NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fremanezumab for preventing migraine [ID1368]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fremanezumab for preventing migraine [ID1368]

Contents:

The following documents are made available to consultees and commentators:

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

Fremanezumab 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.

Confidential until publication

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

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td>Teva</td><td>Section 3.5 of the ACD includes the statement that "FOCUS defined an inadequate treatment response as a lack of clinically meaningful improvement after at least 3 months of therapy, intolerance to the treatment or the treatment was contraindicated or unsuitable. The clinical experts explained that a contraindication would not necessarily represent a treatment failure." Teva wishes to clarify the definitions of an inadequate treatment response in the FOCUS study. Firstly, Teva acknowledges the comments from the clinical experts that a contraindication may not necessarily represent a treatment failure. However, it is also important to note that the published FOCUS results demonstrate that, in the vast majority of cases, a lack of efficacy or intolerability were the reasons for a recorded treatment failure and not contraindications (see data below, reproduced from Supplemental Table 4 of Ferrai et al. Lancet 2019; 394: 1030–1040). Overall, it should be noted that only 42 out of 2,257 failures within FOCUS were recorded as being due to a contraindication (1.9%). In addition, if a treatment is contraindicated, then this treatment is not available for use so surmounts to a failure to be successfully treated.

<u>Proportion of patients selecting 'contraindication or not suitable for use' as reason for failure by therapeutic class</u>
<table>
<tr><th>Preventive treatment class</th><th>Placebo (n=279)</th><th>Fremanezumab Quarterly (n=276)</th><th>Fremanezumab monthly (n=283)</th></tr>
<tr><td>Angiotensin II receptor antagonist n (%)
Contraindicated/not suitable n (%)</td><td>51 (18)

0</td><td>55 (20)

0</td><td>48 (17)

0</td></tr>
<tr><td>Anticonvulsants n (%)
Contraindicated/not suitable n (%)</td><td>184 (66)

1(<1)</td><td>215 (78)

4 (2)</td><td>217 (77)

2 (<1)</td></tr>
<tr><td>Beta-blockers n (%)</td><td>159 (57)</td><td>145 (53)</td><td>164 (58)</td></tr>
</table></td><td>Comment noted. At the second committee meeting, the committee considered Teva's ACD responses on the generalisability of the FOCUS population to NHS clinical practice. The committee noted that only about 2% of all recorded prior treatment failures in FOCUS were due to contraindications. However, the committee maintained its view that FOCUS does not fully reflect the people who may be eligible for fremanezumab in clinical practice. This is because FOCUS excluded patients who had the most severe, unremitting headaches, clinically significant comorbidities or clinically significant psychiatric issues. Also, valproic acid is not frequently used in the UK for migraine prevention, while about 1 in 3 patients in FOCUS have previously had it.

The information on the proportion of treatment failures due to contraindications was added to the Final Appraisal Document (FAD; section 3.6). Also, the rationale why FOCUS may not fully reflect the people who may be eligible for fremanezumab in clinical practice was clarified in section 3.6 of the FAD.</td></tr>
</table>

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><td>Contraindicated/not suitable n (%)</td><td>1 (<1)</td><td>7 (5)</td><td>4 (2)</td></tr>
<tr><td>Calcium channel blocker n (%)
Contraindicated/not suitable n (%)</td><td>58 (21)

0</td><td>39 (14)

0</td><td>47 (17)

0</td></tr>
<tr><td>Onabotulinumtoxin A n (%)
Contraindicated/not suitable n (%)</td><td>77 (28)

0</td><td>78 (28)

1</td><td>73 (26)

0</td></tr>
<tr><td>Tricyclics n (%)
Contraindicated/not suitable n (%)</td><td>140 (50)

0</td><td>125 (45)

1 (<1)</td><td>129 (46)

1 (<1)</td></tr>
<tr><td>Valproic acid n (%)
Contraindicated/not suitable n (%)</td><td>82 (29)

4 (5)</td><td>83 (30)

13 (16)</td><td>88 (31)

3 (3)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Teva</td><td>In Section 3.5 of the ACD, it is stated that, “FOCUS does not fully reflect the people who may be eligible for fremanezumab in clinical practice.” Subsequently, the ACD states that “…valproic acid was considered differently to other preventive treatments in FOCUS and was regarded as being in a class of its own. Therefore, a person whose migraine had an inadequate response to valproic acid, topiramate and propranolol would be included in the subgroup analysis (3 or more preventive treatment failures) even though this represents a failure of 2 treatment classes.” Teva would like to clarify the design of the FOCUS study, with this study designed to include patients based on the number of preventive classes failed rather than individual treatment failures. The rationale for doing so was to enhance the robustness of the study design, and to ensure that patients had utilised (and failed) on preventive treatments with distinct mechanisms of action, and not just failed, for example, on two beta-blockers and one other treatment.

Within the FOCUS study, valproic acid was assigned to a class of its own, rather than being grouped in a class of ‘anticonvulsants’ with topiramate. This decision was taken for a number of reasons. Firstly, the particular risks of valproic acid and its associated restricted usage in women of childbearing potential were considered during the trial design; however, these risks did not appear to have a significant impact on the number of patients who were considered to have failed this treatment for the reason of ‘Contraindicated/not suitable’ (see figures above). Also, it should be noted that although both topiramate and valproic acid can be classified as</td><td>Comment noted. The committee accepted the company’s rationale that the number of prior treatments are aligned with clinical practice. However, the committee maintained its view that FOCUS does not fully reflect the people who may be eligible for fremanezumab in clinical practice. This is because FOCUS excluded patients who had the most severe, unremitting headaches, clinically significant comorbidities or clinically significant psychiatric issues. Also, valproic acid is not frequently used in the UK for migraine prevention, while about 1 in 3 patients in FOCUS have previously had it. Please see the FAD for a summary of these considerations (section 3.6)</td></tr>
</table>

Consultee	Comment [sic]	Response
	anticonvulsants, these drugs have distinctions in their proposed mechanisms of action and have differences within their licensed indications (only topiramate is licensed for use in migraine). This highlights that even though both drugs are anticonvulsants, they have the capability to work on distinct molecular pathways. These differences mean that valproic acid is utilised in patients who have previously failed topiramate, and vice versa; a practice confirmed by clinical experts to be consistent with the management of patients in the UK. As a global multicentre study, FOCUS was influenced by clinical practice within all participating countries, and it is notable that in many countries (Germany is a particular example) valproic acid is used predominantly as a last line treatment. This was therefore an additional reason for separate consideration of valproic acid failure and is why randomisation in FOCUS was stratified by failure with valproic acid to ensure there was an even distribution across the trial arms for these difficult to treat patients. Teva acknowledges that the subgroup analysis of patients whom have failed 3 or more prior preventive therapies may contain a proportion of patients whom have failed both valproic acid and topiramate. However, this population does not represent the majority of patients within the FOCUS study (31% of CM patients and 38% of EM patients had reported failure of both valproic acid and topiramate). It must be noted that the failure history for each patient occurred prior to enrolment into the FOCUS study rather than being driven by the study protocol. Therefore, the documented inadequate response to therapies reported in the FOCUS study reflects real-world clinical practice, including UK, where clinicians would prescribe both valproic acid and topiramate when there is a clinically valid rationale to do so. Also, Teva notes that all previous NICE guidance, and all major clinical guidelines, refer to number of failed treatments and not classes of failed treatment. So whilst Teva accepts that inadequate response to both valproic acid and topiramate may not technically meet our own stricter definition of 'failed classes' employed within the FOCUS study, it does certainly meet the standard definition of failed treatments. To exemplify this point, we note that the NICE recommendation for onabotulinumtoxin A states that a patient must have failed at least three individual treatments and not three classes of preventive therapies. Therefore, a CM patient that has failed topiramate, valproic acid and one other treatment, in the UK, would be eligible to receive treatment with onabotulinumtoxin A. Given this, Teva strongly refutes the ACD conclusion that *'FOCUS does not fully reflect the people who may be eligible for fremanezumab in clinical practice'*.	

Consultee	Comment [sic]	Response
Teva	In Section 3.5 of the ACD, it is stated that, "…*valproic acid was considered differently to other preventive treatments in FOCUS and was regarded as being in a class of its own. Therefore, a person whose migraine had an inadequate response to valproic acid, topiramate and propranolol would be included in the subgroup analysis (3 or more preventive treatment failures) even though this represents a failure of 2 treatment classes*. ***The committee was concerned that because of this a substantial proportion of people in the subgroup may not have had 3 or more failed preventive treatments***." In addition, to the clarifications provided in comment number 2, Teva also finds the specific statement highlighted in bold (above) to be factually incorrect where it is stated that a failure of valproic acid, topiramate and propranolol would not be classed as having three failed preventive treatments. As outlined within comment number 2, these treatments have distinctions and can be prescribed separately to a single patient. These treatments are also recognised as distinct within a number of clinical guidelines. Also, all previous NICE guidance, and other major clinical guidelines, focus on number of failed treatments and not classes of failed treatment. Therefore, it is not factually correct to state that failure on valproic acid and topiramate would only be classed as failure of a single treatment.	Comment noted. The committee accepted the company rationale that failure on valproic acid and topiramate would be counted as failure of 2 preventive treatments. However, the committee maintained its view that FOCUS does not fully reflect the people who may be eligible for fremanezumab in clinical practice. This is because FOCUS excluded patients who had the most severe, unremitting headaches, clinically significant comorbidities or clinically significant psychiatric issues. Also, valproic acid is not frequently used in the UK for migraine prevention, while about 1 in 3 patients in FOCUS have previously had it. Please see section 3.6 of the FAD for a summary of these considerations.
Teva	Section 3.6 of the ACD contains factual errors relating to the loading dose utilised within the clinical trials of fremanezumab. Teva would like to clarify that, as outlined within the company submission, a loading dose was utilised within the HALO CM trial and for patients with CM in the FOCUS trial. Patients in the HALO EM trial and patients with EM in the FOCUS trial did not receive a loading dose. Teva also finds that the wording in this Section around blinding to be unclear. The ACD states "…*the loading dose, consisting of 3 injections, was given to maintain the blinding of treatment allocation*." The loading dose was not given to maintain blinding to treatment allocation. Patients were administered additional placebo injections (where necessary) in order to maintain blinding to treatment allocation.	Comments noted. This has been corrected in the FAD (section 3.7).
Teva	In Section 3.10 of the ACD it is stated that, "…*there was real-world evidence supporting the effectiveness, tolerability and safety of botulinum toxin type A from a UK perspective*." Teva notes that the main part of these data have been collected using a treatment protocol that does not follow NICE guidelines, and comes from a single centre analysis. Therefore, these data have limitations in their generalisability to the population of interest being considered by this appraisal.	Comment noted. The committee recognised the strengths and limitations of evidence for both fremanezumab and botulinum toxin type A.
Teva	Section 3.10 of the ACD concludes that *"…it was appropriate to consider a scenario in which equivalent efficacy was assumed*…" Teva does not feel that this is a reasonable interpretation of the evidence and that the NMA remains the best	Comment noted. The committee extensively discussed the relative clinical efficacy of fremanezumab and botulinum toxin type A during

Consultee	Comment [sic]	Response
	available data for comparison between fremanezumab and onabotulinumtoxin A. The NMA shows an additional benefit for fremanezumab over onabotulinumtoxin A across all endpoints analysed, yet makes a number of assumptions that are conservative with respect to the relative efficacy of fremanezumab. Additionally, the NMA was unable to include a number of additional patient and healthcare burden advantages for fremanezumab (a single monthly subcutaneous injection (or three injections every three months) compared to 31 injections in the head and neck every 12 weeks; the ability for fremanezumab to be self-injected at home compared to administration in hospital by a highly skilled healthcare professional). Teva also notes that, due to limited data available for onabotulinumtoxin A, any advantage for fremanezumab either from reductions in monthly migraine days or the distribution of migraine patients between MMD states could not be accounted for within the economic model. Altogether, these factors demonstrate clear advantages for fremanezumab over onabotulinumtoxin A, and additional benefits that are not currently captured within the economic modelling. Teva has investigated an updated base case and scenarios for the comparison to onabotulinumtoxin A, and these are included within the new evidence Appendix. Under all modelled scenarios using the new value proposition and the NMA efficacy results, fremanezumab was demonstrated to be a cost-effective treatment when compared to onabotulinumtoxin A (and also compared to best supportive care).	both meetings. The committee noted the methodological limitations of the NMA and lack of statistical significance of the results. Therefore it concluded that it is appropriate to consider both scenarios, one in which NMA results are used to inform relative efficacy of the 2 drugs, and another where equal efficacy is assumed. Please see section 3.11 and 3.25 of the FAD for a summary of these considerations.
Teva	In Section 3.14 it is stated that "…*the discontinuation rate in the HALO extension study was higher than that seen in the extension studies of another anti-calcitonin gene-related peptide (CGRP), erenumab.*" Teva would like to reiterate that the discontinuation rate within the model uses the best available data for fremanezumab which comes from the HALO extension trial. These clinical data show the long-term all-cause discontinuation rate for patients receiving fremanezumab and represents the best available data for this treatment.	Comment noted. The committee accepted the all-cause discontinuation rate used in the model but maintained its view that the discontinuation rate was higher than expected and this could affect the cost-effectiveness results. This was because the discontinuation rate was relatively high for what it understood to be a clinically effective and well tolerated treatment. The discontinuation rate in the HALO extension study was higher than that seen in the extension studies of another anti-calcitonin gene-related peptide (CGRP), erenumab. Please see section 3.15 of the FAD for a summary of these considerations.
Teva	Section 3.15 includes a statement that, "*The committee noted that a placebo effect would not be seen in clinical practice when no treatment is given*." Teva does not find this to be an accurate interpretation of the evidence submitted. The Best Supportive Care group was modelled to receive <u>acute medication</u> for their migraine, and this is similar to the placebo treated groups within the clinical trials. Therefore,	Comment noted. The committee considered that a scenario in which people revert to baseline monthly migraine (and not frequency of migraines seen in best supportive care) days after discontinuing treatment is most clinically plausible. Please see

Consultee	Comment [sic]	Response
	the placebo effect modelled within these patients is not based on no treatment being given, but, rather, is based on improvements seen with acute migraine treatment that would form part of a best supportive care regimen for migraine.	section 3.16 of the FAD for a summary of these considerations.
Teva	In Section 3.17, the committee concludes that a positive stopping rule is not appropriate for consideration. Teva finds that this decision limits the suitability of these recommendations for NHS practice. Clinical experts have been clear to Teva that treatment would not be continued indefinitely and that patients who show a sufficient response and who no longer require treatment would have this treatment positively stopped. Positive stopping of preventive treatment within migraine is also recommended within SIGN and BASH guidelines; whilst European Headache Federation guidelines on anti-CGRP migraine treatments recommend that continuation on treatment should be managed in the same way as for other migraine preventative therapies. In addition, the SmPC of fremanezumab states that "*Evaluation of the need to continue treatment is recommended regularly thereafter* [after initial assessment of efficacy]". Therefore, Teva finds that it is clear that a positive stopping rule will be utilised within NHS clinical practice, which has been corroborated by clinical expert opinion gathered by Teva. An updated positive stopping rule is included within the base case outlined in the new evidence Appendix, alongside additional scenario analyses in this area. These scenarios demonstrate that fremanezumab is a cost-effective treatment for both chronic and episodic migraine.	Comment noted. At the second committee meeting, the committee considered this information and the proposed new stopping rule. The committee was aware that professional organisations agree that treatment with fremanezumab would not be continued indefinitely. But it considered that there are no clear criteria for when people should stop treatment and understood that a positive stopping rule could be challenging to implement in clinical practice. It recognised that patients may not be willing to stop treatment that is beneficial to them. It also recalled that no positive stopping criteria were used in FOCUS. Therefore the committee concluded that it was not appropriate to apply a positive stopping rule in the model. Please see section 3.18 of the FAD for a summary of these considerations.
Teva	Section 3.19 states that there was no evidence that differential utility benefits have been shown for people with migraine whilst on-treatment. Teva does not believe that this is a clinically valid interpretation of the available evidence. Firstly, the data presented utilised clinical trial data from the FOCUS trial which demonstrated that, for a patient with a given number of monthly migraine days, their quality of life was higher when being treated with fremanezumab. Similar effects of quality of life benefits in patients with similar migraine/headache day frequencies have been demonstrated in data from a number of migraine clinical trials. This effect has been seen with both erenumab (Lipton RB *et al*. *J Med Econ* 2018; 21: 666–675) and onabotulinumtoxin A (Batty AJ *et al*. *J Med Econ*. 2013; 16: 877–887). Both of these studies are focussed on economic modelling, but utilise data from the key clinical trials of these treatments, and in both cases these analyses result in differential on- and off-treatment utilities. In addition, the previous NICE appraisal of onabotulinumtoxin A concluded that the most plausible ICER included separate on- and off- treatment utilities, with the FAD stating that "*The Committee noted that when the ERG equalised the non-MSQ*	Comment noted. The committee agreed that the impact of migraine on patients' quality of life is likely related not only to migraine frequency but also its severity and associated factors. But it noted that on- and off-treatment utilities were not appropriately generated and applied in the model by Teva. It considered the company's approach was overly simplistic and did not account for possible improvements in quality of life related to being included in a clinical trial (placebo effect). It also explained that the on-treatment utilities were not correctly applied in the model because of how the model was structured. The committee recalled that utility values were generated from MSQ data, which measures the impact of migraine on both role function and emotional function. So it agreed that it was uncertain whether health-related quality of life

Consultee	Comment [sic]	Response
	parameter values, less non-monotonicity was observed, and the deterministic ICER was £18,900 per QALY gained when applying different utility values to each arm. The Committee concluded that this was the most plausible ICER because it incorporated the Committee's preferred inputs and assumptions including a 30% negative stopping rule, applied different utilities to treatment arms (within the Committee's reservations stated in section 4.13), and equalised the non-MSQ parameter values in the utility mapping functions." Furthermore, advice that Teva has received from clinical experts has stated that differences in utilities are well known to exceed reductions in monthly migraine days with this measure unable to capture the full burden of headaches in terms of duration, severity and associated factors (nausea *etc.*). Overall, Teva finds that there is clear evidence for differences between on- and off-treatment utilities and this factor is included within the updated base case included within the new evidence Appendix, alongside additional scenario analyses. These scenarios demonstrate that fremanezumab is a cost-effective treatment for both chronic and episodic migraine.	benefits beyond those achieved by reducing monthly migraine days were not already adequately captured by the MSQ. It also noted that baseline (before treatment) fremanezumab utility values included a benefit over best supportive care, which it agreed was inconsistent with applying an on-treatment utility value benefit. The committee concluded that additional on-treatment utility value benefits applied by the company were not supported by the evidence and should not be included in the economic model. Please see section 3.20 of the FAD for a summary of these considerations.
Teva	In Section 3.23, the ACD quotes an ICER value of £40,297 for when the NMA effectiveness estimate for onabotulinumtoxin A was utilised. During an inspection of the updated economic model supplied by NICE, Teva has noted a coding error on the utilities sheet whereby the treatment benefits were not equalised for onabotulinumtoxin A (so that onabotulinumtoxin A still received the on-treatment utilities). When corrected to ensure that all on- and off-treatment utilities are equal within the model an ICER value of £32,295 is produced.	Comment noted. The committee accepted corrections to the model. At the second committee meeting, the committee considered the revised base case submitted by Teva at consultation, which included an agreed confidential discount for fremanezumab, updated administration costs for botulinum toxin type A, and coding errors fixed. Please see sections 3.24 and 3.25 of the FAD for a summary of these considerations.
Teva	The ICERs within the ACD for fremanezumab match the ICERs presented within the ERG's Addendum #3. Within this document, an additional change to the model is noted beyond those detailed within the ACD. This change was described as the "*Removal of residual fremanezumab effect in non-responders*." This change removes any MMD reductions seen within the fremanezumab non-responders during their 12-week treatment trial. Teva finds this change to be unjustifiable as it goes against the clinical trial evidence used to model this population. The reduction in monthly migraine days modelled within this population was a real effect that occurred within the clinical trial; however, this response was not sufficient for these patients to continue treatment (*i.e.* it did not reach the threshold of a clinically meaningful response of at least 30%/50% reduction in monthly migraine days).	Comment noted. The committee accepted corrections to the model but noted the very small impact on ICERs. The committee considered it plausible that people may have some benefit from the treatment during the initial 12 weeks of treatment (even though it would not meet the definition of response and the treatment would be stopped). It recalled that any treatment benefit seen while on initial treatment would not be maintained after stopping the treatment. Please see section

