. This supports that additional loss of efficacy assumptions in the economic model for erenumab are not appropriate.

Nevertheless, in an attempt to address any remaining uncertainty, we have developed a scenario in the economic model in which it is assumed that any additional patients who experience a loss of treatment efficacy are discontinued every 48 weeks (annual discontinuation rate of 10%, as per appraisals of other biologics). We consider this to be more appropriate than the ERG waning scenarios considered to date in which efficacy is waned but treatment costs continue to accrue as responsible clinicians would not allow patients to lose all response over several years before discontinuing a treatment.

Cost-effectiveness results with this 'additional discontinuation due to loss of efficacy', show that ICERs decrease slightly vs. those in the 'no waning' scenario. This is the expected result given that treatment costs are lower in this new scenario. **ICERs are significantly lower than those in the ERG waning scenarios (rows 3-5 in the results table),** which again is expected given that treatment costs are no longer accrued over the long-term.

In conclusion, in scenarios where at least some ITC benefit vs. Botox is assumed, the ICERs for erenumab remain below £20,000 per QALY (e.g. mid-point ITC benefit & discontinuation-based waning; ICER = [redacted] per QALY gained). This remains the case when the rate of rate of 'additional discontinuation due to loss of efficacy' is varied in sensitivity analysis or if the onset of discontinuation is delayed. Additionally, outside of direct efficacy benefits as evaluated by the ITC, erenumab is also associated with further benefits versus botulinum toxin e.g. reduced burden of administration and benefits to service capacity.

If erenumab was to be recommended following consideration of the analyses with 'additional discontinuation due to loss of efficacy', it would be reasonable for guidance to reflect that erenumab treatment should only be continued if response is maintained and that this should be assessed annually, in line with NICE guidance for some other biologics.

References

1. Ashina, M. et al. Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. Cephalalgia. 2019 May 30; Epub ahead of print
2. Ashina, M. et al. Sustained Efficacy and Long-Term Safety of Erenumab in Patients With Episodic Migraine: 4+-Year Results of a 5-Year, Open-Label Treatment Period. Presentation at American Headache Society, 61st Annual Meeting; Philadelphia, PA; July 11–14, 2019

2 Appendices

2.1 *Appendix A – Pairwise analysis*

Assumptions applied in the model are summarised below:

- **Population:** Adults with chronic migraine for whom ≥3 prior prophylactic treatments have failed
- **Analysis:** Pairwise
- **Comparators:** BSC and botulinum toxin
- **Erenumab dose:** 140mg
- **Time horizon:** Lifetime
- **Relative efficacy vs. botulinum toxin:** ITC, mid-point, OR=1
- **Response assessment:** 30% reduction in monthly migraine days (MMDs)
- **Additional treatment discontinuation due to loss of efficacy (applies to row 2 in results table only):** 9.24% discontinuation rate applied every 4 cycles (every 48 weeks) (discontinuation rates are equivalent to an annual discontinuation of 10%) starting at week 48

Table 2: Summary scenario deterministic results in the chronic migraine population only, erenumab 140 mg, pairwise analysis versus BSC and Botulinum toxin without the revised value proposition

	Scenario Type	Loss of Efficacy/Waning Assumption	Comparison with BSC	Relative efficacy versus Botulinum toxin assumption		
				ITC	Mid-point	No benefit
1	All-cause discontinuation (small proportion due to loss of efficacy)	2.38% all-cause discontinuation per 12 week cycle already included **Novartis base case**	[redacted]	[redacted]	[redacted]	[redacted]
2	As per scenario 1 plus additional discontinuation of treatment due to loss of efficacy	2.38% all-cause discontinuation per 12 week cycle already included AND Additional discontinuation every 4 cycles (based on 10% annual rate) (see section 1.2) **New Novartis scenario**	[redacted]	[redacted]	[redacted]	[redacted]

3	As per scenario 1 plus treatment waning i.e. loss of efficacy and no additional discontinuation	5 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]	[redacted]
		10 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]	[redacted]
		10 years of waning after 5 years **Novartis variant of ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]	[redacted]