Consultee	Comment [sic]	Response
	After the 12-week trial these patients stopped treatment and reverted to their baseline MMDs (a conservative assumption in itself as some treatment benefit may be maintained within these patients). In addition, this alteration to the model impacts its ability to model the observed clinical trial results by removing some of the efficacy of fremanezumab. The modelling of the migraine population as responder and non-responder subpopulations means that the overall results come from the combined analysis of these subpopulations. The removal of the MMD reductions for fremanezumab non-responders therefore impacts the overall results and their ability to accurately reflect the FOCUS clinical trial results. Teva finds no justification for this change to have been provided and finds that this change produces a misrepresentation of the FOCUS trial results.	3.17 of the FAD for a summary of these considerations.
Teva	In Section 3.24 of the ACD, the committee "…*could not consider the use of fremanezumab after botulinum toxin type A because it had not been presented with cost-effectiveness estimates for this group*." Teva has therefore assembled additional evidence to demonstrate the clinical effectiveness and cost-effectiveness of fremanezumab in patients who have failed onabotulinumtoxin A. This evidence is presented in the new evidence Appendix, and demonstrates that fremanezumab is a clinically effective and cost-effective treatment for patients who have previously failed onabotulinumtoxin A.	Comment noted. At the second committee meeting, the committee considered new evidence submitted by Teva. It noted the limitations of the additional evidence, mainly small sample size and post-hoc nature of the subgroup analysis. But it noted the results were aligned with the results for the overall population considered in this appraisal. It also recalled the high unmet need and lack of further treatment options in this patient group. The committee concluded that fremanezumab may be clinically and cost-effective compared with best supportive care for people with chronic migraine after 3 preventive treatments and botulinum toxin type A have failed. Please see section 3.10 and 3.26 of the FAD for a summary of these considerations.
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 needed.
Association of British Neurologists	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**	

Consultee	Comment [sic]	Response
Advisory Group on headache and pain	i) Cost effectiveness should be reconsidered in light of change in pricing of Fremanezumab from £450 to £[redacted] per month ([redacted]) ii) 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. iii) The duration of treatment and waning effect of utility over time is uncertain but we feel the committee should make reasonable assumption for duration of treatment based on the data with existing prophylactic agents. We do not agree with 3.17 which states that '**Positive stopping rule assumptions are not appropriate because it is implausible that treatment benefit is maintained indefinitely'.** We do not agree with the cost-effectiveness model presented that assumes that longer term treatment would be the standard of care: • We agree that treatment should be stopped if there is no significant response at three months (***negative stopping rule***). • The consultation did not accept the advice of UK professional bodies (the ABN and BASH) on a '***positive stopping rule'***. The ABN Advisory Group on Headache and Pain (Technical engagement response form Committee Papers p 635) stated that *'most specialists recommend continuing treatment for chronic migraine until they come down to low frequency episodic migraine i.e. <10 migraine days /month for at least 3 months'*. In practice this usually equates to at least 1 year in total of treatment as this cohort will typically have had long-standing chronic migraine refractory to many other treatments. The European Headache Federation guidelines recommend preventative migraine treatment should be given for 6-12 months in the first instance. If a patient requires longer term use we would certainly advocate re-evaluation of need for treatment every 12 months. A **'**drug holiday**'** would be undertaken to confirm whether or not ongoing treatment was necessary. There is evidence from studies on topiramate that the outcome, and chance of maintained benefit once the drug is withdrawn, is best when treatment is maintained for at least 6-12 months before a treatment break.	i) Comment noted. The committee reconsidered the company's revised base case, which included an agreed confidential PAS discount for fremanezumab. Please see section 3.25 of the FAD for a summary of these considerations. ii) Comment noted. The assessment incorporated 2 key outcomes: reduction in monthly migraine days and responder rates (definition of response: 30% reduction in migraine frequency for people with chronic migraine and 50% reduction for people with episodic migraine) iii) Comment noted. The committee accepted advice from the UK professional bodies about the likely treatment duration in NHS clinical practice. But it considered that there are no clear criteria for when people should stop treatment and understood that a positive stopping rule could be challenging to implement in clinical practice. It recognised that patients may not be willing to stop treatment that is beneficial for them. It also recalled that no positive stopping criteria were used in FOCUS. Therefore the committee concluded that it was not appropriate to apply a positive stopping rule in the model. Please see section 3.18 of the FAD for a summary of these considerations.

Consultee	Comment [sic]	Response
	• We note the scepticism in the Consultation on ***sustained efficacy*** following discontinuation based on the opinion that a lifetime horizon should be assumed, with only a very minor annual discontinuation rate. While we are aware that there are no long-term studies supporting continued benefit after cessation of successful treatment, this opinion runs contrary to what is known about the natural history of migraine. o for **Chronic Migraine**, there little published data on the long term outcomes of those that have stopped treatment following successful conversion to episodic migraine. Data available for patients receiving Botox treatment for chronic migraine from a UK headache centre presented at the International Headache Congress in Dublin 2019 (Ahmed et al, IHC-PO-419) (pg 635, ABN response) shows that at 5 year follow up 85% (160/186) of patients with chronic migraine who had a had a positive response to OnabotulinumtoxinA had discontinued treatment, and only 5% (18/160) had relapsed such that they had restarted OnabotulinumtoxinA treatment within that 5 yr period. o for **episodic migraine** the proportion is more difficult to estimate as it is likely that the number of patients that would require this group of drug will be very few as many would respond to first line treatments (amitriptyline, propranolol, candesartan, and/or topiramate). In summary we consider that a duration of treatment of two years would be reasonable for modelling purposes, and the treatment could be stopped earlier (after an annual review, for example) if the patient improves and this improvement is maintained off treatment. For patients with **chronic migraine**, this improvement should be *at least* a reversion to episodic migraine, and perhaps episodic migraine at <10 days per month. (***positive stopping rule***). iv) There has been no significant change in standard clinical practice with regards 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, 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 a trial of three agents.	iv) Comment noted. The committee agreed that an adequate trial of at least 3 oral preventive treatments represents usual NHS practice before more specialist treatment is considered. It also concluded that the subgroup of people from FOCUS for whom 3 or more preventive treatments had failed provided the most relevant data for the population of interest. Please see sections 3.2 and 3.5 of the FAD for a summary of these considerations.

Consultee	Comment [sic]	Response
Association of British Neurologists Advisory Group on headache and pain	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The draft recommendations 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 fremanezumab in such patients would be highly appropriate to determine responders who have a significant reduction in headache days, and improvement in their quality of life, before considering more invasive and expensive treatment options such as intravenous dihydroergotamine, occipital nerve stimulation or even some of the non-invasive neuromodulation therapies such as vagal nerve stimulation or transcranial magnetic stimulation that have limited NICE recommendations without mandatory funding. In addition we recommend that the company be specifically requested to provide a model for the use of fremanezumab positioned in a treatment pathway *after* the use of onabotulinumtoxinA. It is highly likely that fremanezumab treatment would be cost effective against best supportive care in this significant population of patients with a highly debilitating neurological disorder and a currently unmet clinical need.	Comment noted. The committee considered the revised base case submitted by the company during consultation. It included a confidential PAS discount price for fremanezumab, updated administration costs for botulinum toxin type A, and fixing of coding errors. The committee noted that using its preferred assumptions, the ICER for fremanezumab compared with best supportive care was within the range usually considered a cost-effective use of NHS resources. It also noted that it was plausible that the ICER for fremanezumab compared with botulinum toxin type A was also within that range, although it noted uncertainties about the comparative effectiveness of these 2 treatment options. The committee also considered additional evidence for patients who had inadequate response to 3 oral preventive treatment and botulinum toxin type A, which was submitted by the company at the consultation. Taking all evidence into consideration, the committee concluded that although there are still uncertainties in the model, fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine after 3 preventive treatments have failed. Please see sections 3.10 and 3.25 for a summary of these considerations.
British Association for the Study of Headache	**Has all of the relevant evidence been taken into account?** Yes	Comment noted. No action needed.
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 following comments: i) In the Focus Study, the definition of failure to respond to treatment included those where treatment was contraindicated or discontinued due to adverse events. This is what is seen in real life, and a strict adherence to pure therapeutic failure after three months of therapy is not always possible.	i / ii) Comment noted. The committee noted that only about 2% of all recorded treatment failures were due to contraindications. It also agreed that a separate grouping of sodium valproate may not affect the generalisability of the FOCUS population to NHS clinical practice. However, the committee maintained its view that FOCUS does not fully reflect the people who may be eligible for

Consultee	Comment [sic]	Response
	ii) Sodium valproate should perhaps have been included in the same group as other anticonvulsants, although its use in migraine prophylaxis in the UK is uncommon. However, while sodium valproate is an anticonvulsant, its mode of action in migraine is presumed to be different from other anticonvulsants such as topiramate. The anticonvulsants used for migraine prophylaxis are not a functionally homogenous group in the way that beta-blockers or tricyclic antidepressants can be assumed to be. iii) 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. iv) The committee commented on lack of placebo arm in HALO extension study and the risk of bias, as not everyone continued. However, long-term extension studies are never randomised or controlled, and are done to confirm safety and tolerability, and not just clinical efficacy. v) Real life data does not exist for Fremanezumab, but this is true of any new drug. Such data can only be collected once a recommendation is made to treat a limited refractory population, based on cost effectiveness. vi) Whilst the duration of treatment and waning effect of utility over time is uncertain, the committee should make reasonable assumption for duration of treatment based on the data with existing prophylactic agents (see point (viii) below, for example). Treatment should be stopped if there is no response at three months (negative stopping rule). As most prophylactic agents are required for 6-18 months, with only a small proportion of patients continuing treatment for longer duration, the ongoing need for treatment should be assessed annually, and the treatment could be stopped if patients improve, and that improvement is maintained after a short (three month) period off treatment. For patients with chronic migraine, the minimum acceptable positive stopping rule would be a reversion to episodic migraine (by definition, <15 headache days/month), though an improvement to <10 headache days/month might be modelled as well. Duration of treatment of two years might be reasonable for modelling purposes.	fremanezumab in clinical practice. This is because of patient characteristics and prior treatments they took may be different than characteristics and prior treatments of people who may be eligible for fremanezumab in clinical practice. Please see section 3.6 of the FAD for a summary of these considerations. iii) Comment noted. The assessment incorporated 2 key outcomes: reduction in monthly migraine days and responder rates (definition of response: 30% reduction in migraine frequency for people with chronic migraine and 50% reduction for people with episodic migraine) iv) Comment noted. The committee acknowledged that long-term extension studies are not randomised. But it recognised that because not everyone in the trials continued to the extension phase there was an additional risk of bias. This was because it considered that people not experiencing benefit were more likely to drop out. Please see section 3.9 of the FAD for a summary of these considerations. v) Comment noted. This was clarified in section 3.11. vi) Comment noted. The committee accepted advice from the UK professional bodies about likely treatment duration in NHS clinical practice. But it considered that there are no clear criteria for when people should stop treatment and understood that a positive stopping rule could be challenging to implement in clinical practice. It recognised that patients may not be willing to stop treatment that is beneficial for them. It also recalled that no positive

Consultee	Comment [sic]	Response
	vii) There has been no significant change in standard clinical practice with regards 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, 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. As there is no consensus on where CGRP monoclonal antibodies should sit in the pathway, the cost effectiveness of Fremanezumab should be assessed both at this point, **and in patients who have also failed treatment with OnabotulinumtoxinA**, whose clinical need is paramount. viii) We note the committee's scepticism on sustained efficacy following discontinuation. However, for chronic migraine, there is data on long term outcome for those that have stopped treatment following successful conversion to episodic migraine, from patients receiving Botox treatment for chronic migraine from a UK headache centre (presented at the International Headache Congress in Dublin, 2019): a) 2 year data shows that around 60% of patients (228/380) who had a positive response to Botox were able to stop treatment by two years, most because they reverted to episodic migraine, a few because of pregnancy, development of resistance or lost to follow up. 61 of those who stopped treatment (N=228) relapsed (26.75%) and restarted Botox treatment. 112 out of 380 (29.7%) showed a sustained response and remained episodic (Ahmed et al, IHC-PO-418). b) Five year data shows that 160/186 patients who had a positive response to Botox stopped treatment within 5 years, most because they reverted to episodic migraine, a few because of pregnancy, development of resistance or lost to follow up. 18 of those who stopped treatment relapsed and restarted Botox treatment. The relapse period varied from 4-36 months. 105 patients of 186 (56.4%) showed a sustained response and remained episodic (Ahmed et al, IHC-PO-419) For episodic migraine the proportions are more difficult to estimate.	stopping criteria were used in FOCUS. Therefore the committee concluded that it was not appropriate to apply a positive stopping rule in the model. Please see section 3.18 of the FAD for a summary of these considerations. vii) Comment noted. The committee agreed that an adequate trial of at least 3 oral preventive treatments represents usual NHS practice before more specialist treatment is considered. It also concluded that the subgroup of people from FOCUS for whom 3 or more preventive treatments had failed provided the most relevant data for the population of interest. The committee also considered additional evidence for patients who had inadequate response to 3 oral preventive treatment and botulinum toxin type A, which was submitted by the company at the consultation. Please see sections 3.2, 3.5, 3.10, 3.25 and 3.26 of the FAD for a summary of these considerations. viii) Comment noted. The committee considered the current long-term evidence for botulinum toxin type A. It agreed this evidence indicated that some people may have sustained efficacy even after treatment has stopped. However, the committee was also aware that some patients would improve because of natural variation in disease history (for example, improvement after the menopause for some women). It concluded that long-term efficacy of fremanezumab is uncertain and it is not appropriate to assume treatment benefit continues indefinitely after stopping treatment. Please see section 3.18 of the FAD for a summary of these considerations.

Consultee	Comment [sic]	Response
	ix) We understand that there has been a change in pricing of Fremanezumab. We assume that cost effectiveness will be recalculated on the new pricing.	ix) Comment noted. The committee reconsidered company revised base-case, which included PAS price of fremanezumab. Please see section 3.25 of the FAD for a summary of these considerations.
British Association for the Study of Headache	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. The draft recommendations will deprive a potentially effective treatment to a highly disabled population with chronic migraine who have failed have or been unable to tolerate 3+ standard treatments (in some cases including Botox). A three month trial of Fremanezumab in such patients would clearly be indicated before considering more invasive and expensive treatment options such as intravenous dihydroergotamine, occipital nerve stimulation or even some of the non-invasive neuromodulation therapies such as vagal nerve stimulation or transcranial magnetic stimulation that have limited NICE recommendations without mandatory funding. We iterate the point made above (2 (vii) that the sponsoring company should be asked to ensure they provide data and cost effectiveness modelling for a patient population that have tried and failed three oral preventives and Botox, as this is the population with the greatest clinical need.	Comment noted. The committee considered the revised base case submitted by the company during consultation. It included an agreed confidential PAS discount for fremanezumab, updated administration costs for botulinum toxin type A, and fixing of coding errors. The committee noted that using its preferred assumptions, the ICER for fremanezumab compared with best supportive care was within the range usually considered a cost-effective use of NHS resources. It also noted that it was plausible that the ICER for fremanezumab compared with botulinum toxin type A was also within that range, although it noted uncertainties about the comparative effectiveness of these 2 treatment options. The committee also considered additional evidence for patients who had inadequate response to 3 oral preventive treatment and botulinum toxin type A, which was submitted by the company at the consultation. Taking all evidence into consideration, the committee concluded that although there are still uncertainties in the model, fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine after 3 preventive treatments have failed Please see sections 3.10, 3.25 and 3.26 for a summary of these considerations.
The Migraine Trust	The Migraine Trust welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for fremanezumab for preventing migraine. In this response we will mainly focus on highlighting the patient experience of using CGRP medications, such as fremanezumab, and the other therapies the ACD discusses, such as botulinum toxin type A.	Comment noted. The committee considered the results of both surveys. Please find detailed responses to the individual comments in the relevant sections of this table below.

Consultee	Comment [sic]	Response
	We will do this by presenting new evidence to the committee that we have recently gathered from two surveys (detailed below). The results of these surveys show the main points that we will be discussing in our response: 1. **Clinical effectiveness:** Evidence gathered from The Migraine Trust shows that patients surveyed with direct experience of botulinum toxin type A and CGRP medications, including fremanezumab, report that the CGRP medication was more effective at manging their migraine than botulinum toxin type A was. 2. **Cost-effectiveness:** Evidence gathered from The Migraine Trust shows that a clear majority of patients surveyed who take fremanezumab or other CGRP inhibitors were able to stop or reduce their use of other migraine medications while they were taking it. This can prevent medication overuse headache and reduce demand on resources elsewhere. 3. **Suitability of the guidance:** Evidence gathered from The Migraine Trust shows that there is a significant sub-group of patients who are not able to access botulinum toxin type A or do not respond to that treatment. These patients are left with few effective or tolerable alternatives. We would urge the committee to take all necessary steps to consider this technology for use for a smaller group of patients than outlined in the marketing authorisation. We are happy to share the results of these surveys in full with committee members if that would be useful.	
The Migraine Trust	**Q: Has all of the relevant evidence been taken into account?** We believe that all currently available peer reviewed trials have been included in the analysis. However, The Migraine Trust has recently conducted two surveys of relevance to this appraisal which have not been taken into account: **1. CGRP Patient Experience Survey:** We surveyed 203 patients between 14 October and 19 November 2019 who are currently taking (or had recently taken) a CGRP drug for the prevention of their migraine. The survey asks a variety of questions about the patient experience of using CGRP inhibitors, including about effectiveness, tolerability, and comparisons with Botox.	Comment noted. The committee considered the results of both surveys in the context of an expert opinion. This was because of the methodological limitations of the surveys, which are susceptible to bias.

Consultee	Comment [sic]	Response
	2. Snap poll of neurologists and headache nurses: There are currently 59 headache nurses and 28 neurologists with a special interest in headache according to the Association of British Neurologists (ABN). We surveyed 5 headache nurses and 11 neurologists between 22 November and 05 December 2019 about the experiences of their chronic migraine patients with Botox and CGRP drugs. In total, the snap poll results speak to the experiences of 9,490 chronic migraine patients across the UK.	
The Migraine Trust	**Q: Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** The Migraine Trust would like to comment on a few key points: **1. The ACD states that the most relevant comparators are best supportive care for episodic migraine and botulinum toxin type A for chronic migraine.** There is no direct comparison for fremanezumab and botulinum toxin type A. However, direct comparisons for new therapies are rarely available. Therefore, we believe the best comparator for fremanezumab for chronic and episodic migraine is best supportive care and not botulinum toxin type A. **2. The ACD states that it is uncertain whether fremanezumab is more clinically effective than botulinum toxin type A.** While we recognise that the company did not present direct evidence comparing the clinical effectiveness of fremanezumab with botulinum toxin type A, the findings from our CGRP Patient Experience survey can shed more light on the question of clinical effectiveness in the real-world context. Our CGRP Patient Experience Survey shows that for patients who have received both botulinum toxin type A and a CGRP inhibitor for their chronic migraine (n=145), 78% agree or strongly agree that the CGRP drug that they are currently taking (or have taken in the past) is more effective at managing their migraine than Botox and 76% agree or strongly agree that the CGRP drug that they are currently taking (or have taken in the past) has improved their quality of life more than Botox. Our snap poll of neurologists and headache nurses shows that 62% of those surveyed believe that CGRP drugs are as or more effective than Botox based on their real-world experience of treating migraine patients. None of the neurologists or headache nurses we surveyed believed that CGRP drugs are less effective than	Comment noted. The committee agreed that both best supportive care and botulinum toxin type A are relevant comparators for chronic migraine. This has been clarified in section 3.3 of the FAD. Comment noted. The committee considered 2 scenarios in its decision-making, in which the relative efficacy of fremanezumab and botulinum toxin type A: • Was based on results of network meta-analysis done by the company • Was assumed to be equal. The committee acknowledged that the relative efficacy of the 2 treatments was uncertain. When considering the first scenario (based on network meta-analysis results), using the revised base case submitted by the company set to committee preferred assumptions, the ICER was within the range usually considered a cost-effective use of NHS resources. When assuming equal efficacy, fremanezumab produced similar number of QALYs at a slightly higher cost. But the committee noted

Consultee	Comment [sic]	Response
	Botox. 75% of those surveyed agree that their patients would prefer to receive CGRP drugs over Botox. **3. The cost-effectiveness calculations may not consider all of the benefits of fremanezumab** We know that many patients taking oral preventives for their migraine also take acute medication. For example, a recent survey we conducted of people with migraine found that of those currently taking a daily oral preventive for their migraine (n= 703), 68% were also taking an acute medication regularly. Of those surveyed who are currently receiving Botox injections for their migraine (n=169), 70% were also found to be taking an acute medication regularly as part of their treatment. Our CGRP Patient Experience Survey found that the use of CGRP drugs reduces the need for patients to take other medication to help them manage their migraine, with 70% of respondees reporting that they were able to stop or reduce their use of other acute medications for their migraine while they were receiving CGRP treatment. This will help prevent the onset of medication overuse headache and reduce demand on resources elsewhere. This is a step change in migraine management for patients and we would ask that this is accounted for in cost-effective calculations.	that a small QALY benefit would be sufficient to produce an ICER within the range usually considered a cost-effective use of NHS resources. Based on expert opinion captured in Migraine Trust surveys, the committee agreed it could be plausible that fremanezumab may have a small QALY benefit over botulinum toxin type A. Taking this into consideration, the committee concluded that although there are still uncertainties in the model, fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine after 3 preventive treatments have failed. Comment noted. The model accounted for wider resource use in the NHS, depending on the frequency of migraine days. It included: • General practitioner visits • Emergency department visits • Hospitalisations • Nurse practitioner visits • Neurologist visits • Oral triptan usage The committee noted the limitations of the evidence used to estimate the resource use in the model but concluded that these were appropriate for decision making. Please see section 3.21 of the FAD for a summary of these considerations.
The Migraine Trust	**Q: Are the recommendations sound and a suitable basis for guidance to the NHS?** The Migraine Trust would like to raise the following key points: **1. The draft recommendation does not account for the significant sub-group of patients who will fail to respond to botulinum toxin type A**	Comment noted. The committee considered the revised base case submitted by the company during consultation. It included an agreed confidential PAS discount for fremanezumab, updated administration costs for botulinum toxin type A, and fixing of coding errors. The committee noted that using its preferred assumptions, the

Consultee	Comment [sic]	Response
	We agree with the committee's conclusion that there is real-world evidence from the UK to support the effectiveness, tolerability, and safety of botulinum toxin type A. However, not all patients who are eligible to receive this treatment under current NICE guidelines will respond to it. We are not aware of the total size of the UK botulinum toxin type A non-responder population and our understanding is that no one else knows either. However, our snap poll of headache nurses and neurologists sheds some light on the size of this population. Of the 9,490 chronic migraine patients the health professionals polled have seen in their clinic in the past year, 5,085 patients have also received Botox injections. Of those 5,085 patients, an estimated 801 (15.7%) failed to respond to that therapy. This means that an estimated 8.4% of chronic migraine patients are not having their treatment needs met by current treatment options. Our CGRP Patient Experience Survey shows that CGRP drugs are answering a significant unmet need in this patient sub-group, delivering an effective and well-tolerated treatment that many report as 'life changing'. For example, of the patients we surveyed who had failed to respond to Botox (n=125), 76% agree or strongly agree that the CGRP drug they are currently taking (or have taken in the past) has improved their quality of life. **2. The draft recommendation does not account for the difficulties some patients are currently experiencing in accessing botulinum toxin type A** Our snap poll of neurologists and headache nurses shows that over the past year, 9% of their patients receiving Botox (437 patients) have been forced to skip or delay a course of Botox injections due to access, availability, or capacity issues. These findings chime with the results of our CGRP Patient Experience Survey, which show that 12% of eligible patients surveyed had to wait over one year to receive their first course of injections from the time they were first prescribed it. This survey also found that 27% of respondees who had received Botox injections had to pay privately in order to do so.	ICER for fremanezumab compared with best supportive care was within the range usually considered a cost-effective use of NHS resources. It also noted that it was plausible that the ICER for fremanezumab compared with botulinum toxin type A was also within that range, although it noted uncertainties about the comparative effectiveness of these 2 treatment options. The committee also considered additional evidence for patients who had inadequate response to 3 oral preventive treatment and botulinum toxin type A, which was submitted by the company at the consultation. Taking all evidence into consideration, the committee concluded that although there are still uncertainties in the model, fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine after 3 preventive treatments have failed. Please see sections 3.10, 3.25 and 3.26 for a summary of these considerations.

Consultee	Comment [sic]	Response
	We would note that the committee has stated that it cannot consider the use of fremanezumab after botulinum toxin type A because it had not been presented with cost-effectiveness estimates for this group. However, we believe it may be appropriate to evaluate this group of patients, e.g. Botox non-responders and those who face difficulty in accessing Botox, separately as their need is considerable. We urge the committee to take all necessary steps to consider this technology for use in this smaller group of patients than originally stated in the marketing authorisation.	
The Migraine Trust	**Q: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination about any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The Migraine Trust would like to raise the following key point: **1. Migraine can be classed as a disability under the Equality Act 2010** In our most recent survey, nearly half (48%) of respondents with migraine consider themselves to have a disability as defined by the Equality Act 2010. However, for the particular group of patients under consideration for fremanezumab, i.e. chronic migraine patients who have failed at least three oral preventives, 84% of respondents said they considered themselves as having a disability as defined by the Equality Act 2010. This is a group of people who are particularly disabled by their migraine.	Comment noted. The committee acknowledged migraine is a highly disabling disease. Please see section 3.1 for a summary of these considerations.

Comments received from commentators

Commentator	Comment [sic]	Response
Allergen	Allergan welcomes the opportunity to respond to the Appraisal Consultation Document for fremanezumab for the prevention of 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. **Allergan Response – Key Points**	Comment noted. The committee acknowledged there are no head-to-head data for fremanezumab and botulinum toxin type A. It also noted the limitations of the indirect treatment comparison. So it considered 2 scenarios, one where relative efficacy of the 2 treatments is based on network meta-analysis and another where equal efficacy

Commentator	Comment [sic]	Response
	▪ Allergan concurs with the Committee's assessment that there is no robust evidence that fremanezumab is more clinically effective than onabotulinumtoxinA. This is consistent with the view reached in other international health technology assessments of fremanezumab, including a recent review by the Institute for Clinical and Economic Research (ICER) in the United States.	was assumed. The committee also agreed that both botulinum toxin type A and best supportive care are relevant comparators for chronic migraine. Please see sections 3.11 and 3.25 for a summary of these considerations.
	▪ Allergan concurs with the Committee's assessment that the long-term effectiveness of fremanezumab is uncertain. In contrast, the long-term effectiveness of onabotulinumtoxinA has been demonstrated extensively in both clinical trials and real-world settings (onabotulinumtoxinA evidence section below). The long-term safety of onabotulinumtoxinA has been similarly demonstrated.	Comment noted. The committee acknowledged that there was real-world evidence supporting the effectiveness, tolerability and safety of botulinum toxin type A from a UK perspective (see section 3.11 of the FAD for details).
	▪ There is a lack of evidence specifically for the population relevant to the submission: patients who have previously failed 3 or more prior migraine preventive therapies. All data to support the clinical effectiveness of fremanezumab for people with episodic or chronic migraine were taken from the post-hoc subgroup analysis of FOCUS trial. Allergan agrees with the Committee's assessment that this reduces the reliability of the findings.	Comment noted. The committee acknowledged the limitations of the post-hoc analysis (see section 3.8 of the FAD for details).
	▪ Allergan believes that the economic evidence provided to the Committee underestimates the degree of uncertainty regarding the cost-effectiveness of fremanezumab 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. For instance, one key issue in the economic model is the assumption that the patients who stop treatment with fremanezumab due to positive response would never recommence the treatment when the symptoms return. This is not substantiated by evidence. Evidence from Andreou et al. in the UK clinical practice shows that 20% of patients whose treatment with onabotulinumtoxinA was discontinued relapsed into a chronic pattern after 6 months and hence subsequent treatments were scheduled. In addition, the manufacturer's assumption that patients will likely maintain the treatment benefit after discontinuation of fremanezumab is unrealistic as the treatment effect will diminish over time.	Comment noted. The committee agreed it was unrealistic to assume that the treatment effect would be maintained indefinitely after stopping treatment. Therefore the committee concluded that it was not appropriate to apply a positive stopping rule in the model (that is, the model results considered by the committee in its decision-making allowed no positive discontinuation). Please see section 3.18 of the FAD for a summary of these considerations.

Commentator	Comment [sic]	Response
	The manufacture's model also assumes that all patients will self-administer fremanezumab, which is highly optimistic, especially in the context of monthly injections and/or in patients with physical or mental disabilities and those who have a phobia of needles or a preference for oral tablets. This assumption has already been challenged in the NICE assessment of erenumab where the situation is comparable. Based on clinical practice, it is more realistic that a number of migraine patients will need fremanezumab to be administered to them, and patients to be monitored by specialists to monitor compliance to the regimen. Therefore, Allergan believes that the manufacture's assumption of a zero-cost administration is highly optimistic leading to underestimation of cost per QALY gained. ▪ Allergan agrees with the Committee that cost-effective and well-tolerated treatment options are needed, especially for chronic migraine that is especially burdensome to patients. As our response here 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 a large number of centres across the UK where onabotulinumtoxinA is administered for chronic migraine and service capacity continues to expand. Allergan is working extensively with the NHS to increase capacity and access for patients.	Comment noted. The committee agreed that some people will need fremanezumab to be administered for them. The committee's preferred assumption was that 10% of people having fremanezumab would need the treatment to be administered for them. Please see section 3.22 of the FAD for a summary of these considerations. Comment noted. No action needed.
Allergan	Allergan also provided updated data for Botox	Comment noted. No action needed.
Novartis Pharmaceuticals UK	The fremanezumab manufacturer's rationale for the inclusion of data from Study 295, which compared erenumab and placebo, is reported as being "to strengthen the network". This rationale is not challenged in the Appraisal Consultation Document. However, it is unclear how the inclusion of Study 295 would strengthen the network – a point made by the Evidence Review Group in their report ("In addition, the company noted that while trials relating to erenumab were included to 'strengthen the network', it was unclear how this would have been the case given that included erenumab trials were connected to the network only via the placebo node" [Evidence Review Group report, pg 151]). Based on the framework for considering inclusion of evidence as outlined in NICE Decision Support Unit Technical Support Document 1, the synthesis comparator set for the fremanezumab appraisal would consist of fremanezumab, botulinum toxin and placebo, and included trials should be "all trials on the target population that compare two or more of the treatments from the synthesis comparator set". This would not include Study	Comment noted. The ERG highlighted that Study 295 was incorrectly included in the network meta-analysis (see committee papers for details). The committee considered this as one of the limitations of the network meta-analysis. But it noted that because including this study did not strengthen (or weaken) the network, is not expected to have an effect on the results. Please see section 3.11 of the FAD for a summary of these considerations.

Commentator	Comment [sic]	Response
	295, as this includes only one treatment (placebo) from the synthesis comparator set. Whilst Technical Support Document 1 does discuss extension of the synthesis comparator set to incorporate other trials, it notes both advantages and *disadvantages* to such extension and states that "while extension of the network is not ruled out….it would not be considered as the "base-case" analysis". Therefore, we suggest that the results of the indirect treatment comparison that incorporates Study 295 should be treated with caution, and that an indirect treatment comparison excluding Study 295 would be more appropriate for decision-making.	
Novartis Pharmaceuticals UK	The fremanezumab manufacturer's approach to utility values modelled that patients on treatment receive a utility benefit over and above that resulting from the reductions in monthly migraine days due to treatment effect. In this context, the Appraisal Consultation Document states that the Committee "noted that the application of treatment-specific utility values was consistent with previous migraine appraisals". However, we consider that this statement is misleading. There have only been two prior technology appraisals in migraine (botulinum toxin [TA260] and erenumab [ID1188]). In the botulinum toxin appraisal it is correct that treatment-specific utility values were used: the mapping algorithm was used to derive utilities by treatment arm separately in order to "understand the broader effects of treatment beyond the number of headaches experienced by patients". However, for the more recent erenumab appraisal, utility was modelled to be only dependent upon frequency of monthly migraine days; no additional on-treatment utility benefit was incorporated above and beyond any beneficial impact of treatment on improvement in frequency of migraine. Therefore the statement in the Appraisal Consultation Document that use of treatment-specific utility values was consistent with previous migraine appraisals is at least partially incorrect. In this context, we agree with the Committee's stated conclusion in the Appraisal Consultation Document that "additional on-treatment utility value benefits were not supported by the evidence and should not be included in the economic model", which would represent an approach consistent with the assumptions underlying decision-making in the erenumab appraisal.	Comment noted. The committed agreed additional on-treatment utility value benefits should not be included in the model. This was because additional on-treatment utility value benefits applied by the company were not supported by the evidence. Please see section 3.20 of the FAD for a summary of these considerations.
Novartis Pharmaceuticals UK	The Appraisal Consultation Document states that the Committee concluded that it preferred a lifetime time horizon of at least 30 years to ensure that all relevant costs and benefits associated with fremanezumab were captured. Given that the considerations contributing to the decision on time horizon in the fremanezumab appraisal are similar to those in the erenumab appraisal (limits to long-term data, requirement to capture all relevant costs and benefits, same patient population [and hence same patient ages in clinical practice]), we consider that the Committee	Comment noted. The committee considered that a model time horizon of at least 30 years should be used to ensure that all relevant costs and benefits associated with fremanezumab were captured. The ERG applied 58-year horizon in their analyses, based on the mean age of patients entering the

Commentator	Comment [sic]	Response
	preferences over time horizon should be consistent for the fremanezumab and erenumab appraisals. In the erenumab appraisal, a lifetime time horizon was similarly preferred by the Evidence Review Group and subsequently the Committee. However, the Evidence Review Group's adjustment to model a lifetime time horizon resulted in a time horizon of 64 years. Therefore, we consider that defining a lifetime time horizon as 30 years for the fremanezumab appraisal versus 64 years for the erenumab appraisal results in the potential for inconsistency in decision-making. As such, an approximately 64 year time horizon should be considered as the definition of a lifetime time horizon for the fremanezumab appraisal, or otherwise more full justification for a choice of a 30 year time horizon as "lifetime" should be provided.	model of 42 years. This has been clarified in sections 3.24 and 3.25 of the FAD.
Novartis Pharmaceuticals UK	The Appraisal Consultation Document describes the HALO-EM and HALO-CM studies as evaluating fremanezumab in patients with chronic/episodic migraine "when fewer than 3 classes of preventive treatment have failed". We believe this is incorrect, as the exclusion criteria for these studies specify patients who have experienced a lack of efficacy after ≥3 months of treatment *of at least two of four classes* of preventive treatments. This implies that patients for whom two prior preventive treatment classes have failed would be excluded from the trial, and the Appraisal Consultation Document wording should therefore be adjusted to state that the study populations comprised patients "when fewer than **2** classes of preventive treatment have failed". In addition, this exclusion criterion specifies that patients had to have experienced lack of efficacy after *at least 3 months of treatment* to be counted as having had a prior treatment failure. This suggests that the HALO study populations may have still included patients for whom three prior therapies had 'failed', where this failure was defined on the basis of lack of tolerability or perhaps lack of efficacy as determined by less than 3 months of treatment. For the FOCUS trial, an inadequate treatment response was defined as a lack of clinically meaningful improvement after at least three months of therapy, but also as intolerance to the treatment or the treatment being contraindicated or unsuitable – this highlights that considerations over tolerability may constitute part of the definition of treatment failure. Additionally, as topiramate (a treatment relevant to UK clinical practice) was not included within the list of exclusion criteria relating to 'failed' prior lines of treatment (see the fremanezumab manufacturer's response to Evidence Review Group clarification question A18), the HALO trials would have potentially included patients with prior failure to topiramate. From the Committee papers it does not appear that the appraisal has explored the potential availability of data from the HALO studies for patients who might meet the decision problem of 3 prior treatment failures where 'failure' is defined on the basis of prior topiramate failure, tolerability issues,	Comment noted. The ERG has highlighted the differences in inclusion and exclusion criteria between HALO-EM, HALO-CM and FOCUS. Because of this, it considered it is unlikely that many (if any) patients enrolled in HALO studies would fulfil the criteria of prior failure of at least 3 oral preventive treatments, even if broader definition of treatment failure was used. The committee agreed that FOCUS trial provides the most relevant clinical evidence for the population of interest (see section 3.5 of the FAD).

Commentator	Comment [sic]	Response
	contraindication or lack of efficacy after <3 months treatment (all of which may potentially be relevant criteria for 'failure' in clinical practice). As such, the appraisal may not currently be taking into account potentially relevant data from the HALO studies, which could be important in fully understanding the treatment effect of fremanezumab in the population of 3 prior treatment failures that is under consideration in the decision problem. Such data, if available, could be informative given that the only other data in this subgroup is from the FOCUS study.	
Novartis Pharmaceuticals UK	We agree with the comments in the ACD that the per cycle all-cause discontinuation rate for fremanezumab appears high, and that this has the potential to affect cost-effectiveness results as it has a direct influence on accrual of treatment costs into the long-term. As the direct source of the all-cause discontinuation rate is not provided it is difficult to comment on the appropriateness of the value used for the per cycle discontinuation rate – however, we agree that because treatment allocation was not blinded in the HALO open-label extension study, the impact of additional injections to preserve blinding does not offer an explanation as to any potentially higher discontinuation rate. As such, there does not appear in the Committee papers to be a valid explanation for why discontinuation from fremanezumab in the longer-term is higher than seen with erenumab. In the absence of any robust explanation for the use of an all-cause discontinuation that, as judged by the NICE Committee, is higher than expected, we agree that the preferred scenario regarding post-discontinuation assumptions is not the manufacturer's default approach but is instead the ERG's scenario in which patients revert to baseline monthly migraine days after all-cause discontinuation.	Comment noted. The all-cause discontinuation rate in the model was based on all-cause discontinuation in the HALO open-label extension. The committee noted this rate was higher than expected but accepted that the rate was based on clinical trial data. However, the committee noted that post-discontinuation assumptions used by the company were overly optimistic. It concluded that ERG approach should be used in which patients revert to their baseline monthly migraine days (rather than migraine days frequency observed in best supportive care arm). Please see sections 3.15 and 3.16 for a summary of these considerations.

Summary of comments received from members of the public

Theme	Response
Do not agree with the ACD decision to not recommend fremanezumab	Comment noted. At the second committee meeting, the committee discussed responses to the ACD, the company's revised base case and new evidence submitted by Teva at consultation. The committee concluded that although there are still uncertainties in the model, fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine (but not episodic migraine) after 3 preventive treatments have failed. Please see sections 1 of the FAD for revised wording of the recommendation, and sections 3.24, 3.25, 3.29 and 3.30 of the FAD for a summary of committee considerations.

Theme	Response
Disease impact	
Highly debilitating/crippling disease, with severe impact on patients' quality of life, social activities, relationships with family and friends; the wording of the ACD does not reflect how severe the impact is	Comment noted. The committee recognised that migraine is a highly debilitating disease with substantially effects on both physical and psychological aspects of quality of life and employment. The wording in the FAD has been adjusted to make this clear (section 3.1)
WHO classed migraine as more disabling than blindness, paraplegia and acute psychosis and on the same level of disability as quadriplegia and dementia	Comment noted. The committee recognised that migraine is a highly debilitating disease. The wording in the FAD has been adjusted to make this clear (section 3.1)
Can be bedbound during attacks	Comment noted. The committee recognised that migraine is a highly debilitating disease. The wording in the FAD has been adjusted to make this clear (section 3.1)
Impact on employment – forced to quit employment (benefits / early retirement), missed attendance, affects the quality of work, fear for job security, stress at work	Comment noted. The committee recognised that migraine is a highly debilitating disease which can adversely affect quality of life, affecting people's ability to do their usual activities, including work. The wording in the FAD has been adjusted to make this clear (section 3.1)
Impact on career progression, not realised potential	Comment noted. The committee recognised that migraine is a highly debilitating disease which can slow personal and professional development so that people feel they have unachieved potential. The wording in the FAD has been adjusted to make this clear (section 3.1)
Impact on mental health: depression, anxiety, feeling worthless, feeling life is not worth living, suicidal thoughts	Comment noted. The committee recognised that migraine is a highly debilitating disease with considerable impact on mental health. The wording in the FAD has been adjusted to make this clear (section 3.1)
Impact of family members, in particular kids and partners	Comment noted. The committee recognised that migraine is a highly debilitating disease. The wording in the FAD has been adjusted to make this clear (section 3.1)
"Invisible disability" – feeling isolated and abandoned	Comment noted. The committee recognised that migraine is a highly debilitating disease. The wording in the FAD has been adjusted to make this clear (section 3.1)
Current treatments	

Theme	Response
High unmet need for new treatment options	Comment noted. The committee recognised high unmet need for additional treatment options after 3 preventive treatments had failed (see section 3.3 of the FAD). It also recognised this unmet need is particularly high in people for whom botulinum toxin type A has failed, because of high disease burden and no further treatment options (see section 3.10 of the FAD). The committee was also aware that some people who are eligible for botulinum toxin type A are unable to access this treatment in a timely manner. This is because few clinics in the UK are offering this treatment, and there are long waiting lists to access it (see section 3.3 of the FAD).
Existing treatments don't work for many people and have bad side effects; trialling 4th ineffective oral treatment has high impact on patients' lives (lack of relief, side effects); some patients tried 10+ treatments with no relief	Comment noted. The committee recognised high unmet need for additional treatment options after 3 preventive treatments had failed (see section 3.3 of the FAD). It noted that there was no clear evidence that using oral preventives after 3rd line was of benefit, and side effects of may outweigh any benefits.
No viable treatment options for people who did not respond to oral preventive treatment and botox, or don't want to receive botox	Comment noted. The committee recognised the high disease burden and high unmet need for new treatment options for people for whom 3 oral preventive therapies and botulinum toxin type A have failed (see section 3.10 of the FAD). The committee was also aware that some people who are eligible for botulinum toxin type A are unable to access this treatment in a timely manner. This is because few clinics in the UK are offering this treatment, and there are long waiting lists to access it (see section 3.3 of the FAD).
Botox not effective for many patients	Comment noted. The committee acknowledged that botulinum toxin type A is ineffective for about 1 in 3 people. It recognised the high disease burden and high unmet need for new treatment options in this population (see section 3.10 of the FAD).
Botox not available to everyone; it needs to be administered in specialist services – long waiting lines (capacity issues), need to travel to larger centres	Comment noted. The committee recognised that some people who are eligible for botulinum toxin type A are unable to access this treatment in a timely manner. This is because few clinics in the UK are offering this treatment, and there are long waiting lists to access it (see section 3.3 of the FAD).
Botox needs 32 injections which can be painful/stressful to patients	Comment noted. The committee recognised that the administration of botulinum toxin type A may be considered more inconvenient and unpleasant compared to monthly or quarterly administration of fremanezumab.
Botox can have side effects	Comment noted. The committee recognised the high disease burden and high unmet need for new treatment options for people for whom 3 oral preventive therapies and botulinum toxin type A have failed – either because of insufficient efficacy of tolerability issues (see section 3.10 of the FAD).