2.2 *Appendix B – change in annual waning discontinuation rate from 10% to 5%*

Assumptions applied in the model are summarised below:

- **Population:** Adults with chronic migraine for whom ≥3 prior prophylactic treatments have failed
- **Analysis:** Incremental
- **Comparators:** BSC and botulinum toxin
- **Erenumab dose:** 140mg
- **Time horizon:** Lifetime
- **Relative efficacy vs. botulinum toxin:** ITC, mid-point, OR=1
- **Response assessment:** 30% reduction in monthly migraine days (MMDs)
- **Additional treatment discontinuation due to loss of efficacy (applies to row 2 in results table only):** 4.61% discontinuation rate applied every 4 cycles (every 48 weeks) (discontinuation rates are equivalent to an annual discontinuation of 5%) starting at week 48

Table 3: Summary scenario deterministic results in the chronic migraine population only, erenumab 140 mg

	Scenario Type	**Loss of Efficacy/Waning Assumption**	**Relative efficacy versus Botulinum toxin assumption**		
			ITC	**Mid-point**	**No benefit**

1	All-cause discontinuation (small proportion due to loss of efficacy)	2.38% all-cause discontinuation per 12 week cycle already included **Novartis base case**	[redacted]	[redacted]	[redacted]
2	As per scenario 1 plus additional discontinuation of treatment due to loss of efficacy	2.38% all-cause discontinuation per 12 week cycle already included AND Additional discontinuation every 4 cycles (based on 5% annual rate) (see section 1.2) **New Novartis scenario**	[redacted]	[redacted]	[redacted]
3	As per scenario 1 plus treatment waning i.e. loss of efficacy and no additional discontinuation	5 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]
		10 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]
		10 years of waning after 5 years **Novartis variant of ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]

** ICER for erenumab 140mg compared with Botox

*** ICER for erenumab 140mg compared with BSC

2.3 *Appendix C - Change in annual waning discontinuation rate from 10% to 20%*

Assumptions applied in the model are summarised below:

- **Population:** Adults with chronic migraine for whom ≥3 prior prophylactic treatments have failed
- **Analysis:** Incremental
- **Comparators:** BSC and botulinum toxin
- **Erenumab dose:** 140mg
- **Time horizon:** Lifetime
- **Relative efficacy vs. botulinum toxin:** ITC, mid-point, OR=1

- **Response assessment:** 30% reduction in monthly migraine days (MMDs)
- **Additional treatment discontinuation due to loss of efficacy (applies to row 2 in results table only):** 18.56% discontinuation rate applied every 4 cycles (every 48 weeks) (discontinuation rates are equivalent to an annual discontinuation of 20%) starting at week 48

Table 4: Summary scenario deterministic results in the chronic migraine population only, erenumab 140 mg

	Scenario Type	Loss of Efficacy/Waning Assumption	Relative efficacy versus Botulinum toxin assumption		
			ITC	Mid-point	No benefit
1	All-cause discontinuation (small proportion due to loss of efficacy)	2.38% all-cause discontinuation per 12 week cycle already included **Novartis base case**	[redacted]	[redacted]	[redacted]
2	As per scenario 1 plus additional discontinuation of treatment due to loss of efficacy	2.38% all-cause discontinuation per 12 week cycle already included AND Additional discontinuation every 4 cycles (based on 20% annual rate) (see section 1.2) **New Novartis scenario**	[redacted]	[redacted]	[redacted]
3	As per scenario 1 plus treatment waning i.e. loss of efficacy and no additional discontinuation	5 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]
		10 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]
		10 years of waning after 5 years **Novartis variant of ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]

** ICER for erenumab 140mg compared with Botox

*** ICER for erenumab 140mg compared with BSC

2.4 *Appendix D – change to start time for loss of efficacy*

Assumptions applied in the model are summarised below:

- **Population:** Adults with chronic migraine for whom ≥3 prior prophylactic treatments have failed
- **Analysis:** Incremental
- **Comparators:** BSC and botulinum toxin
- **Erenumab dose:** 140mg
- **Time horizon:** Lifetime
- **Relative efficacy vs. botulinum toxin:** ITC, mid-point, OR=1
- **Response assessment:** 30% reduction in monthly migraine days (MMDs)
- **Additional treatment discontinuation due to loss of efficacy (applies to row 2 in results table only):** 9.24% discontinuation rate applied every 4 cycles (every 48 weeks) (discontinuation rates are equivalent to an annual discontinuation of 10%)and treatment waning initiated from 4 years (192 weeks)

Table 5: Summary scenario deterministic results in the chronic migraine population only, erenumab 140 mg

	Scenario Type	Loss of Efficacy/Waning Assumption	Relative efficacy versus Botulinum toxin assumption		
			ITC	Mid-point	No benefit
1	All-cause discontinuation (small proportion due to loss of efficacy)	2.38% all-cause discontinuation per 12 week cycle already included **Novartis base case**	[redacted]	[redacted]	[redacted]
2	As per scenario 1 plus additional discontinuation of treatment due to loss of efficacy	2.38% all-cause discontinuation per 12 week cycle already included AND Additional discontinuation every 4 cycles (based on 10% annual rate) (see section 1.2) starring at 192 weeks **New Novartis scenario**	[redacted]	[redacted]	[redacted]
3	As per scenario 1 plus treatment waning i.e. loss of efficacy and no additional discontinuation	5 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]
		10 year waning **ERG scenario** (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)	[redacted]	[redacted]	[redacted]
		10 years of waning after 5 years	[redacted]	[redacted]	[redacted]

		Novartis variant of ERG scenario (N.B. 2.38% all-cause discontinuation per 12 week cycle already included)			

** ICER for erenumab 140mg compared with Botox

*** ICER for erenumab 140mg compared with BSC

Cost-effectiveness analyses considering waning of treatment effect

The company submitted additional evidence concerning a revised discontinuation-based approach to reflect that treatment may be discontinued if patients no longer experience a clinically meaningful benefit due to waning of treatment effect. Specifically, a discontinuation rule was implemented so that every 48 weeks an additional 9.24% of responders would transition to the "long-term negative discontinuation health state" where they did not experience treatment effectiveness or treatment costs. The ERG agrees that a waning of treatment effect may lead to treatment discontinuation once it is detected that a clinically meaningful benefit is no longer evident, but considers that the approach used by the company, adjusting discontinuation probabilities, does not reflect the potential impact of treatment waning. The modelling approach takes patients off treatment without a previous loss of effectiveness; this does not reflect the gradual loss of effectiveness and the continuation of treatment costs entailed by treatment effect waning. Additionally, the ERG believes that waning of treatment effect and treatment discontinuation are two separate (though potentially related) issues. The waning of treatment effect is a reduction in relative treatment effect over time for those on erenumab treatment (i.e. related to the long-term extrapolation). Hence, adjusting discontinuation probabilities does not reflect the uncertainty of potential waning of treatment effect that was expressed by the committee. Therefore, the ERG would prefer the treatment waning scenarios as implemented by the ERG. In this ERG waning scenario, health state costs and utilities for responders gradually revert to BSC non-responder values (over a specific treatment waning period) to reflect the loss of treatment effect while treatment costs continued to accumulate. The analyses results for the chronic migraine population could be reproduced by the ERG and are presented in Table 1 [results redacted - commercial in confidence].