Theme	Response
Not all treatments work for everyone – more treatment options needed	Comment noted. The committee recognised high unmet need for additional treatment options after 3 preventive treatments had failed (see section 3.3 of the FAD).
Experience with fremanezumab	
Fremanezumab was shown to be effective with few side effects	Comment noted. The committee concluded that that fremanezumab appears to be more clinically effective than best supportive. But it also acknowledged limitations of the post-hoc nature of the evidence, lack of long-term data to show sustained efficacy, and unclear relative efficacy of fremanezumab and botulinum toxin type A (see sections 3.8 and 3.11 of the FAD).
Fremanezumab is specifically developed to treat migraine	Comment noted. The committee recognised that fremenezumab is a specialist treatment and that current oral treatment options for preventing migraine include drugs that are used to treat other conditions.
Fremanezumab can decrease both frequency and severity of migraine attacks	Comment noted. The committee recognised that fremanezumab was shown to reduce monthly migraine frequency compared with best supportive care at 12 weeks of treatment.
Fremanezumab can improve quality of social and work lives, can be “life-changing” for some patients	Comment noted. The committee recognised that fremanezumab may improve patients’ quality of life. But it also acknowledged the limitations of the post-hoc nature of the evidence, lack of long-term safety and efficacy data, and unclear relative effectiveness of fremanezumab and botulinum toxin type A (see sections 3.8 and 3.11 of the FAD).
Fremanezumab can have positive impact on mental health and suicidal thoughts	Comment noted. The committee recognised that migraine can adversely affect quality of life, and that some people with migraine have severe depression and suicidal thoughts. The committee concluded that fremanezumab is a clinically effective treatment for the prevention of migraine. But it also acknowledged limitations of the post-hoc nature of the evidence, lack of long-term efficacy and safety data, and unclear relative effectiveness of fremanezumab and botulinum toxin type A (see sections 3.1, 3.8 and 3.11 of the FAD).
Fremanezumab can be self-administered (or could be administered by a family member/friend) – preferred and less stressful for patients than botox and could free up NHS resources	Comment noted. The committee recognised that most patients would be able to self-administer the treatment, and this may be preferred over administration for botulinum toxin type A.
Fremanezumab may not be effective for everyone	Comment noted. The committee recognised fremanezumab will not be effective for everyone.

Theme	Response
Initially could be available for defined patient population – for example, only those for whom botox did not work / those with chronic migraine only / chronic migraine and high frequency episodic migraine	Comment noted. The committee recommended fremanezumab as a treatment option for preventing migraines in adults with chronic migraines for whom at least 3 preventive treatments have failed.
Further trials may be needed to define which patients are likely to benefit more with fremanezumab and which with botox – none of the drugs likely to be suitable for all patients	Comment noted. No action needed.
Wider benefits	
Cost effectiveness analyses should consider the wider impact on economy: "migraine costs the UK economy £8.8 billion per year and a total of 86 million workdays"	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 fremanezumab in practice had been captured in the model (see FAD section 3.21).
Fremanezumab could have broader benefits to the health care system: use of mental health and emergency care services	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 fremanezumab in practice had been captured in the model (see FAD section 3.21).
All-Party Parliamentary Group on Primary Headache Disorders 2014, and the National Audit Office suggested that greater savings can be made by averting indirect costs of patients accessing services in an emergency setting, than by focusing on directs costs of migraine.	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 fremanezumab in practice had been captured in the model (see FAD section 3.21).
Fremanezumab could free up botox clinical from those who need it most	Comment noted. The committee was aware of capacity issues at clinics able to deliver botulinum toxin type A treatment.
Equality	
Affects more women than men – contribution to increase in gender pay gap; women' diseases understudies and underfunded	Comment noted. The committee discussed equality issues, and agreed that its recommendations do not have a different impact on people protected by the equality legislation than on the wider population.

Theme	Response
Recommendation discriminates against people with migraine – many of whom are considered having disability	Comment noted. There are no sub-group populations within this guidance so no group within the population of people with episodic or chronic migraine has been treated less favourably.
Available in Scotland – discrimination on grounds of race and postcode	Comment noted. The Committee cannot speculate about the deliberations of another body. NICE and the Scottish Medicines Consortium make decisions using different processes and, in the case of any individual technology, submissions to SMC and NICE may not be identical.
The recommendation may discriminate against people on lower incomes who won't afford private prescription	Comment noted. In accordance with NICE's social value judgement principles, no priority is given based on individuals' income, social class, position in life or social roles in guidance developed for the NHS. NICE's standard approach to economic modelling (the 'reference case') does not compare NHS healthcare with privately funded healthcare.

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

The Royal College of Physicians endorsed the response submitted by the Association of British Neurologists

NICE National Institute for Health and Care Excellence

Fremanezumab for preventing migraine [ID1368]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 6 December 2019 **email:** NICE DOCS

ID1368 frem Teva ACD response 06122	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):	[**Teva**]
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]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fremanezumab for preventing migraine [ID1368]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 6 December 2019 **email:** NICE DOCS

<table>
<tr><th>Comment number</th><th>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.</th></tr>
<tr><td>1</td><td>Section 3.5 of the ACD includes the statement that "FOCUS defined an inadequate treatment response as a lack of clinically meaningful improvement after at least 3 months of therapy, intolerance to the treatment or the treatment was contraindicated or unsuitable. The clinical experts explained that a contraindication would not necessarily represent a treatment failure." Teva wishes to clarify the definitions of an inadequate treatment response in the FOCUS study. Firstly, Teva acknowledges the comments from the clinical experts that a contraindication may not necessarily represent a treatment failure. However, it is also important to note that the published FOCUS results demonstrate that, in the vast majority of cases, a lack of efficacy or intolerability were the reasons for a recorded treatment failure and not contraindications (see data below, reproduced from Supplemental Table 4 of Ferrai et al. Lancet 2019; 394: 1030–1040). Overall, it should be noted that only 42 out of 2,257 failures within FOCUS were recorded as being due to a contraindication (1.9%). In addition, if a treatment is contraindicated, then this treatment is not available for use so surmounts to a failure to be successfully treated.

<u>Proportion of patients selecting 'contraindication or not suitable for use' as reason for failure by therapeutic class</u>
<table>
<tr><th>Preventive treatment class</th><th>Placebo (n=279)</th><th>Fremanezumab Quarterly (n=276)</th><th>Fremanezumab monthly (n=283)</th></tr>
<tr><td>Angiotensin II receptor antagonist n (%)
Contraindicated/not suitable n (%)</td><td>51 (18)

0</td><td>55 (20)

0</td><td>48 (17)

0</td></tr>
<tr><td>Anticonvulsants n (%)
Contraindicated/not suitable n (%)</td><td>184 (66)

1(<1)</td><td>215 (78)

4 (2)</td><td>217 (77)

2 (<1)</td></tr>
<tr><td>Beta-blockers n (%)
Contraindicated/not suitable n (%)</td><td>159 (57)

1 (<1)</td><td>145 (53)

7 (5)</td><td>164 (58)

4 (2)</td></tr>
<tr><td>Calcium channel blocker n (%)
Contraindicated/not suitable n (%)</td><td>58 (21)

0</td><td>39 (14)

0</td><td>47 (17)

0</td></tr>
<tr><td>Onabotulinumtoxin A n (%)
Contraindicated/not suitable n (%)</td><td>77 (28)

0</td><td>78 (28)

1</td><td>73 (26)

0</td></tr>
<tr><td>Tricyclics n (%)
Contraindicated/not suitable n (%)</td><td>140 (50)

0</td><td>125 (45)

1 (<1)</td><td>129 (46)

1 (<1)</td></tr>
<tr><td>Valproic acid n (%)
Contraindicated/not suitable n (%)</td><td>82 (29)

4 (5)</td><td>83 (30)

13 (16)</td><td>88 (31)

3 (3)</td></tr>
</table>
</td></tr>
<tr><td>2</td><td>In Section 3.5 of the ACD, it is stated that, "FOCUS does not fully reflect the people who may be eligible for fremanezumab in clinical practice." Subsequently, the ACD states that "…valproic acid was considered differently to other preventive treatments in FOCUS and was regarded as being in a class of its own. Therefore, a person whose migraine had an inadequate response to valproic acid, topiramate and propranolol would be included in the subgroup analysis (3 or more preventive treatment failures) even though this represents a failure of 2 treatment classes." Teva would like to</td></tr>
</table>

	clarify the design of the FOCUS study, with this study designed to include patients based on the number of preventive classes failed rather than individual treatment failures. The rationale for doing so was to enhance the robustness of the study design, and to ensure that patients had utilised (and failed) on preventive treatments with distinct mechanisms of action, and not just failed, for example, on two beta-blockers and one other treatment. Within the FOCUS study, valproic acid was assigned to a class of its own, rather than being grouped in a class of 'anticonvulsants' with topiramate. This decision was taken for a number of reasons. Firstly, the particular risks of valproic acid and its associated restricted usage in women of childbearing potential were considered during the trial design; however, these risks did not appear to have a significant impact on the number of patients who were considered to have failed this treatment for the reason of 'Contraindicated/not suitable' (see figures above). Also, it should be noted that although both topiramate and valproic acid can be classified as anticonvulsants, these drugs have distinctions in their proposed mechanisms of action and have differences within their licensed indications (only topiramate is licensed for use in migraine). This highlights that even though both drugs are anticonvulsants, they have the capability to work on distinct molecular pathways. These differences mean that valproic acid is utilised in patients who have previously failed topiramate, and vice versa; a practice confirmed by clinical experts to be consistent with the management of patients in the UK. As a global multicentre study, FOCUS was influenced by clinical practice within all participating countries, and it is notable that in many countries (Germany is a particular example) valproic acid is used predominantly as a last line treatment. This was therefore an additional reason for separate consideration of valproic acid failure and is why randomisation in FOCUS was stratified by failure with valproic acid to ensure there was an even distribution across the trial arms for these difficult to treat patients. Teva acknowledges that the subgroup analysis of patients whom have failed 3 or more prior preventive therapies may contain a proportion of patients whom have failed both valproic acid and topiramate. However, this population does not represent the majority of patients within the FOCUS study (31% of CM patients and 38% of EM patients had reported failure of both valproic acid and topiramate). It must be noted that the failure history for each patient occurred prior to enrolment into the FOCUS study rather than being driven by the study protocol. Therefore, the documented inadequate response to therapies reported in the FOCUS study reflects real-world clinical practice, including UK, where clinicians would prescribe both valproic acid and topiramate when there is a clinically valid rationale to do so. Also, Teva notes that all previous NICE guidance, and all major clinical guidelines, refer to number of failed treatments and not classes of failed treatment. So whilst Teva accepts that inadequate response to both valproic acid and topiramate may not technically meet our own stricter definition of 'failed classes' employed within the FOCUS study, it does certainly meet the standard definition of failed treatments. To exemplify this point, we note that the NICE recommendation for onabotulinumtoxin A states that a patient must have failed at least three individual treatments and not three classes of preventive therapies. Therefore, a CM patient that has failed topiramate, valproic acid and one other treatment, in the UK, would be eligible to receive treatment with onabotulinumtoxin A. Given this, Teva strongly refutes the ACD conclusion that *'FOCUS does not fully reflect the people who may be eligible for fremanezumab in clinical practice'*.
3	In Section 3.5 of the ACD, it is stated that, "…*valproic acid was considered differently to other preventive treatments in FOCUS and was regarded as being in a class of its own. Therefore, a person whose migraine had an inadequate response to valproic acid, topiramate and propranolol would be included in the subgroup analysis (3 or more preventive treatment failures) even though this represents a failure of 2 treatment classes*. ***The committee was concerned that because of this a substantial proportion of people in the subgroup may not have had 3 or more failed preventive treatments***." In addition, to the clarifications provided in comment number 2, Teva also finds the specific statement highlighted in bold (above) to be factually incorrect where it is stated that a failure of valproic acid, topiramate and propranolol would not be classed as having three failed preventive treatments. As outlined within comment number 2, these treatments have distinctions and can be prescribed separately to a single patient. These treatments are also recognised as distinct

	within a number of clinical guidelines. Also, all previous NICE guidance, and other major clinical guidelines, focus on number of failed treatments and not classes of failed treatment. Therefore, it is not factually correct to state that failure on valproic acid and topiramate would only be classed as failure of a single treatment.
4	Section 3.6 of the ACD contains factual errors relating to the loading dose utilised within the clinical trials of fremanezumab. Teva would like to clarify that, as outlined within the company submission, a loading dose was utilised within the HALO CM trial and for patients with CM in the FOCUS trial. Patients in the HALO EM trial and patients with EM in the FOCUS trial did not receive a loading dose. Teva also finds that the wording in this Section around blinding to be unclear. The ACD states "…*the loading dose, consisting of 3 injections, was given to maintain the blinding of treatment allocation*." The loading dose was not given to maintain blinding to treatment allocation. Patients were administered additional placebo injections (where necessary) in order to maintain blinding to treatment allocation.
5	In Section 3.10 of the ACD it is stated that, "…*there was real-world evidence supporting the effectiveness, tolerability and safety of botulinum toxin type A from a UK perspective*." Teva notes that the main part of these data have been collected using a treatment protocol that does not follow NICE guidelines, and comes from a single centre analysis. Therefore, these data have limitations in their generalisability to the population of interest being considered by this appraisal.
6	Section 3.10 of the ACD concludes that *"…it was appropriate to consider a scenario in which equivalent efficacy was assumed*…" Teva does not feel that this is a reasonable interpretation of the evidence and that the NMA remains the best available data for comparison between fremanezumab and onabotulinumtoxin A. The NMA shows an additional benefit for fremanezumab over onabotulinumtoxin A across all endpoints analysed, yet makes a number of assumptions that are conservative with respect to the relative efficacy of fremanezumab. Additionally, the NMA was unable to include a number of additional patient and healthcare burden advantages for fremanezumab (a single monthly subcutaneous injection (or three injections every three months) compared to 31 injections in the head and neck every 12 weeks; the ability for fremanezumab to be self-injected at home compared to administration in hospital by a highly skilled healthcare professional). Teva also notes that, due to limited data available for onabotulinumtoxin A, any advantage for fremanezumab either from reductions in monthly migraine days or the distribution of migraine patients between MMD states could not be accounted for within the economic model. Altogether, these factors demonstrate clear advantages for fremanezumab over onabotulinumtoxin A, and additional benefits that are not currently captured within the economic modelling. Teva has investigated an updated base case and scenarios for the comparison to onabotulinumtoxin A, and these are included within the new evidence Appendix. Under all modelled scenarios using the new value proposition and the NMA efficacy results, fremanezumab was demonstrated to be a cost-effective treatment when compared to onabotulinumtoxin A (and also compared to best supportive care).
7	In Section 3.14 it is stated that "…*the discontinuation rate in the HALO extension study was higher than that seen in the extension studies of another anti-calcitonin gene-related peptide (CGRP), erenumab.*" Teva would like to reiterate that the discontinuation rate within the model uses the best available data for fremanezumab which comes from the HALO extension trial. These clinical data show the long-term all-cause discontinuation rate for patients receiving fremanezumab and represents the best available data for this treatment.
8	Section 3.15 includes a statement that, "*The committee noted that a placebo effect would not be seen in clinical practice when no treatment is given*." Teva does not find this to be an accurate interpretation of the evidence submitted. The Best Supportive Care group was modelled to receive acute medication for their migraine, and this is similar to the placebo treated groups within the clinical trials. Therefore, the placebo effect modelled within these patients is not based on no treatment being given, but, rather, is based on improvements seen with acute migraine treatment that would form part of a best supportive care regimen for migraine.
9	In Section 3.17, the committee concludes that a positive stopping rule is not appropriate for consideration. Teva finds that this decision limits the suitability of these recommendations for NHS practice. Clinical experts have been clear to Teva that treatment would not be continued indefinitely and that patients who show a sufficient response and who no longer require treatment would have

	this treatment positively stopped. Positive stopping of preventive treatment within migraine is also recommended within SIGN and BASH guidelines; whilst European Headache Federation guidelines on anti-CGRP migraine treatments recommend that continuation on treatment should be managed in the same way as for other migraine preventative therapies. In addition, the SmPC of fremanezumab states that "*Evaluation of the need to continue treatment is recommended regularly thereafter* [after initial assessment of efficacy]". Therefore, Teva finds that it is clear that a positive stopping rule will be utilised within NHS clinical practice, which has been corroborated by clinical expert opinion gathered by Teva. An updated positive stopping rule is included within the base case outlined in the new evidence Appendix, alongside additional scenario analyses in this area. These scenarios demonstrate that fremanezumab is a cost-effective treatment for both chronic and episodic migraine.
10	Section 3.19 states that there was no evidence that differential utility benefits have been shown for people with migraine whilst on-treatment. Teva does not believe that this is a clinically valid interpretation of the available evidence. Firstly, the data presented utilised clinical trial data from the FOCUS trial which demonstrated that, for a patient with a given number of monthly migraine days, their quality of life was higher when being treated with fremanezumab. Similar effects of quality of life benefits in patients with similar migraine/headache day frequencies have been demonstrated in data from a number of migraine clinical trials. This effect has been seen with both erenumab (Lipton RB *et al*. *J Med Econ* 2018; 21: 666–675) and onabotulinumtoxin A (Batty AJ *et al*. *J Med Econ*. 2013; 16: 877–887). Both of these studies are focussed on economic modelling, but utilise data from the key clinical trials of these treatments, and in both cases these analyses result in differential on- and off-treatment utilities. In addition, the previous NICE appraisal of onabotulinumtoxin A concluded that the most plausible ICER included separate on- and off- treatment utilities, with the FAD stating that "*The Committee noted that when the ERG equalised the non-MSQ parameter values, less non-monotonicity was observed, and the deterministic ICER was £18,900 per QALY gained when applying different utility values to each arm. The Committee concluded that this was the most plausible ICER because it incorporated the Committee's preferred inputs and assumptions including a 30% negative stopping rule, applied different utilities to treatment arms (within the Committee's reservations stated in section 4.13), and equalised the non-MSQ parameter values in the utility mapping functions*." Furthermore, advice that Teva has received from clinical experts has stated that differences in utilities are well known to exceed reductions in monthly migraine days with this measure unable to capture the full burden of headaches in terms of duration, severity and associated factors (nausea *etc.*). Overall, Teva finds that there is clear evidence for differences between on- and off-treatment utilities and this factor is included within the updated base case included within the new evidence Appendix, alongside additional scenario analyses. These scenarios demonstrate that fremanezumab is a cost-effective treatment for both chronic and episodic migraine.
11	In Section 3.23, the ACD quotes an ICER value of £40,297 for when the NMA effectiveness estimate for onabotulinumtoxin A was utilised. During an inspection of the updated economic model supplied by NICE, Teva has noted a coding error on the utilities sheet whereby the treatment benefits were not equalised for onabotulinumtoxin A (so that onabotulinumtoxin A still received the on-treatment utilities). When corrected to ensure that all on- and off-treatment utilities are equal within the model an ICER value of £32,295 is produced.
12	The ICERs within the ACD for fremanezumab match the ICERs presented within the ERG's Addendum #3. Within this document, an additional change to the model is noted beyond those detailed within the ACD. This change was described as the "*Removal of residual fremanezumab effect in non-responders*." This change removes any MMD reductions seen within the fremanezumab non-responders during their 12-week treatment trial. Teva finds this change to be unjustifiable as it goes against the clinical trial evidence used to model this population. The reduction in monthly migraine days modelled within this population was a real effect that occurred within the clinical trial; however, this response was not sufficient for these patients to continue treatment (*i.e.* it did not reach the threshold of a clinically meaningful response of at least 30%/50% reduction in monthly migraine days). After the 12-week trial these patients stopped treatment and reverted to their baseline MMDs (a conservative assumption in itself as some treatment benefit may be maintained within these

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	patients). In addition, this alteration to the model impacts its ability to model the observed clinical trial results by removing some of the efficacy of fremanezumab. The modelling of the migraine population as responder and non-responder subpopulations means that the overall results come from the combined analysis of these subpopulations. The removal of the MMD reductions for fremanezumab non-responders therefore impacts the overall results and their ability to accurately reflect the FOCUS clinical trial results. Teva finds no justification for this change to have been provided and finds that this change produces a misrepresentation of the FOCUS trial results.
13	In Section 3.24 of the ACD, the committee "…*could not consider the use of fremanezumab after botulinum toxin type A because it had not been presented with cost-effectiveness estimates for this group*." Teva has therefore assembled additional evidence to demonstrate the clinical effectiveness and cost-effectiveness of fremanezumab in patients who have failed onabotulinumtoxin A. This evidence is presented in the new evidence Appendix, and demonstrates that fremanezumab is a clinically effective and cost-effective treatment for patients who have previously failed onabotulinumtoxin A.

Insert extra rows as needed

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fremanezumab for preventing chronic and episodic migraine [ID1368]

New evidence appendix (post-ACD)

December 2019

File name	Version	Contains confidential information	Date
New evidence appendix		No	06 December 2019

Evidence for fremanezumab post-onabotulinumtoxin A

The population of interest for this appraisal is focussed on both episodic migraine (EM) and chronic migraine (CM) patients who have had an inadequate response to at least three prior preventive therapies (with an inadequate response defined as a lack of a clinically meaningful improvement, intolerance or contraindication/ unsuitability). However, it is recognised that within the UK patient population there is a subgroup of CM patients who have failed three therapies and then treatment with onabotulinumtoxin A, consistent with current NICE guidance for this medicine.[1] Given the significant burden of illness suffered by this very difficult to treat population, we understand that anti-CGRP therapies will be an important treatment option for such patients moving forward. Therefore, we are providing additional evidence in this submission from the FOCUS clinical trial on patients who have had an inadequate response to three prior preventive treatments and onabotulinumtoxin A.