Clinical Evidence of Long-Term Treatment Effect

The company presented additional clinical data on the long-term treatment effectiveness of erenumab for episodic migraine from an open-label trial following an RCT. In the trial, patients who completed a 12-week RCT in any arm switched to erenumab 70mg, and two years later to erenumab 140mg. The results showed that 3.1% of patients had discontinued erenumab 70mg due to lack of efficacy and none had discontinued erenumab 140mg one year after the start of the increased dosage.[1] Some long-term effectiveness data, from the same study, were provided in a separate PowerPoint presentation;[2] the mean change in monthly migraine days, from baseline in the open-label extension study to month 57 (year 4.5), was -5.8 (SE 0.3) days and 76.5% of participants had achieved ≥50% reduction in mean monthly migraine days at this time point. The ERG considers the evidence presented in support of the long-term maintenance of the effectiveness of erenumab to be weak, as the open-label uncontrolled design of the trial means that no comparative effectiveness data of erenumab vs. comparators were obtained. In addition, the ERG does not consider this open-label study to be directly applicable to the current submission, in that the specified population for the submission was patients with chronic migraine who had ≥3 failed prior prophylactic treatments, whereas the open-label study was conducted in patients with episodic migraine and did not specify prior treatment failure. The majority (56%) of patients included in the open-label study were treatment naïve and 36% were classified as having prior treatment failure (number of prior treatments not specified), including discontinuations due to lack of efficacy and/or adverse events.

Table 1. Results in the chronic migraine population

#	Scenario	Comparison	Relative efficacy versus Botulinum toxin assumption		
			ITC	**Mid-point**	**No benefit**
1	**Novartis base case** (2.4% all-cause discontinuation per 12 weeks)	Erenumab 140mg versus BSC	[redacted]	[redacted]	[redacted]
		Erenumab 140mg versus Botox	[redacted]	[redacted]	[redacted]
		Botox versus BSC	[redacted]	[redacted]	[redacted]
2	**Increased discontinuation scenario** (Additional discontinuation probability of 9.2% every 48 weeks)	Erenumab 140mg versus BSC	[redacted]	[redacted]	[redacted]
		Erenumab 140mg versus Botox	[redacted]	[redacted]	[redacted]
		Botox versus BSC	[redacted]	[redacted]	[redacted]
3	**ERG treatment waning scenario** (5 year waning; starting after 12 weeks)	Erenumab 140mg versus BSC	[redacted]	[redacted]	[redacted]
		Erenumab 140mg versus Botox	[redacted]	[redacted]	[redacted]
		Botox versus BSC	[redacted]	[redacted]	[redacted]
4	**ERG treatment waning scenario** (10 year waning; starting after 12 weeks)	Erenumab 140mg versus BSC	[redacted]	[redacted]	[redacted]
		Erenumab 140mg versus Botox	[redacted]	[redacted]	[redacted]
		Botox versus BSC	[redacted]	[redacted]	[redacted]
5	**Novartis treatment waning scenario** (10 year waning; starting after 5 year)	Erenumab 140mg versus BSC	[redacted]	[redacted]	[redacted]
		Erenumab 140mg versus Botox	[redacted]	[redacted]	[redacted]
		Botox versus BSC	[redacted]	[redacted]	[redacted]
Source: Additional cost-effectiveness documents and HE model submitted by the company[3, 4]					

References

[1] Ashina M, Goadsby PJ, Reuter U, Silberstein S, Dodick D, Rippon GA, et al. Long-term safety and tolerability of erenumab: three-plus year results from a five-year open-label extension study in episodic migraine. *Cephalalgia* 2019:333102419854082.

[2] Ashina M, Goadsby PJ, Reuter U, Silberstein S, Dodick D, Chou DE, et al. Sustained efficacy and long-term safety of erenumab in patients with episodic migraine: 4+-year results of a 5-year, open-label treatment period. Presented at American Headache Society 61st Annual Meeting; 11-14 July 2019: Philadelphia, PA. 2019.

[3] Novartis Pharmaceuticals UK Ltd. *Single technology appraisal (STA). Erenumab for preventing migraine: company evidence submission to National Institute for Health and Care Excellence [ID1188]. Additional cost-effectiveness analyses*, 2019. 14p.

[4] Novartis Pharmaceuticals UK Ltd. *Single technology appraisal (STA). Erenumab for preventing migraine: company evidence submission to National Institute for Health and Care Excellence [ID1188]. Cost-effectiveness model: ERG analyses response model [Excel spreadsheet]*, 2019