Furthermore, we also note that within the ACD, it was commented that Teva had not previously provided evidence specifically focussed on patients with migraine who have failed on onabotulinumtoxin A, and thus use of fremanezumab in this population could not be considered.

Evidence of clinical effectiveness post-onabotulinumtoxin A

Introduction to the clinical need for treatment in this patient subgroup

People affected by migraine can present with either EM or CM. Classification of migraine may vary over an individual's lifetime, as often the course of the condition may improve or worsen with or without any treatment intervention. Globally, it is recognised that approximately 3% of patients *per* year can progress from EM to CM,[2] and a similar or higher number revert from CM to EM.[3] Improvements in migraine frequency can be experienced due to hormonal fluctuations, for example with the onset of menopause.[4] Worsening of migraine symptoms can be due to a number of lifestyle factors, stressful life events or poor management of the condition due to ineffective treatments. The latter is a particular concern for CM patients, where poor disease control can lead to the exacerbation of migraine symptoms.[5]

The vast majority of patients with migraine are able to gain symptomatic relief and disease control with oral preventive therapies. However, it is recognised that not all patients will respond to, or are suitable for, all the oral preventive treatment options available to them. This inadequate response may be due to a lack of efficacy, intolerability or unsuitability due to a contraindication. A web-based survey conducted in the UK showed that 28% of CM respondents had tried more than three

preventive therapies.[6] This is most likely due to the fact that the current available therapies for migraine prevention are repurposed drugs that are not designed to target the underlying pathophysiology of migraine and are associated with a range of adverse events.[7]

Throughout this appraisal process, clinical experts have stated that, for patients who have had an inadequate response to three prior preventive treatments, there is no clear evidence of benefit for using additional oral treatments as a fourth line therapies. They also advised that the usual NHS clinical practice consists of giving each patient an adequate trial of three oral preventive treatments before considering more specialised therapies. For CM patients that have had an inadequate response to three oral preventive therapies, onabotulinumtoxin A is the fourth line NICE and BASH recommended specialised treatment available.[1,8] Patients with EM do not have any further recommended specialised treatment options.

In the UK, onabotulinumtoxin A is licensed for the prophylaxis of headache in adults with CM.[9] NICE recommends treatment with onabotulinumtoxin A in adults with chronic migraine that have failed to respond to at least three prior oral preventives.[1] There are many patients that are currently receiving migraine preventive treatment with onabotulinumtoxin A and are experiencing a clinically meaningful response to treatment; such as improvements in the number of migraine days that they experience and improved quality of life.[10,11] However, real-world evidence from the UK demonstrates that not all patients receiving onabotulinumtoxin A treatment are experiencing a clinically meaningful benefit.[10,12] Recent published data, from a single centre study, demonstrated that from a total of 254 patients receiving onabotulinumtoxin A treatment, of which 94.4% of patients had failed at least three prior oral preventive therapies, approximately a third of patients did not respond to therapy.[10] Response in this study was defined as at least a 50% reduction in either headache days or migraine days, or alternatively an increment in headache free days twice that of the baseline period.[10] These observations have also been reproduced in the more recently published European REPOSE study,[11] which included patients from the UK. This multicentre study demonstrated that 23% of patients discontinued onabotulinumtoxin A therapy.[11] The most common reason for discontinuation was due to a lack of efficacy as determined by the patient and/or physician.[11] Additionally, UK clinical experts have corroborated, including at the first committee meeting for fremanezumab, that these figures are broadly consistent with their own experience whereby approximately a third of patients do not respond to treatment with onabotulinumtoxin A.

For this population of CM patients, who have had an inadequate response to three oral preventive therapies and have had no clinically meaningful benefit with onabotulinumtoxin A, there are no further recommended treatment options, or treatments with a good level of evidence for providing clinical benefit. Clinical experts state that these patients may be treated with a range of other non-licensed and often unsatisfactory treatments, which have little or no documented evidence of therapeutic benefit in migraine. Those who have access to specialist tertiary centre services may be considered for invasive and expensive treatments such as intravenous dihydroergotamine, Occipital Nerve Stimulation, and Deep Brain Stimulation; alternatively, non-invasive neuromodulation may be trialled. However, not all patients would be suitable or have access to these options and thus are managed using best supportive care, *i.e.* acute headache medications. Unsurprisingly, clinical experts have shared with us that patients who have not responded to therapy with onabotulinumtoxin A often have a high rate of clinic attendance and an increased risk of developing further complications, such as the overuse of acute medications, and all its associated sequelae, as well as other comorbidities.

Taken together, it is very apparent that there is a clear unmet need for patients with CM that have had an inadequate response to onabotulinumtoxin A. These patients require access to a clinically effective, well-tolerated preventive therapy, designed specifically to target the underlying pathways of migraine pathophysiology, to regain control of their condition and improve their quality of life. In contrast to currently available therapies, fremanezumab is a fully humanised anti-CGRP monoclonal antibody designed to specifically target the underlying pathophysiology of migraine. During a migraine attack, it has been demonstrated that CGRP levels are elevated. Fremanezumab sequesters CGRP, thus interfering with the ligands ability to bind to its receptor and hence prevent downstream signalling induced by the receptor.[13] This in turn is thought to lead to the reduction in the frequency and severity of migraines experienced by individuals.

Evidence for efficacy of fremanezumab from the FOCUS clinical trial

The FOCUS clinical trial was conducted in both chronic and episodic migraine patients, and was a prospective, multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase IIIb study. The objective of this clinical trial was to assess the efficacy and tolerability of fremanezumab in migraine patients with a documented inadequate response to 2-4 classes of preventive therapies. Data submitted previously during this appraisal, demonstrated that fremanezumab is effective in reducing migraine days, headache days of at least moderate severity, improving migraine related disability and quality of life and reducing the consumption of acute headache medications in

patients that have had an inadequate response to at least three prior preventive therapies. Furthermore, results from this clinical study also demonstrated that fremanezumab is a generally well-tolerated treatment.

Patients that have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A

Herein we will consider the clinical effectiveness of fremanezumab in CM patients that have previously had an inadequate response to onabotulinumtoxin A. In order to select the subpopulation that reflects UK clinical practice and NICE guidelines, a further *post-hoc* analysis has been conducted on patients with CM that have had an inadequate response to three prior oral preventive classes and onabotulinumtoxin A. In the overall FOCUS study population, the most commonly failed preventive treatment classes were anticonvulsants, beta-blockers and tricyclic antidepressants. These classes of drugs are recommended by NICE for the preventive treatment of migraine, and thus patients who have failed these drugs, would be eligible to receive onabotulinumtoxin A treatment in the UK. This subpopulation data therefore provides the best available evidence to demonstrate effectiveness of fremanezumab in this difficult to treat patient cohort, which, as discussed above, continues to have a significant unmet need.

It must be noted that the FOCUS trial was not designed nor powered to assess the efficacy of fremanezumab specifically in patients who had an inadequate response to three oral preventive treatments and onabotulinumtoxin A. Altogether, there were [redacted] patients in the FOCUS study that fall into this population of interest. Given this, and the relatively small number of patients *per* arm of the study, the data presented herein include an analysis on the placebo group *versus* fremanezumab monthly and quarterly dosing regimens, and an additional analysis consisting of the placebo group *versus* the pooled fremanezumab arms. This approach enables the comparison of larger groups of data to better demonstrate the robustness of effect of fremanezumab in this patient population. We believe this approach is justified as throughout the clinical trial programme both dosing regimens have demonstrated equivalent safety and efficacy. Correspondingly, the licence awarded to fremanezumab also makes no distinction between the monthly or quarterly dosing regimens, with these being interchangeable treatment options based on clinician and patient preference.

Both of the data analyses have been conducted using identical statistical methods in order to allow comparability between the individual and pooled fremanezumab dosing data. Due to this, when the fremanezumab monthly and quarterly dosing regimens are pooled, the degrees of freedom

calculated for the least square mean analysis change. For this reason there are very small numerical differences in the results seen for the placebo arms in the two datasets, however, these differences are of no clinical significance.

Table 1 Summary of efficacy outcomes for patients with chronic migraine who have had an inadequate response to three oral preventive therapies and onabotulinumtoxin A in FOCUS clinical trial

	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Mean monthly migraine days			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Patients with at least 30% reduction in monthly average migraine days			
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Mean headache days of at least moderate severity			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]
Mean monthly days of use of any acute headache medication			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Headache Impact Test score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]

	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Migraine Disability Assessment score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Role function – Restrictive			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Role function – Preventive			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Emotional function			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]

CI: confidence intervals; LSM: least square means; MSQoL: Migraine-Specific Quality of Life Questionnaire; SD: standard deviation

Table 2 Summary of efficacy outcomes for patients with chronic migraine who have had an inadequate response to three oral preventive therapies and onabotulinumtoxin A in FOCUS clinical trial for pooled fremanezumab

	Placebo (n=[redacted])	**Fremanezumab (n=[redacted])**
Mean monthly migraine days		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]

	Placebo (n=[redacted])	**Fremanezumab (n=[redacted])**
Patients with at least 30% reduction in monthly average migraine days		
Number achieving endpoint (%)	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
Mean headache days of at least moderate severity		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]
P-value vs placebo		[redacted]
Mean monthly days of use of any acute headache medication		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
Headache Impact Test score		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
Migraine Disability Assessment score		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
MSQoL Role function – Restrictive		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
MSQoL Role function – Preventive		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]

	Placebo (n=[redacted])	Fremanezumab (n=[redacted])
MSQoL Emotional function		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]

CI: confidence intervals; LSM: least square means; MSQoL: Migraine-Specific Quality of Life Questionnaire; SD: standard deviation

In the FOCUS study, CM patients who had an inadequate response to three prior oral preventive treatments and onabotulinumtoxin A experienced [redacted] migraine days on average at baseline. In addition, these patients used acute headache medication to manage their migraines on approximately [redacted] days, and had a Headache Impact Test (HIT-6) and Migraine Disability Assessment Test (MIDAS) score of approximately [redacted] and [redacted], respectively. This indicates that this subpopulation of patients have a high disease burden, are heavily using acute medications to try to manage their condition, and are severely impacted by their migraines; where the latter is demonstrated by the high HIT-6 and MIDAS scores. This patient population, of individuals who have had an inadequate response to onabotulinumtoxin A treatment, is reflective of those seen in everyday UK clinical practice, as verified by clinical expert opinion, and once again highlights the significant unmet need which remains in these difficult to treat patients.

Efficacy of fremanezumab in reducing monthly migraine days

The primary endpoint of the FOCUS study was to assess the change from baseline in the monthly average number of migraine days. This is deemed to be a highly relevant endpoint for migraine patients, as it not only captures the days a patient experiences a disabling headache, but also incorporates the migraine associated symptoms, such as nausea and/or vomiting, photophobia and phonophobia.

Fremanezumab was able to substantially reduce the number of migraine days in the subpopulation of interest, a CM patient population with a high disease burden and unmet need. Following 12-weeks of treatment with either monthly or quarterly fremanezumab, patients who had an inadequate response to three preventive therapies and onabotulinumtoxin A, experienced a [redacted] or [redacted] day reduction in the average monthly number of migraine days, respectively, compared to placebo (Table 1; [redacted] days, [redacted], respectively). This reduction in migraine days demonstrated by fremanezumab, in this highly disabled population, is consistent with the results of

the analysis when monthly and quarterly fremanezumab treatment groups are pooled. Here, all fremanezumab patients experience a reduction in migraine days of [redacted] days *versus* placebo (Table 2; [redacted]). Together the data demonstrate that fremanezumab is effective in reducing migraine days in patients who have had an inadequate response to three oral preventives and onabotulinumtoxin A.

Responder rates (at least a 30% reduction in monthly migraine days) in patients treated with fremanezumab

A reduction of migraine days by at least 30% is considered to be a clinically meaningful endpoint in CM patients and is used to assess the effectiveness of a preventive therapy in this patient cohort. In patients who had an inadequate response to onabotulinumtoxin A, as well as three other preventive therapy classes, [redacted] and [redacted] of patients receiving either monthly or quarterly fremanezumab dosing regimens, respectively, met this clinically important milestone. This was significantly greater that what was observed in the placebo group (Table 1; [redacted], respectively). Again, the magnitude of effect was replicated in the analysis where the fremanezumab treatment groups were pooled, where there was a significantly greater proportion of patients experiencing at least a 30% reduction in migraine days in patients receiving fremanezumab ([redacted]) *versus* placebo (Table 2; [redacted]).

To emphasise the impact of this benefit on individual patients, it is worth noting that in practise these reductions, observed in almost half of the patients, would translate to regaining at least a [redacted] of migraine free days. This alone is postulated to have a significant effect on the day-to-day lives of patients.

Efficacy of fremanezumab in reducing headache days of at least moderate severity

The international definition of chronic migraine is based on the presence of at least 15 headache days *per* month, of which 8 are migraine days, for at least three months. This definition is based primarily on the number of headache days. The rationale for this is that a CM patient will likely have more migraine days than an episodic patient, however, they will, by definition, have a greater number of headache days. Therefore, the mean change from baseline in the average number of monthly headache days of at least moderate severity was measured in the FOCUS study.

The subpopulation of interest for this new evidence experienced on average [redacted] headache days of at least moderate severity at baseline. Following the 12-week double-blind treatment period, patients receiving either monthly or quarterly fremanezumab experienced a reduction in their

monthly average number of headache days of at least moderate severity by [redacted] days or [redacted] days *versus* placebo (Table 1; [redacted] days, [redacted], respectively). These results were consistent in the pooled fremanezumab analysis where there was a significant reduction in headache days of at least moderate severity ([redacted] days) compared to placebo (Table 2; [redacted] days, [redacted]).

Efficacy of fremanezumab on days of acute headache medication use

In the FOCUS study, participants were allowed to continue to use acute headache medications as and when required. It is important to note that no education was provided to trial participants on acute medication overuse. Patients using opioid or barbiturate containing medicines for more than 4 days during the pre-treatment period were excluded from the study, as well as those who used NSAIDS or triptans as preventive therapies. The latter approaches were used to reduce the risk of including patients in the trial that may have been suffering from the secondary headache disorder of medication overuse headache at baseline.

At baseline, CM patients who had an inadequate response to onabotulinumtoxin A and three other oral preventive classes, were using acute headache medication on approximately [redacted] days *per* month. Following treatment with fremanezumab there was a substantial reduction in the number of days where any acute headache medication was used compared to baseline ([redacted] days for monthly fremanezumab; [redacted] days for quarterly fremanezumab) *versus* placebo (Table 1; [redacted] days [redacted], respectively). Results of the pooled fremanezumab treatment group analysis show a significant reduction in the number of days of acute medication use ([redacted] days) compared to placebo (Table 2; [redacted] days, [redacted]).

In addition to the absolute reduction seen, taking less acute headache medications is likely to reduce the overall risk of medication overuse and thus reduce the likelihood of the patients' condition worsening.

The impact of fremanezumab on headache related disability

Migraine is a highly disabling condition and the leading cause of disability for patients under the age of 50 years.[14] Migraine is thought to be particularly disabling for those individuals who are unable to manage their condition effectively with treatments that are currently available. Therefore, it is important to assess the effects of new migraine therapies on migraine related disability. Furthermore, the British Association for the Study of Headaches have recently added a recommendation to their headache management guidelines that states that the HIT-6 PROM should

be used in everyday clinical practice to monitor quality of life in migraine patients, and in addition, to monitor treatment response in patients receiving therapy with onabotulinumtoxin A.[8]

In the FOCUS study, both HIT-6 and MIDAS was used to assess migraine related disability. At baseline, patients who had an inadequate response to three oral preventive treatment classes and onabotulinumtoxin A had an average HIT-6 score of [redacted]. A HIT-6 score of 60 or above denotes that headaches experienced by the individual are severely impacting their disability levels. This subgroup of FOCUS CM patients experienced a greater improvement in disability levels from baseline *versus* placebo (Table 1; [redacted] for monthly fremanezumab and [redacted] for quarterly fremanezumab *versus* [redacted] placebo, [redacted], respectively). These results are congruous with the improvement in disability when analysed in the pooled fremanezumab data set. Here HIT-6 scores were significantly changed by [redacted] in comparison to patients receiving placebo (Table 2; [redacted]). Furthermore, these reductions exceeded the minimum clinically important difference (MCID) reported for HIT-6, of 2.3 points,[15] demonstrating that the reduction in disability levels experienced following 12-weeks of treatment with fremanezumab was clinically meaningful for the patients.

MIDAS is a validated tool used to measure migraine related disability; however, to date, a validated MCID is yet to be established. Patients who had a documented inadequate response to three classes of prior preventive therapies and onabotulinumtoxin A had an average baseline MIDAS score of [redacted]. This score is equates to a grade IV MIDAS category, the highest MIDAS grade, meaning that the individuals are severely disabled by their migraines.[16,17]

MIDAS scores were reduced in these patients to a substantially greater extent in those receiving either monthly ([redacted]) or quarterly fremanezumab ([redacted]) *versus* placebo (Table 1; [redacted], respectively); where the placebo group experienced a worsening in their disability levels over the 12-week double-blind treatment period. When all patients receiving fremanezumab are pooled in this analysis a similar magnitude of improvement is observed ([redacted]) which is significantly greater than the worsening experienced by the placebo group (Table 2; [redacted]).

The effect of fremanezumab on migraine related quality of life

The Migraine-Specific Quality of Life Questionnaire (MSQoL) is a validated tool that is used to measure the impact of migraine on an individual's quality of life over the previous four weeks across three domains, where higher scores indicate a better health-related quality of life.[18] During the

FOCUS study, participants completed the MSQoL at baseline and at four weeks after the last study dose.

At baseline, patients who had an inadequate response to three prior preventive therapies and onabotulinumtoxin A had on average scores of [redacted], [redacted] and [redacted] for the role function-restrictive, role function-preventive, and emotional function domains of MSQoL, respectively. Following the 12-week double-blind treatment period, patients receiving fremanezumab monthly (role function-restrictive: [redacted]; role function-preventive: [redacted]; emotional function: [redacted]) or quarterly dosing regimens (role function-restrictive: [redacted]; role function-preventive: [redacted]; emotional function: [redacted]) had a substantial improvement across all domains *versus* placebo (Table 1; role function-restrictive: [redacted], [redacted], respectively; role function-preventive: [redacted], [redacted], respectively; emotional function: [redacted], [redacted], respectively). Changes in the role function restrictive and preventive domains, compared to placebo, exceeded the MCID reported for this tool.[19] The robustness of fremanezumab's ability to improve migraine-related quality of life is demonstrated by analysis of the pooled fremanezumab treatment groups (Table 2), where the mean change from baseline in the MSQoL scores at four weeks after the final dose showed differences from placebo in favour of fremanezumab for all three domains.

Taken together, the results across disability and quality of life measures show that patients who have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A, achieve a benefit after receiving fremanezumab.

Further evidence on the clinical efficacy of fremanezumab in patients with CM who have had an inadequate response to onabotulinumtoxin A

As discussed in the section above, the FOCUS trial was not designed to specifically assess the efficacy of fremanezumab in patients that have had an inadequate response to three prior oral preventive therapies and onabotulinumtoxin A. In addition, analysis of this subgroup was not a pre-defined population of interest, resulting in a relatively small number of patients in the placebo and fremanezumab treatment groups. However, as demonstrated above, data from this population shows a robust effect of fremanezumab for each of the key endpoints analysed above. Although it is recognised that p-values are for descriptive purposes only when undertaking *post-hoc* analyses, Teva still believe further confidence can be drawn from results of the pooled analysis, whereby endpoints that demonstrated a p-value of greater than 0.05 when assessed as individual fremanezumab arms became less than 0.05 when the fremanezumab arms were pooled.

To further strengthen the confidence in this data and the clinical efficacy of fremanezumab, an additional two subgroup analyses have been conducted from the FOCUS study population. Firstly, the efficacy of fremanezumab was investigated in patients with CM that have had an inadequate response to at least three prior preventive treatments, of which one was onabotulinumtoxin A (Table 3), and secondly, all patients with CM in the FOCUS study that reported a documented inadequate response to onabotulinumtoxin A (Table 4).

Table 3 Summary of efficacy outcomes for patients with chronic migraine who have had an inadequate response to at least three oral preventive therapies (one of which was onabotulinumtoxin A) in FOCUS clinical trial

	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Mean monthly migraine days			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Patients with at least 30% reduction in monthly average migraine days			
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Mean headache days of at least moderate severity			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]
Mean monthly days of use of any acute headache medication			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]

	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Headache Impact Test score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Migraine Disability Assessment score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Role function – Restrictive			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Role function – Preventive			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Emotional function			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]

CI: confidence intervals; LSM: least square means; MSQoL: Migraine-Specific Quality of Life Questionnaire; SD: standard deviation

Table 4 Summary of efficacy outcomes for patients with chronic migraine who have had an inadequate response to onabotulinumtoxin A in FOCUS clinical trial

	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Mean monthly migraine days			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Patients with at least 30% reduction in monthly average migraine days			
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Mean headache days of at least moderate severity			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]
Mean monthly days of use of any acute headache medication			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Headache Impact Test score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]

	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Migraine Disability Assessment score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Role function – Restrictive			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Role function – Preventive			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Emotional function			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]

CI: confidence intervals; LSM: least square means; MSQoL: Migraine-Specific Quality of Life Questionnaire; SD: standard deviation

The rationale for these additional analyses is to demonstrate the consistent effect of fremanezumab for all endpoints analysed herein, across larger cohorts of patients who have had an inadequate response to onabotulinumtoxin A. These data are highly consistent with the results observed in patients who have had an inadequate response to three prior oral preventive therapies and onabotulinumtoxin A (the subpopulation of interest for this new evidence appendix). It is also reassuring to see that the results discussed herein are consistent with the results for the overall FOCUS study population.

In conclusion, the data taken together demonstrate that an individual's lack of clinically meaningful response to onabotulinumtoxin A does not dictate the response to treatment with fremanezumab,

despite the high burden of disease in what may be perceived as a refractory patient population. The data shows that patients who have had an inadequate response to onabotulinumtoxin A, irrespective of the number of prior oral preventive treatment failures, are still able to experience a clinically meaningful response to therapy with fremanezumab. Scientifically, this is indeed what would be expected, given that both onabotulinumtoxin A and fremanezumab have differing mechanisms of action. Therefore, the data herein demonstrate the clinical efficacy of fremanezumab in this difficult to treat patient cohort, with a substantial disease burden, high unmet need, and currently have limited further effective migraine treatment options. This once again emphasises the need for fremanezumab, a novel therapy option specifically designed to target the underlying pathophysiology of migraine.

Evidence of cost-effectiveness post-onabotulinumtoxin A

Population considered within the model

The most directly relevant group of patients within the FOCUS clinical trial that can be used for this analysis are those who have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A, as this group most closely represents patients with an inadequate response to onabotulinumtoxin A within NHS clinical practice. This group also matches the main group considered within the above clinical effectiveness data. When considering the cost-effectiveness within this group, an additional analysis has been conducted on a wider patient group to provide added confidence in the cost-effectiveness results produced. For this cost-economic analysis, therefore, two patient groups have been considered to provide evidence for cost-effectiveness post-onabotulinumtoxin A. These patient populations are:

- Patients who have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A
- Patients who have had an inadequate response to four preventive treatments.

The group of all patients who have had an inadequate response to four preventive treatments in the FOCUS trial was chosen as it represents the patients with the most difficult-to-treat disease and a high disease burden, and was considered to be the next most closely representative of NHS patients eligible for fremanezumab under this positioning (*i.e.* in a fifth-line positioning following failure of four preventive treatments). Whilst these patients, have not necessarily previously received onabotulinumtoxin A, they match the line of treatment (and therefore expected disease characteristics) of the likely NHS patients under this positioning. Also, as discussed above, the clinical efficacy results have demonstrated that an individuals' lack of clinically meaningful response to onabotulinumtoxin A does not dictate the response to treatment with fremanezumab. This additional analysis allowed for a larger number of patients to be included and to therefore demonstrate the robustness of the analyses conducted in the most relevant group (patients who have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A).

Clinical data used within the model

For these two additional patient populations, the required clinical data were extracted from the FOCUS clinical trial paper to populate the economic model. These updated values are outlined in Table 5, which shows monthly migraine day data, and in Table 6 which shows responder rates (assessed using the criteria of at least a 30% reduction in monthly migraine days).

Table 5 Baseline monthly migraine days, migraine day changes and initial migraine day distributions

	Chronic migraine patients who have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A		Chronic migraine patients who have had an inadequate response to any four preventive treatments	
	Responders	**Non-responders**	**Responders**	**Non-responders**
Initial migraine days *per* 28 days	[redacted]	[redacted]	[redacted]	[redacted]
Mean reduction in monthly migraine days for fremanezumab *versus* placebo at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Modelled absolute monthly migraine days value for fremanezumab at efficacy assessment (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
Modelled absolute monthly migraine days value for BSC at efficacy assessment (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
Monthly migraine days	**Migraine day distribution**			
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]

	Chronic migraine patients who have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A		Chronic migraine patients who have had an inadequate response to any four preventive treatments	
	Responders	**Non-responders**	**Responders**	**Non-responders**
18	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care

Table 6 Responder rates at 12 weeks

	Chronic migraine patients who have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A	Chronic migraine patients who have had an inadequate response to any four preventive treatments
Fremanezumab	[redacted]	[redacted]
BSC	[redacted]	[redacted]

BSC: best supportive care

These data were entered into the 'config' sheets of the economic model, and represent the only changes made to incorporate these new patient populations into the model. Table 7 gives the complete data added to the relevant 'config' sheet with the relevant row names included as they are titled within the model; this is provided to allow for this data to be incorporated into the model with the greatest ease for checking and verification of the results presented from this analysis.

Table 7 Efficacy data as entered into model config sheets

	Chronic migraine patients who have had an inadequate response to three oral preventive treatments and onabotulinumtoxin A		Chronic migraine patients who have had an inadequate response to four preventive treatments	
	Responders	**Non-responders**	**Responders**	**Non-responders**
MD dispersion param- treatment inputs				
Chronic	[redacted]	[redacted]	[redacted]	[redacted]
Episodic	[redacted]	[redacted]	[redacted]	[redacted]
Chronic	[redacted]	[redacted]	[redacted]	[redacted]
Episodic	[redacted]	[redacted]	[redacted]	[redacted]
MD dispersion param- placebo inputs				
Chronic	[redacted]	[redacted]	[redacted]	[redacted]
Episodic	[redacted]	[redacted]	[redacted]	[redacted]
Chronic	[redacted]	[redacted]	[redacted]	[redacted]
Episodic	[redacted]	[redacted]	[redacted]	[redacted]
Initial MMDs				
Chronic	[redacted]	[redacted]	[redacted]	[redacted]
Episodic	[redacted]	[redacted]	[redacted]	[redacted]
Placebo MD curve parameters - Chronic Migraine				
theta 1	[redacted]	[redacted]	[redacted]	[redacted]
theta 2	[redacted]	[redacted]	[redacted]	[redacted]
theta 3	[redacted]	[redacted]	[redacted]	[redacted]
Placebo MD curve parameters - Episodic Migraine				
theta 1	[redacted]	[redacted]	[redacted]	[redacted]
theta 2	[redacted]	[redacted]	[redacted]	[redacted]
theta 3	[redacted]	[redacted]	[redacted]	[redacted]
Chronic Migraine - Mean Reduction in MD from Placebo for model				
Fremanezumab at 12 Weeks	[redacted]	[redacted]	[redacted]	[redacted]
Onabotulinumtoxin A at 24 Weeks	[redacted]	[redacted]	[redacted]	[redacted]
Episodic Migraine - Mean Reduction in MD from Placebo for model				
Fremanezumab at 12 Weeks	[redacted]	[redacted]	[redacted]	[redacted]
Responder rates				
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]

MD: migraine days; MMD: monthly migraine days

New value proposition

Teva has also produced a new value proposition for consideration by NICE. This consists of a simple Patient Access Scheme (PAS), which is currently under consideration by PASLU and would [redacted]. This PAS is included in the economic analyses presented below.

Cost-effectiveness results

The full cost-effectiveness results for this population are presented in the section below. Under the Teva base case (details outlined below) the following ICERs were produced for the comparison to best supportive care; in patients with failures to three oral therapies and onabotulinumtoxin A the ICER is £[redacted], and for patients with failures to four therapies the ICER is £[redacted]. These ICERs show that fremanezumab would be a highly cost-effective treatment within this population of patients with an inadequate response to onabotulinumtoxin A, and a full presentation of these results is included in the following section. It is also worthy of note that this is a conservative comparison that is unlikely to include the full costs and impacts of best supportive care. In patients that have an inadequate on onabotulinumtoxin A, other more invasive treatment options (such as nerve blocks) may be considered. The impact of these treatments (in terms of cost and quality of life) has not been included within this analysis and so can be seen to be conservative, as clinical opinion is that at least a proportion of these patients would be treated with these more invasive treatment options as a treatment of last resort.

Updated cost-effectiveness modelling parameters

Areas of change from committee's preferences

Corrections

Within the latest version of the ERG model provided to Teva, a small number of coding errors have been found. These coding errors can be summarised as:

- Within the scenario modelling the committee's preferred assumptions, the utilities for onabotulinumtoxin A are not corrected to the off-treatment utilities and remain using the on-treatment values. This is in contrast to the handling of fremanezumab where the off-treatment utilities are used and therefore does not represent a fair comparison between treatments. To correct this, within the 'Utilities' sheet of the model, the formulae used for fremanezumab have been replicated for onabotulinumtoxin A to ensure a consistent handling of utilities within the model.
- Within the scenario investigating the 'removal of residual fremanezumab effect in non-responders', the efficacy of fremanezumab in non-responders has been removed such that these patients remain on their baseline monthly migraine days throughout the time horizon. Teva were not able to find justification for this change within the ACD. Teva finds that the removal of treatment benefit in patients where clinical trial evidence shows a real benefit occurred (but that did not meet the threshold for continuation of treatment) to be an unjustified change to the model(see updated base case below). However, in addition, such a change was not applied to onabotulinumtoxin A non-responders, which Teva considers to have been an oversight and therefore has been corrected so that fremanezumab and onabotulinumtoxin are considered in the same manner. This has been done by replicating the coding used for monthly migraine day calculations in fremanezumab non-responders within the 'Tx2 Calculations (Ch) (ERG)' sheet of the model.
- Within the 'Results' sheet, the fremanezumab response rate in CM has been entered as a static value. This has no impact on the analyses within the base case population, but causes erroneous results when alternative patient populations are considered. This error has therefore been corrected to restore the formula originally included in this cell in the previous model version supplied by Teva.

Teva has applied these corrections to all of the analyses presented below.

New Patient Access Scheme

Teva has also included a new value proposition within this modelling. Teva has applied for a Patient Access Scheme (PAS), which is currently under consideration by PASLU. The modelling results presented below include this PAS which [redacted]. The additional analyses reported herein included this new PAS for fremanezumab.

Updated onabotulinumtoxin A administration costs

Teva has updated the economic model to reflect the cost of onabotulinumtoxin A administration as used within the budget impact analysis conducted by NICE and NHS England ('ID1368 Fremanezumab NICE BIT submission v 3.0 14.10.19_with stopping rule (redacted)'). Within this analysis the administration cost of onabotulinumtoxin A is assumed to £218 for the first appointment and £125 for subsequent appointments (based on the use of the treatment function code 400 for neurology). Teva has therefore utilised the value of £125 as the treatment administration cost for onabotulinumtoxin A within the economic model to reflect the assumptions of the budget impact analysis. Clinical expert opinion gathered by Teva also made it clear that the previously used value (based on the NICE appraisal of onabotulinumtoxin A) did not reflect the higher actual cost in clinical practice; Teva also notes that it was found that this value was also considered as being low during the NICE appraisal of onabotulinumtoxin A. Now that there is an updated cost from NICE and NHS England in the budget impact analysis, Teva has updated the health economic model accordingly.

Utilities

Teva believes that the inclusion of separate on- and off-treatment utilities is clinically valid and accepted practice within migraine modelling. The utility data presented utilised clinical trial data from the FOCUS trial which demonstrated that, for a patient with a given number of monthly migraine days, their quality of life was higher when being treated with fremanezumab. Similar effects of quality of life benefits in patients with similar migraine/headache day frequencies have been demonstrated in data from a number of migraine clinical trials. This effect has been seen with both erenumab and onabotulinumtoxin A.[20,21] Both of these studies are focussed on economic modelling, and utilise data from the key clinical trials of these treatments, and in both cases these analyses result in differential on- and off-treatment utilities. In addition, the previous NICE appraisal of onabotulinumtoxin A concluded that the most plausible ICER included separate on- and off-treatment utilities. Furthermore, advice that Teva has received from clinical experts has stated that

differences in utilities are well known to exceed reductions in monthly migraine days with this measure unable to capture the full burden of headaches in terms of duration, severity and associated factors (nausea *etc.*).

Therefore, Teva believes the restoration of the on- and off-treatment utilities is the most clinically justified scenario, and the scenario based on the available evidence from the FOCUS clinical trial, and has therefore included this within the updated base case analysis. In addition, to recognise some of the concerns that the committee had in this area, Teva has also conducted an analysis where the treatment benefit for utilities is reduced by 50%. This scenario investigates the potential that the treatment benefit is smaller than the results seen in the FOCUS clinical trial; these alternative on-treatment utilities are listed in Table 8.

Table 8 Utility values for each monthly migraine day state

Monthly migraine days	Alternative on-treatment utility values	Monthly migraine days	Alternative on-treatment utility values
0	[redacted]	15	[redacted]
1	[redacted]	16	[redacted]
2	[redacted]	17	[redacted]
3	[redacted]	18	[redacted]
4	[redacted]	19	[redacted]
5	[redacted]	20	[redacted]
6	[redacted]	21	[redacted]
7	[redacted]	22	[redacted]
8	[redacted]	23	[redacted]
9	[redacted]	24	[redacted]
10	[redacted]	25	[redacted]
11	[redacted]	26	[redacted]
12	[redacted]	27	[redacted]
13	[redacted]	28	[redacted]
14	[redacted]		

Fremanezumab effect in non-responders

The change described as the "r*emoval of residual fremanezumab effect in non-responders*" involved the removal of any monthly migraine day reductions seen within the fremanezumab non-responders during their 12-week treatment trial. Teva was unable to find justification for this change within the ACD and considers it to be unjustified as it goes against the clinical trial evidence used to model this

population. The reduction in monthly migraine days modelled within this population was a real effect that occurred within the clinical trial; however, this response was not sufficient for these patients to continue treatment (*i.e.* it did not reach the threshold of a clinically meaningful response of at least 30%/50% reduction in monthly migraine days). After the 12-week trial these patients stopped treatment and reverted to their baseline MMDs (a conservative assumption in itself as some treatment benefit may be maintained within these patients).

In addition, this alteration to the model impacts its ability to model the observed clinical trial results by removing some of the efficacy of fremanezumab. The modelling of the migraine population as responder and non-responder subpopulations means that the overall results come from the combined analysis of these subpopulations. The removal of the MMD reductions for fremanezumab non-responders therefore impacts the overall results and their ability to accurately reflect the FOCUS clinical trial results.

Therefore, Teva do not find this change to be justifiable and have reversed it within the updated base case.

Positive stopping rule

Teva considers a positive stopping rule to be an expected part of clinical practice with fremanezumab. Clinical experts have been clear to Teva that treatment would not be continued indefinitely and that patients who show a sufficient response would have this treatment positively stopped when appropriate. Positive stopping of preventive treatment within migraine is also recommended within SIGN and BASH guidelines; whilst European Headache Federation guidelines on anti-CGRP migraine treatments recommend that continuation on treatment should be managed in the same way as for other migraine preventative therapies. In addition, the SmPC of fremanezumab states that "*Evaluation of the need to continue treatment is recommended regularly thereafter* [after initial assessment of efficacy]". All these points outline how a positive stopping rule is part of the expected clinical practice with fremanezumab.

An issue in the modelling of a positive stopping rule has been the lack of availability of data on which to base this rule. During the appraisal process, NICE has highlighted the real-world data available for onabotulinumtoxin A. The most relevant data for UK practice comes from the prospective analysis conducted at the Hull migraine clinic. However, it must be noted that these data have been collected using a treatment protocol that does not follow NICE guidelines, and come from a single centre. However, these are the most relevant data available and therefore Teva has utilised these to

provide an evidence base for the positive stopping rule, which has been supported by clinical experts within BASH as the most relevant data for modelling of a positive stopping rule. Within the available published data, it was reported that 32.3% (95/294) of responder patients permanently stopped treatment under a positive stopping rule over two years,[22] and that 57.9% (73/126) of responder patients permanently stopped treatment under a positive stopping rule over five years.[23] It should be noted that the number of patients who positively stopped treatment may be higher, but only figures for those patients that permanently stopped treatment are included within the abstract. These figures equate to an annual stopping of around 17% of currently treated patients. This would therefore justify a positive stopping rate of around 15% within the model, and so Teva have utilised this as the updated value for this modified positive stopping rule. Teva has also conducted an additional scenario analysis using a value of 10% as a conservative assumption in this area for patients who would permanently discontinue fremanezumab treatment each year.

Within the ACD, the main concern of the committee was that the treatment benefit was maintained indefinitely after treatment cessation. Teva has therefore looked to address this and has taken the investigative positive stopping rule developed by the ERG and extended it. The ERG positive stopping rule considered a wane in treatment efficacy after positive stopping, and when combined with the committee's other assumptions, this waning consists of a reduction in efficacy back to baseline monthly migraine days over one year after treatment cessation. Teva believes that this is a highly conservative and clinically unlikely scenario, but accepts that there is a lack of evidence to demonstrate maintained long-term efficacy in fremanezumab after discontinuation. Teva feels that this adaptation the positive stopping rule adequately addresses this previous perceived concern.

The second part of this investigative positive stopping rule developed by the ERG was the ability for treatment to be restarted after 50% of the treatment effect had been lost. Teva does not feel that this restart is necessary as the data utilised to inform the positive stopping rule comes from patients who permanently discontinued treatment. In addition, the modelled treatment continuation rates within the model (with this modified positive stopping rule applied) are still much higher than those reported in real-life onabotulinumtoxin A data.[22,23] However, in order to investigate the impact of patients who do require restart of treatment Teva has also investigated a further scenario in this regard. Treatment restarting as modelled by the ERG considered each group of patients who had positively stopped and modelled the migraine day progression of this group. Once the mean migraine days of this group reached the restart threshold, all patients within the group were restarted on treatment. Teva feels that this is not a realistic scenario, as individual patients will

respond differently after stopping treatment and not all will require treatment to be restarted. An additional option has been added to the model to allow a variable proportion of positively stopped patients to be restarted onto treatment. Again, real-life data from onabotulinumtoxin A has been used to inform this assumption. Within the data from the Hull migraine clinic it was reported that at two years 25% (45/177) of stopped patients had restarted treatment and at five years 15% (15/98) of stopped patients had restarted treatment. These figures indicate that relatively low proportions of patients were requiring additional treatment, and so a conservative assumption of 50% of patients restarting treatment was utilised as an additional positive stopping scenario.

Three updated positive stopping scenarios were therefore considered:

- 15% of patients permanently stopped treatment after each annual assessment (base case)
- 10% of patients permanently stopped treatment after each annual assessment
- 15% of patients stopped treatment after each annual assessment, with 50% resuming treatment once half the treatment effect had been lost.

Efficacy compared to onabotulinumtoxin A

Teva considers that the only justifiable data to utilise for the comparison to onabotulinumtoxin A is the network meta-analysis (NMA). The NMA results remain the best available data for comparison between fremanezumab and onabotulinumtoxin A. The NMA shows an additional benefit for fremanezumab over onabotulinumtoxin A across all endpoints analysed, yet makes a number of assumptions that are conservative with respect to the relative efficacy of fremanezumab. Additionally, the NMA was unable to include a number of additional patient and healthcare burden advantages for fremanezumab (a single monthly subcutaneous injection (or three injections every three months) compared to 31 injections in the head and neck every 12 weeks; the ability for fremanezumab to be self-injected at home compared to administration in hospital by a highly skilled healthcare professional). Teva also notes that, due to limited data available for onabotulinumtoxin A, any advantage for fremanezumab either from reductions in monthly migraine days or the distribution of migraine patients between MMD states could not be accounted for within the economic model. Altogether, these factors demonstrate clear advantages for fremanezumab over onabotulinumtoxin A, and additional benefits that are not currently captured within the economic modelling. Teva has therefore utilised the NMA efficacy results within the updated base case analysis.

Updated Teva base case

The updated Teva base case was based on the committee's preferred assumptions as outlined in the ACD and ERG Addendum #3, with the following changes made:

- Correction of coding errors (as outlined above)
- New PAS price for fremanezumab included
- Updated onabotulinumtoxin A administration costs (£125 *per* administration)
- Restoring fremanezumab (and onabotulinumtoxin A) efficacy in non-responder patients
- Restoring treatment impact on utilities using separated on- and off-treatment utilities
- Updated positive stopping rule where 15% of patients stop treatment after each annual assessment and treatment effect wanes to baseline over one year after treatment cessation
- Restoration of onabotulinumtoxin A efficacy as based on network meta-analysis results.

The Teva base case considers three patient populations:

- Adults with chronic migraine who have had an inadequate response to three or more prior preventive migraine treatments
- Adults with episodic migraine who have had an inadequate response to three or more prior preventive migraine treatments
- Adults with chronic migraine who receive fremanezumab post-onabotulinumtoxin A (new patient group).

The new patient group focusses on post-onabotulinumtoxin A patients, as this is a novel group of patients identified within the ACD. There are a number of patients in the UK who have received onabotulinumtoxin A, and so the cost-effectiveness in this patient group is of high relevance to UK clinical practice.

Updated scenario analyses

In addition to the updated base case, scenario analyses were conducted as detailed in Table 9

Table 9 Scenario analyses

Scenario	Explanation of scenario
A – Updated costs	All assumptions set to the committee's preferences with updated PAS price for fremanezumab, updated onabotulinumtoxin A administration costs and onabotulinumtoxin A efficacy based on the NMA results
B – Updated costs plus original utilities	As scenario A but with the original on- and off-treatment utilities restored
C – Updated costs plus blended utilities	As scenario B but with treatment effect of on-utilities reduced by half
D – Updated costs plus restoring fremanezumab effect	As scenario A but with fremanezumab effectiveness in non-responder patients restored (also restores efficacy in onabotulinumtoxin A to reverse change of coding correction)
E – Updated costs plus PSR (15% stop) and no restart	As scenario A but with inclusion of an updated positive stopping rule whereby 15% of treated patients permanently stop treatment each year
F – Updated costs plus PSR (10% stop) and no restart	As scenario A but with inclusion of an updated positive stopping rule whereby 10% of treated patients permanently stop treatment each year
G – Updated costs plus PSR (15%) with restart	As scenario A but with inclusion of an updated positive stopping rule whereby 15% of treated patients stop treatment each year and 50% of patients restart treatment after half of treatment effect is lost

NMA: network meta-analysis

Updated cost-effectiveness results

Chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

Within this population of patients with chronic migraine, the results of the updated base case analysis are presented in Table 10 and show fremanezumab to be a cost-effective treatment.

Table 10 Base case results in chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER *versus* BSC (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
OBA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; OBA: onabotulinumtoxin A; QALY: quality-adjusted life year

Additional scenarios exploring the impact of the changes from the committee's preferred assumptions are presented in Table 11. These results show that fremanezumab remains a highly cost-effective treatment in all of these scenarios.

Table 11 Scenario analyses in chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

Scenario	ICER vs OBA	ICER vs BSC
A – Updated costs	[redacted]	[redacted]
B – Updated costs plus original utilities	[redacted]	[redacted]
C – Updated costs plus blended utilities	[redacted]	[redacted]
D – Updated costs plus restoring fremanezumab effect	[redacted]	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]	[redacted]
G – Updated costs plus PSR (15%) with restart	[redacted]	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; OBA: onabotulinumtoxin A

Episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

Within this population of patients with chronic migraine, the results of the updated base case analysis are presented in Table 12 and show fremanezumab to be a cost-effective treatment.

Table 12 Base case results in episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

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

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

Additional scenarios exploring the impact of the changes from the committee's preferred assumptions are presented in Table 13. These results show that fremanezumab is a cost-effective treatment at a threshold of £30,000 *per* quality-adjusted life year gained in almost all scenarios considered.

Table 13 Scenario analyses in episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

Scenario	ICER vs BSC
A – Updated costs	[redacted]
B – Updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring fremanezumab effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15%) with restart	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio

Chronic migraine patients with post-onabotulinumtoxin A positioning of fremanezumab

The first results presented for this population are those from the most directly relevant patient population, namely patients with failures to three oral therapies and onabotulinumtoxin A. The results of the updated base case analysis are presented in Table 14 and show fremanezumab to be a highly cost-effective treatment in this patient group.

Table 14 Base case results for post-onabotulinumtoxin A chronic migraine patients who have had an inadequate response to three prior preventive migraine treatments and onabotulinumtoxin A

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

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

Additional scenarios exploring the impact of the changes from the committee's preferred assumptions are presented in Table 15. These results show that fremanezumab remains a highly cost-effective treatment in all of the scenarios considered, including under the committee's preferred assumptions.

Table 15 Scenario analyses for post-onabotulinumtoxin A chronic migraine patients who have had an inadequate response to three prior preventive migraine treatments and onabotulinumtoxin A

Scenario	ICER vs BSC
A – Updated costs	[redacted]
B – Updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring fremanezumab effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15%) with restart	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio

The additional post-onabotulinumtoxin A analysis conducted utilised a patient population of those with failures to four therapies. The results in this wider patient group are presented in Table 16 and show fremanezumab to be a highly cost-effective treatment in this patient group. These results are also similar to those found in the group of patients with failures to three oral therapies and onabotulinumtoxin A. This therefore gives confidence in the robustness of these cost-effectiveness analyses and in the cost-effectiveness of fremanezumab in patients who have had an inadequate response to onabotulinumtoxin A. It must also be considered that this analysis has been unable to capture the benefits of fremanezumab when compared to more invasive treatment options that are likely to be utilised in some patients who have failed onabotulinumtoxin A.

Table 16 Base case results for post-onabotulinumtoxin A chronic migraine patients who have had an inadequate response to four prior preventive migraine treatments

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

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

Additional scenarios exploring the impact of the changes from the committee's preferred assumptions are presented in Table 17. These results show that fremanezumab remains a highly

cost-effective treatment in all of the scenarios considered, including under the committee's preferred assumptions.

Table 17 Scenario analyses for post-onabotulinumtoxin A chronic migraine patients who have had an inadequate response to four prior preventive migraine treatments

Scenario	ICER vs BSC
A – Updated costs	[redacted]
B – Updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring fremanezumab effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15%) with restart	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio

Summary

The updated base case analysis presented here represents the most clinically justified assumptions for this modelling. Teva has used additional evidence identified during the appraisal process to inform the modelling of the positive stopping rule, and has sought to align all assumptions as closely as possible with the available clinical expert opinion. Teva therefore believes that this updated base case analysis provides the best estimates for the cost-effectiveness of fremanezumab. The results of these cost-effectiveness analyses show that in all populations considered, fremanezumab is a cost-effective treatment. Additional scenario analyses have investigated areas where these assumptions have not matched the committee's preferences, and these have demonstrated that fremanezumab remains a cost-effective treatment under almost all of these additional scenarios.

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Fremanezumab for preventing migraine [ID1368]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 6 December 2019 **email:** 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):	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]

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Fremanezumab for preventing migraine [ID1368]

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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.
Example 1	We are concerned that this recommendation may imply that ……..
1	The Migraine Trust welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for fremanezumab for preventing migraine. In this response we will mainly focus on highlighting the patient experience of using CGRP medications, such as fremanezumab, and the other therapies the ACD discusses, such as botulinum toxin type A. We will do this by presenting new evidence to the committee that we have recently gathered from two surveys (detailed below). The results of these surveys show the main points that we will be discussing in our response: 1. **Clinical effectiveness:** Evidence gathered from The Migraine Trust shows that patients surveyed with direct experience of botulinum toxin type A and CGRP medications, including fremanezumab, report that the CGRP medication was more effective at manging their migraine than botulinum toxin type A was. 2. **Cost-effectiveness:** Evidence gathered from The Migraine Trust shows that a clear majority of patients surveyed who take fremanezumab or other CGRP inhibitors were able to stop or reduce their use of other migraine medications while they were taking it. This can prevent medication overuse headache and reduce demand on resources elsewhere. 3. **Suitability of the guidance:** Evidence gathered from The Migraine Trust shows that there is a significant sub-group of patients who are not able to access botulinum toxin type A or do not respond to that treatment. These patients are left with few effective or tolerable alternatives. We would urge the committee to take all necessary steps to consider this technology for use for a smaller group of patients than outlined in the marketing authorisation. We are happy to share the results of these surveys in full with committee members if that would be useful.
2	**Q: Has all of the relevant evidence been taken into account?** We believe that all currently available peer reviewed trials have been included in the analysis. However, The Migraine Trust has recently conducted two surveys of relevance to this appraisal which have not been taken into account:

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Fremanezumab for preventing migraine [ID1368]

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	1. CGRP Patient Experience Survey: We surveyed 203 patients between 14 October and 19 November 2019 who are currently taking (or had recently taken) a CGRP drug for the prevention of their migraine. The survey asks a variety of questions about the patient experience of using CGRP inhibitors, including about effectiveness, tolerability, and comparisons with Botox. **2. Snap poll of neurologists and headache nurses:** There are currently 59 headache nurses and 28 neurologists with a special interest in headache according to the Association of British Neurologists (ABN). We surveyed 5 headache nurses and 11 neurologists between 22 November and 05 December 2019 about the experiences of their chronic migraine patients with Botox and CGRP drugs. In total, the snap poll results speak to the experiences of 9,490 chronic migraine patients across the UK.
3	**Q: Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** The Migraine Trust would like to comment on a few key points: **1. The ACD states that the most relevant comparators are best supportive care for episodic migraine and botulinum toxin type A for chronic migraine.** There is no direct comparison for fremanezumab and botulinum toxin type A. However, direct comparisons for new therapies are rarely available. Therefore, we believe the best comparator for fremanezumab for chronic and episodic migraine is best supportive care and not botulinum toxin type A. **2. The ACD states that it is uncertain whether fremanezumab is more clinically effective than botulinum toxin type A.** While we recognise that the company did not present direct evidence comparing the clinical effectiveness of fremanezumab with botulinum toxin type A, the findings from our CGRP Patient Experience survey can shed more light on the question of clinical effectiveness in the real-world context. Our CGRP Patient Experience Survey shows that for patients who have received both botulinum toxin type A and a CGRP inhibitor for their chronic migraine (n=145), 78% agree or strongly agree that the CGRP drug that they are currently taking (or have taken in the past) is more effective at managing their migraine than Botox and 76% agree or strongly agree that the CGRP drug that they are currently taking (or have taken in the past) has improved their quality of life more than Botox. Our snap poll of neurologists and headache nurses shows that 62% of those surveyed believe that CGRP drugs are as or more effective than Botox based on their real-world experience of treating migraine patients. None of the neurologists or headache nurses we surveyed believed that CGRP drugs are less effective than Botox. 75% of those surveyed agree that their patients would prefer to receive CGRP drugs over Botox. **3. The cost-effectiveness calculations may not consider all of the benefits of fremanezumab**

Fremanezumab for preventing migraine [ID1368]

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	We know that many patients taking oral preventives for their migraine also take acute medication. For example, a recent survey we conducted of people with migraine found that of those currently taking a daily oral preventive for their migraine (n= 703), 68% were also taking an acute medication regularly. Of those surveyed who are currently receiving Botox injections for their migraine (n=169), 70% were also found to be taking an acute medication regularly as part of their treatment. Our CGRP Patient Experience Survey found that the use of CGRP drugs reduces the need for patients to take other medication to help them manage their migraine, with 70% of respondees reporting that they were able to stop or reduce their use of other acute medications for their migraine while they were receiving CGRP treatment. This will help prevent the onset of medication overuse headache and reduce demand on resources elsewhere. This is a step change in migraine management for patients and we would ask that this is accounted for in cost-effective calculations.
4	**Q: Are the recommendations sound and a suitable basis for guidance to the NHS?** The Migraine Trust would like to raise the following key points: **1. The draft recommendation does not account for the significant sub-group of patients who will fail to respond to botulinum toxin type A** We agree with the committee's conclusion that there is real-world evidence from the UK to support the effectiveness, tolerability, and safety of botulinum toxin type A. However, not all patients who are eligible to receive this treatment under current NICE guidelines will respond to it. We are not aware of the total size of the UK botulinum toxin type A non-responder population and our understanding is that no one else knows either. However, our snap poll of headache nurses and neurologists sheds some light on the size of this population. Of the 9,490 chronic migraine patients the health professionals polled have seen in their clinic in the past year, 5,085 patients have also received Botox injections. Of those 5,085 patients, an estimated 801 (15.7%) failed to respond to that therapy. This means that an estimated 8.4% of chronic migraine patients are not having their treatment needs met by current treatment options. Our CGRP Patient Experience Survey shows that CGRP drugs are answering a significant unmet need in this patient sub-group, delivering an effective and well-tolerated treatment that many report as 'life changing'. For example, of the patients we surveyed who had failed to respond to Botox (n=125), 76% agree or strongly agree that the CGRP drug they are currently taking (or have taken in the past) has improved their quality of life. **2. The draft recommendation does not account for the difficulties some patients are currently experiencing in accessing botulinum toxin type A** Our snap poll of neurologists and headache nurses shows that over the past year, 9% of their patients receiving Botox (437 patients) have been forced to skip or delay a course of Botox injections due to access, availability, or capacity issues.

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	These findings chime with the results of our CGRP Patient Experience Survey, which show that 12% of eligible patients surveyed had to wait over one year to receive their first course of injections from the time they were first prescribed it. This survey also found that 27% of respondees who had received Botox injections had to pay privately in order to do so. We would note that the committee has stated that it cannot consider the use of fremanezumab after botulinum toxin type A because it had not been presented with cost-effectiveness estimates for this group. However, we believe it may be appropriate to evaluate this group of patients, e.g. Botox non-responders and those who face difficulty in accessing Botox, separately as their need is considerable. We urge the committee to take all necessary steps to consider this technology for use in this smaller group of patients than originally stated in the marketing authorisation.
5	**Q: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination about any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The Migraine Trust would like to raise the following key point: **1. Migraine can be classed as a disability under the Equality Act 2010** In our most recent survey, nearly half (48%) of respondents with migraine consider themselves to have a disability as defined by the Equality Act 2010. However, for the particular group of patients under consideration for fremanezumab, i.e. chronic migraine patients who have failed at least three oral preventives, 84% of respondents said they considered themselves as having a disability as defined by the Equality Act 2010. This is a group of people who are particularly disabled by their migraine.
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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]

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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?** i) Cost effectiveness should be reconsidered in light of change in pricing of Fremanezumab from £450 to [redacted] per month ([redacted]) ii) 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. iii) The duration of treatment and waning effect of utility over time is uncertain but we feel the committee should make reasonable assumption for duration of treatment based on the data with existing prophylactic agents. We do not agree with 3.17 which states that '**Positive stopping rule assumptions are not appropriate because it is implausible that treatment benefit is maintained indefinitely'.** We do not agree with the cost-effectiveness model presented that assumes that longer term treatment would be the standard of care: • We agree that treatment should be stopped if there is no significant response at three months (***negative stopping rule***). • The consultation did not accept the advice of UK professional bodies (the ABN and BASH) on a '***positive stopping rule'***. The ABN Advisory Group on Headache and Pain (Technical engagement response form Committee Papers p 635) stated that *'most specialists recommend continuing treatment for chronic migraine until they come down to low frequency episodic migraine i.e. <10 migraine days /month for at least 3 months'*. In practice this usually equates to at least 1 year in total of treatment as this cohort will typically have had long-standing chronic migraine refractory to many other treatments. The European Headache Federation guidelines recommend preventative migraine treatment should be given for 6-12 months in the first instance. If a patient requires longer term use we would certainly advocate re-evaluation of need for treatment every 12 months. A **'**drug holiday**'** would be undertaken to confirm whether or not ongoing treatment was necessary. There is evidence from studies on topiramate that the outcome, and chance of maintained benefit once the drug is withdrawn, is best when treatment is maintained for at least 6-12 months before a treatment break. • We note the scepticism in the Consultation on ***sustained efficacy*** following discontinuation based on the opinion that a lifetime horizon should be assumed, with only a very minor annual discontinuation rate. While we are aware that there are no long-term studies supporting continued benefit after cessation of successful treatment, this opinion runs contrary to what is known about the natural history of migraine.

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	○ for **Chronic Migraine**, there little published data on the long term outcomes of those that have stopped treatment following successful conversion to episodic migraine. Data available for patients receiving Botox treatment for chronic migraine from a UK headache centre presented at the International Headache Congress in Dublin 2019 (Ahmed et al, IHC-PO-419) (pg 635, ABN response) shows that at 5 year follow up 85% (160/186) of patients with chronic migraine who had a had a positive response to OnabotulinumtoxinA had discontinued treatment, and only 5% (18/160) had relapsed such that they had restarted OnabotulinumtoxinA treatment within that 5 yr period. ○ for **episodic migraine** the proportion is more difficult to estimate as it is likely that the number of patients that would require this group of drug will be very few as many would respond to first line treatments (amitriptyline, propranolol, candesartan, and/or topiramate). In summary we consider that a duration of treatment of two years would be reasonable for modelling purposes, and the treatment could be stopped earlier (after an annual review, for example) if the patient improves and this improvement is maintained off treatment. For patients with **chronic migraine**, this improvement should be *at least* a reversion to episodic migraine, and perhaps episodic migraine at <10 days per month. (***positive stopping rule***). iv) There has been no significant change in standard clinical practice with regards 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, 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 a trial of three agents.
3	are the provisional recommendations sound and a suitable basis for guidance to the NHS? The draft recommendations 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 fremanezumab in such patients would be highly appropriate to determine responders who have a significant reduction in headache days, and improvement in their quality of life, before considering more invasive and expensive treatment options such as intravenous dihydroergotamine, occipital nerve stimulation or even some of the non-invasive neuromodulation therapies such as vagal nerve stimulation or transcranial magnetic stimulation that have limited NICE recommendations without mandatory funding. In addition we recommend that the company be specifically requested to provide a model for the use of fremanezumab positioned in a treatment pathway *after* the use of

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	onabotulinumtoxinA. It is highly likely that fremanezumab treatment would be cost effective against best supportive care in this significant population of patients with a highly debilitating neurological disorder and a currently unmet clinical need.
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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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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 following comments: i) In the Focus Study, the definition of failure to respond to treatment included those where treatment was contraindicated or discontinued due to adverse events. This is what is seen in real life, and a strict adherence to pure therapeutic failure after three months of therapy is not always possible. ii) Sodium valproate should perhaps have been included in the same group as other anticonvulsants, although its use in migraine prophylaxis in the UK is uncommon. However, while sodium valproate is an anticonvulsant, its mode of action in migraine is presumed to be different from other anticonvulsants such as topiramate. The anticonvulsants used for migraine prophylaxis are not a functionally homogenous group in the way that beta-blockers or tricyclic antidepressants can be assumed to be. iii) 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. iv) The committee commented on lack of placebo arm in HALO extension study and the risk of bias, as not everyone continued. However, long-term extension studies are never randomised or controlled, and are done to confirm safety and tolerability, and not just clinical efficacy. v) Real life data does not exist for Fremanezumab, but this is true of any new drug. Such data can only be collected once a recommendation is made to treat a limited refractory population, based on cost effectiveness. vi) Whilst the duration of treatment and waning effect of utility over time is uncertain, the committee should make reasonable assumption for duration of treatment based on the data with existing prophylactic

	agents (see point (viii) below, for example). Treatment should be stopped if there is no response at three months (negative stopping rule). As most prophylactic agents are required for 6-18 months, with only a small proportion of patients continuing treatment for longer duration, the ongoing need for treatment should be assessed annually, and the treatment could be stopped if patients improve, and that improvement is maintained after a short (three month) period off treatment. For patients with chronic migraine, the minimum acceptable positive stopping rule would be a reversion to episodic migraine (by definition, <15 headache days/month), though an improvement to <10 headache days/month might be modelled as well. Duration of treatment of two years might be reasonable for modelling purposes. vii) There has been no significant change in standard clinical practice with regards 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, 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. As there is no consensus on where CGRP monoclonal antibodies should sit in the pathway, the cost effectiveness of Fremanezumab should be assessed both at this point, **and in patients who have also failed treatment with OnabotulinumtoxinA**, whose clinical need is paramount. viii) We note the committee's scepticism on sustained efficacy following discontinuation. However, for chronic migraine, there is data on long term outcome for those that have stopped treatment following successful conversion to episodic migraine, from patients receiving Botox treatment for chronic migraine from a UK headache centre (presented at the International Headache Congress in Dublin, 2019): a) 2 year data shows that around 60% of patients (228/380) who had a positive response to Botox were able to stop treatment by two years, most because they reverted to episodic migraine, a few because of pregnancy, development of resistance or lost to follow up. 61 of those who stopped treatment (N=228) relapsed (26.75%) and restarted Botox treatment. 112 out of 380 (29.7%) showed a sustained response and remained episodic (Ahmed et al, IHC-PO-418). b) Five year data shows that 160/186 patients who had a positive response to Botox stopped treatment within 5 years, most

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	because they reverted to episodic migraine, a few because of pregnancy, development of resistance or lost to follow up. 18 of those who stopped treatment relapsed and restarted Botox treatment. The relapse period varied from 4-36 months. 105 patients of 186 (56.4%) showed a sustained response and remained episodic (Ahmed et al, IHC-PO-419) For episodic migraine the proportions are more difficult to estimate. ix) We understand that there has been a change in pricing of Fremanezumab. We assume that cost effectiveness will be recalculated on the new pricing.
3	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. The draft recommendations will deprive a potentially effective treatment to a highly disabled population with chronic migraine who have failed have or been unable to tolerate 3+ standard treatments (in some cases including Botox). A three month trial of Fremanezumab in such patients would clearly be indicated before considering more invasive and expensive treatment options such as intravenous dihydroergotamine, occipital nerve stimulation or even some of the non-invasive neuromodulation therapies such as vagal nerve stimulation or transcranial magnetic stimulation that have limited NICE recommendations without mandatory funding. We iterate the point made above (2 (vii) that the sponsoring company should be asked to ensure they provide data and cost effectiveness modelling for a patient population that have tried and failed three oral preventives and Botox, as this is the population with the greatest clinical need.
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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]

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1	Allergan welcomes the opportunity to respond to the Appraisal Consultation Document for fremanezumab for the prevention of 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. **Allergan Response – Key Points** ▪ Allergan concurs with the Committee's assessment that there is no robust evidence that fremanezumab is more clinically effective than onabotulinumtoxinA. This is consistent with the view reached in other international health technology assessments of fremanezumab, including a recent review by the Institute for Clinical and Economic Research (ICER) in the United States. ▪ Allergan concurs with the Committee's assessment that the long-term effectiveness of fremanezumab is uncertain. In contrast, the long-term effectiveness of onabotulinumtoxinA has been demonstrated extensively in both clinical trials and real-world settings (onabotulinumtoxinA evidence section below). The long-term safety of onabotulinumtoxinA has been similarly demonstrated. ▪ There is a lack of evidence specifically for the population relevant to the submission: patients who have previously failed 3 or more prior migraine preventive therapies. All data to support the clinical effectiveness of fremanezumab for people with episodic or chronic migraine were taken from the post-hoc subgroup analysis of FOCUS trial. Allergan agrees with the Committee's assessment that this reduces the reliability of the findings. ▪ Allergan believes that the economic evidence provided to the Committee underestimates the degree of uncertainty regarding the cost-effectiveness of fremanezumab 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. For instance, one key issue in the economic model is the assumption that the patients who stop treatment with fremanezumab due to positive response would never recommence the treatment when the symptoms return. This is not substantiated by evidence. Evidence from Andreou et al. in the UK clinical practice shows that 20% of patients whose treatment with onabotulinumtoxinA was discontinued relapsed into a chronic pattern after 6 months and hence subsequent treatments were scheduled. In addition, the manufacturer's assumption that patients will likely maintain the treatment benefit after discontinuation of fremanezumab is unrealistic as the treatment effect will diminish over time. The manufacture's model also assumes that all patients will self-administer fremanezumab, which is highly optimistic, especially in the context of monthly injections and/or in patients with physical or mental disabilities and those who have a phobia of needles or a preference for oral tablets. This assumption has already been challenged in the NICE assessment of erenumab where the situation is comparable. Based on clinical practice, it is more realistic that a number of migraine patients will need fremanezumab to be administered to them, and patients to be monitored by specialists to monitor compliance to the regimen. Therefore, Allergan believes that the manufacture's assumption of a zero-cost administration is highly optimistic

leading to underestimation of cost per QALY gained.

- Allergan agrees with the Committee that cost-effective and well-tolerated treatment options are needed, especially for chronic migraine that is especially burdensome to patients. As our response here 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 a large number of centres across the UK where onabotulinumtoxinA is administered for chronic migraine and service capacity continues to expand. Allergan is working extensively with the NHS to increase capacity and access for patients.

Evidence for onabotulinumtoxinA in chronic migraine

The long-term efficacy and tolerability of onabotulinumtoxinA in chronic migraine has been demonstrated in both clinical trials as well as large real-world studies across different clinical settings. The studies summarised in this response comprise a total of over 5,000 patients (including over 1,000 from the UK) treated with onabotulinumtoxinA with up to seven years of patient exposure (HULL Migraine Clinic). These studies 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.

HULL Migraine Clinic provide the largest consolidated source of UK real-world evidence for the effect of onabotulinumtoxinA in chronic migraine prophylaxis, and results extend for up to seven years of treatment. In this dataset, all patients had failed at least three prior preventive treatments (except for 14 patients who initiated treatment before the NICE guidance came into effect in 2012). This makes the evidence from HULL Migraine Clinic particularly relevant to the decision problem in this appraisal.

- 2-year data: HULL Migraine Clinic reported 294 patients with an initial response to onabotulinumtoxinA of which 87.4% (n=257) experienced a successful treatment response over two years of follow up: patients were either still on treatment or had successfully withdrawn treatment without relapse to chronic migraine.
- 5-year data: HULL Migraine Clinic reported that over five years of follow up, 80.2% (n=101) of initial responders (n=126) experienced a successful treatment response, i.e., were either still on treatment or had successfully withdrawn treatment without relapse to chronic migraine.
- 7-year data: HULL Migraine Clinic reported 56.4% responders (388 out of 687) based on Hull Criteria with a good safety profile.

Evidence from “real-life” also demonstrates that clinical improvement in chronic migraine patients who responded to onabotulinumtoxinA is maintained in the long-term following discontinuation of therapy:

- HULL Migraine Clinic reported 177 responders to onabotulinumtoxinA who had stopped treatment of which 53.6% (95 out of 177) remained episodic at the end of year two.
- Ching et al. reported that 80% of patients (105/131) reported no clinical worsening or need to resume prophylactic therapy over the 6 months following discontinuation of onabotulinumtoxinA therapy.

Additional "real-life" studies from Italy and Australia further confirm the long-term safety and effectiveness of onabotulinumtoxinA in chronic migraine:

- Two-year outcomes from a prospective observational study of patients treated at the Sant Andrea Hospital in Italy.

- A multicentre, retrospective chart review of 211 medical records of adults with inadequately controlled chronic migraine from 7 private neurology practices in Australia.

OnabotulinumtoxinA was originally licensed on the basis of data from two phase III studies (PREEMPT 1 & 2). 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 chronic migraine. 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. One third of patients in these trials had not responded to ≥ 3 prior oral preventive therapies.

The findings from the PREEMPT programme have been both confirmed and extended by the results of a long-term phase IV study (COMPEL) in which onabotulinumtoxinA was well tolerated over 108 weeks and 9 cycles of treatment with no new safety concerns being identified. The findings of COMPEL study were also confirmed by the prospective multinational REPOSE and CM-PASS studies.

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). 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. 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 or REPOSE studies, while adverse events in the 52-week CM-PASS study (N=1,160) were also consistent with the product label and the results of PREEMPT 1 & 2.

PREDICT is a Canadian, multicentre, prospective, observational study in 196 patients with chronic migraine which aimed to assess onabotulinumtoxinA treatment utilisation, safety and long-term health-related quality of life. This interim analysis demonstrated that

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	onabotulinumtoxinA for chronic migraine improved health related QoL and work productivity and reduced healthcare resource utilization.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
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	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
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	The fremanezumab manufacturer's rationale for the inclusion of data from Study 295, which compared erenumab and placebo, is reported as being "to strengthen the network". This rationale is not challenged in the Appraisal Consultation Document. However, it is unclear how the inclusion of Study 295 would strengthen the network – a point made by the Evidence Review Group in their report ("In addition, the company noted that while trials relating to erenumab were included to 'strengthen the network', it was unclear how this would have been the case given that included erenumab trials were connected to the network only via the placebo node" [Evidence Review Group report, pg 151]). Based on the framework for considering inclusion of evidence as outlined in NICE Decision Support Unit Technical Support Document 1, the synthesis comparator set for the fremanezumab appraisal would consist of fremanezumab, botulinum toxin and placebo, and included trials should be "all trials on the target population that compare two or more of the treatments from the synthesis comparator set". This would not include Study 295, as this includes only one treatment (placebo) from the synthesis comparator set. Whilst Technical Support Document 1 does discuss extension of the synthesis comparator set to incorporate other trials, it notes both advantages and *disadvantages* to such extension and states that "while extension of the network is not ruled out….it would not be considered as the "base-case" analysis". Therefore, we suggest that the results of the indirect treatment comparison that incorporates Study 295 should be treated with caution, and that an indirect treatment comparison excluding Study 295 would be more appropriate for decision-making.
2	The fremanezumab manufacturer's approach to utility values modelled that patients on treatment receive a utility benefit over and above that resulting from the reductions in monthly migraine days due to treatment effect. In this context, the Appraisal Consultation Document states that the Committee "noted that the application of treatment-specific utility values was consistent with previous migraine appraisals". However, we consider that this statement is misleading. There have only been two prior technology appraisals in migraine (botulinum toxin [TA260] and erenumab [ID1188]). In the botulinum toxin appraisal it is correct that treatment-specific utility values were used: the mapping algorithm was used to derive utilities by treatment arm separately in order to "understand the broader effects of treatment beyond the number of headaches experienced by patients". However, for the more recent erenumab appraisal, utility was modelled to be only dependent upon frequency of monthly migraine days; no additional on-treatment utility benefit was incorporated above and beyond any beneficial impact of treatment on improvement in frequency of migraine. Therefore the statement in the Appraisal Consultation Document that use of treatment-specific utility values was consistent with previous migraine appraisals is at least partially incorrect. In this context, we agree with the Committee's stated conclusion in the Appraisal Consultation Document that "additional on-treatment utility value benefits were not supported by the evidence and should not be included in the economic model", which would represent an approach consistent with the assumptions underlying decision-making in the erenumab appraisal.
3	The Appraisal Consultation Document states that the Committee concluded that it preferred a lifetime time horizon of at least 30 years to ensure that all relevant costs and benefits associated with fremanezumab were captured. Given that the considerations contributing to the decision on time horizon in the fremanezumab appraisal are similar to those in the erenumab appraisal (limits to long-term data, requirement to capture all relevant costs and benefits, same patient population [and hence same patient ages in clinical practice]), we consider that the Committee preferences over time horizon should be consistent for the fremanezumab and erenumab appraisals. In the erenumab appraisal, a lifetime time horizon was similarly preferred by the Evidence Review Group and subsequently the Committee. However, the Evidence Review Group's adjustment to model a lifetime time horizon resulted in a time horizon of 64 years. Therefore, we consider that defining a lifetime time horizon as 30 years for the fremanezumab appraisal versus 64 years for the

	erenumab appraisal results in the potential for inconsistency in decision-making. As such, an approximately 64 year time horizon should be considered as the definition of a lifetime time horizon for the fremanezumab appraisal, or otherwise more full justification for a choice of a 30 year time horizon as "lifetime" should be provided.
4	The Appraisal Consultation Document describes the HALO-EM and HALO-CM studies as evaluating fremanezumab in patients with chronic/episodic migraine "when fewer than 3 classes of preventive treatment have failed". We believe this is incorrect, as the exclusion criteria for these studies specify patients who have experienced a lack of efficacy after ≥3 months of treatment *of at least two of four classes* of preventive treatments. This implies that patients for whom two prior preventive treatment classes have failed would be excluded from the trial, and the Appraisal Consultation Document wording should therefore be adjusted to state that the study populations comprised patients "when fewer than **2** classes of preventive treatment have failed". In addition, this exclusion criterion specifies that patients had to have experienced lack of efficacy after *at least 3 months of treatment* to be counted as having had a prior treatment failure. This suggests that the HALO study populations may have still included patients for whom three prior therapies had 'failed', where this failure was defined on the basis of lack of tolerability or perhaps lack of efficacy as determined by less than 3 months of treatment. For the FOCUS trial, an inadequate treatment response was defined as a lack of clinically meaningful improvement after at least three months of therapy, but also as intolerance to the treatment or the treatment being contraindicated or unsuitable – this highlights that considerations over tolerability may constitute part of the definition of treatment failure. Additionally, as topiramate (a treatment relevant to UK clinical practice) was not included within the list of exclusion criteria relating to 'failed' prior lines of treatment (see the fremanezumab manufacturer's response to Evidence Review Group clarification question A18), the HALO trials would have potentially included patients with prior failure to topiramate. From the Committee papers it does not appear that the appraisal has explored the potential availability of data from the HALO studies for patients who might meet the decision problem of 3 prior treatment failures where 'failure' is defined on the basis of prior topiramate failure, tolerability issues, contraindication or lack of efficacy after <3 months treatment (all of which may potentially be relevant criteria for 'failure' in clinical practice). As such, the appraisal may not currently be taking into account potentially relevant data from the HALO studies, which could be important in fully understanding the treatment effect of fremanezumab in the population of 3 prior treatment failures that is under consideration in the decision problem. Such data, if available, could be informative given that the only other data in this subgroup is from the FOCUS study.
5	We agree with the comments in the ACD that the per cycle all-cause discontinuation rate for fremanezumab appears high, and that this has the potential to affect cost-effectiveness results as it has a direct influence on accrual of treatment costs into the long-term. As the direct source of the all-cause discontinuation rate is not provided it is difficult to comment on the appropriateness of the value used for the per cycle discontinuation rate – however, we agree that because treatment allocation was not blinded in the HALO open-label extension study, the impact of additional injections to preserve blinding does not offer an explanation as to any potentially higher discontinuation rate. As such, there does not appear in the Committee papers to be a valid explanation for why discontinuation from fremanezumab in the longer-term is higher than seen with erenumab. In the absence of any robust explanation for the use of an all-cause discontinuation that, as judged by the NICE Committee, is higher than expected, we agree that the preferred scenario regarding post-discontinuation assumptions is not the manufacturer's default approach but is instead the ERG's scenario in which patients revert to baseline monthly migraine days after all-cause discontinuation.

Insert extra rows as needed

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

Name	[redacted]
Comments on the ACD:	
In comparing Fremanezumab to botox injections, the difference in administration has not been considered. Even if botox does in fact have an equal chance of success, there is a big difference in the level of interference in a patients day to day life. Botox involves 32 injections across the scalp and must be administered by a medical professional. It involves days off to travel to a treatment facility every 3 months, several days of soreness, and a much more unpleasant process, taking up the time and money of an already short-staffed NHS. In contrast Fremanezumab requires only one injection and can be self-administered by the patient at home, resulting in a reduction of patient stress and a reduction in time and staff requirements for the NHS. In addition to this, botox itself (like most preventative treatments) has only a 1 in 4 chance of working for a patient. If 3 out of 4 people treated in this way (who will only have been approved after multiple tablet options have failed) will not be fit from it, I believe it is unfair and inhumane to deny them access to what may be their last chance at effective treatment. For example I have personally tried 8 different preventative tablet treatments. I had adverse reactions to several, and the partially successful one I am currently on has not improved my condition enough to stop me from losing my full-time job. I am on the waiting list for botox but am very anxious about the process itself and will likely have to travel to and from London for treatment due to my local pain clinic being over-subscribed, which as a now unemployed person is not a cost I can easily afford. I believe Fremanezumab could have a significant impact on my quality of life and having the possibility of effective treatment (one of very few I have not tried) witheld by financial barriers has a negative effect on my mental health.	

Name	[redacted]
Comments on the ACD:	
Are the recommendations sound and a suitable basis for guidance to the NHS? My neurologist says that you have not conducted the tests on AIMOVIG properly and that you used the lower dose 70mg dose to conduct your comparison with Botox as a preventative. I'd like to know if you used the full dose with AJOVY. Also how can you dismiss these drugs for use with English people when the scots are getting them? And most of Europe and North America? I suffer from Chronic migraine and you are discriminating against us.	

Name	[redacted]
Comments on the ACD:	
Has all of the relevant evidence been taken into account? Yes, but I believe the consideration of this for episodic migraine is an error. I think you should review your position based on the chronic migraine evidence.	

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No. The clinical efficacy only considers comparison of Botox as a treatment for chronic migraine. It fails to consider that this treatment could be used as another line of treatment, such as where Botox has not been effective.
Moving people to best management is ineffective, and is washing your hands of people's ill health. This is a groundbreaking treatment which could change the lives of people disabled by their chronic neurological condition. Clinical efficacy demonstrates it works. Just add it to the treatment list with conditions about accessibility.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No. I believe this drug is absolutely needed for patients with migraine. I believe it should NOT be made available for episodic migraine, but it should be available for chronic migraine in accordance with the existing definitions.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Migraine predominantly affects women. Women are often primary caregivers, often earning less then male counterparts, and this may be discriminating against women who want to stay in work. This could have a significant impact on women more so than men.

Name	[redacted]
Comments on the ACD:	
I have been taking aimovig for 6 months and it has helped so much I cant even put it into words I was getting migraines everyday and nothing help we tried all the triptons and topimax and I was taking excedrin like it was candy just to get out of bed. After starting aimovig I maybe get one migraine a month and it has even helped with my trigeminal neuralgia too	

Name	[redacted]
Comments on the ACD:	
As a chronic migraine sufferer for over 30 years I have been following the use of CGRPs in the US and there is ample evidence demonstrating its success. I have had both cancer and migraine this year and can testify that the pain and distress caused by constant migraine is worse than the horrendous experience of cancer and chemo/radiotherapy. We desperately need CGRP drugs licensed in the UK. Botox is expensive and doesn't work for all. Please consider carefully how debilitating living with migraine is and how desperately we need these drugs to enable us to have quality of life.	

Name	[redacted]
Comments on the ACD:	
We need to see support from NICE to get effective treatment and prevention medication specifically designed for the prevention of migraine. This affects such a huge number of individuals detrimentally, and yet unbelievably, this class of	

medication is only the first preventative specifically designed for this complex and debilitating neurological condition. I live (badly) with migraine that moves constantly between chronic and episodic classifications. With an effective medication, my life could be hugely different. The previous consultation on the first CRGP in the UK - erenumab - was genuinely heartbreaking for me. The constant comparison with Botox - which in itself is not readily accessible (my specialist does not choose always to help in this respect, due to the fact that my condition changes from chronic to episodic over some months) and seems to be a stumbling block here against approving new treatment. People are different, and there should be more than one effective treatment option available. The other block here seems to be the idea of only approving preventative treatments of this kind for chronic suffers, for whom existing treatment does not work. This is unhelpful - if people with episodic migraine were effectively treated with targeted preventatives early enough there may well be fewer people who fall into a chronic cycle of migraine pain and frequent pain medication overuse etc.

It's really time that migraine sufferers were really considered a worthwhile community to help. It's appalling that we are waiting this long to see a real investment in our quality of life

Name	[redacted]
Comments on the ACD:	
How can you say it is cheaper to administer Botox, which requires specialist trained nurses over several courses in order to administer? Also please note that Botox is NOT offered nor available to everyone under the care of a specialist or Neurologist on the NHS. I have tried all sorts of your the other ‘preventable’ treatments and have had no viable relief and horrendous side effects. I am now on Aimovig which I’m having to struggle through to pay for privately and my improvement from av. 20 migraines a month is down to 1 or 2!! I have been off work for years now as kept getting managed out every job due to sickness and the stress that entails, hopefully I am now in a position to start working again and paying back into the tax system. These CGRPs are made solely for migraines, no other preventable on the market is, this condition should be given the respect it deserves and patients offered a treatment that works and does not cause bad side effects. You will have the numbers on the severity of this condition so I dont need to go there. I was ready to give up on life before these CGRPs came available and now I can see hope but this should not restricted to only those who can afford or just about afford. With more of these types coming onto the scene, surely this will drive costs down? Please reconsider, this drug as you say will only be given to those who meet the worse criteria and it can help those live a life again.	

Name	[redacted]
Comments on the ACD:	
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. Many people do not respond any medicines or to botox and it is this group who most need new treatments. Fremanezumab would be cost effective to administer to this group of patients.	

Are the recommendations sound and a suitable basis for guidance to the NHS?
No, see above. The NHS should be guided to administer fremanezumab to those who have not responded top other treatments, including Botox.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
I think this decision discriminates against those most disabled by chronic migraines and most in need of new treatments.

Research shows that women are disproportionately affected by chronic migraines (Buse et al. 2012 doi: 10.1111/j.1526-4610.2012.02223.x), thus this decision discriminates against women.

Name	[redacted]
Comments on the ACD:	
I am very disappointed that this new CGRP drug is not recommended for use by the NHS in England. Having struggled with chronic migraines for nearly 40 years I have run through a huge number of preventative and acute medication. Apart from the triptan medication, which was developed specifically for migraine sufferers, all the other medication I have tried has not had a primary usage for the treatment of migraines. With the CGRP medication we have the opportunity to use the first preventative actually created for migraine sufferers and it's not going to be available to them. I have retired early as a result of my migraines. I feel sorry for those younger people who struggle with them who will never reach their full potential owing to the debilitating nature of the disease. I certainly never did. Please reconsider even if it is just in an effort to reduce sickness days and allow people to be at their productive best.	

Name	[redacted]
Comments on the ACD:	
Has all of the relevant evidence been taken into account? I suffer from Medically intractable chronic familial hemiplegic migraine. This means I suffer stroke like symptoms on a daily basis. 5 years ago I went from an eloquent primary school teacher to someone who could no longer speak or function literally overnight when a malignant hypertensive crisis triggered status migrainous. I have now had migraine everyday for the last 5 years and migraine over 26 days per month for 25 years. I have tried EVERY migraine treatment that is available and have had Botox, GON injections, multicrainial nerve blocks, DHE infusions, Lidocaine infusions and drug therapy that stretches to 4 sides of A4. I would do absolutely anything to be free of this relentless disease and if I could give away one of my health conditions and never have again it would be chronic migraine. It defines what I am able to do, how I am able to function, how I'm perceived by the world and disables me beyond belief. There is so little sympathy and understanding for migraine sufferers as everyone relates to their worst headache and calls it a migraine whether it is or not. I wouldn't wish this debilitating condition on my worst enemies. It seemed so very unfair that FINALLY there has been drugs developed specifically for chronic migraine sufferers yet we are being denied access to these life changing drugs because of our post code and the chance to	

function in a more normal state. Why have biological drugs been allowed for other conditions such as Crohns, Rheumatoid and psoriasis been allowed and people with those conditions have been able to have their lives changed but chronic migraine sufferers are being devised this opportunity and are stuck using outdated, ineffective drugs with horrendous side effects and are left to function in a zombie state. Unless you sufferer from chronic migraine you can never really appreciate how awful this condition is and what struggles we all go through to stay positive and continue our personal quests to be free. Please, please, please give us a chance to be able to access these drugs. The cost to th UK economy of chronic migraine is substantial and significant surely this would be weighted in the benefits of offering this drug. A £400 per month injection could literally change lives!

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
By offering the drug and making it available in certain parts of the UK yet denying it to people in others, puts people at an unfair disadvantage and discriminating against people upon grounds of race and postcode area.

General comment
I suffer from Medically intractable chronic familial hemiplegic migraine. This means I suffer stroke like symptoms on a daily basis. 5 years ago I went from an eloquent primary school teacher to someone who could no longer speak or function literally overnight when a malignant hypertensive crisis triggered status migrainous. I have now had migraine everyday for the last 5 years and migraine over 26 days per month for 25 years. I have tried EVERY migraine treatment that is available and have had Botox, GON injections, multicrainial nerve blocks, DHE infusions, Lidocaine infusions and drug therapy that stretches to 4 sides of A4. I would do absolutely anything to be free of this relentless disease and if I could give away one of my health conditions and never have again it would be chronic migraine. It defines what I am able to do, how I am able to function, how I'm perceived by the world and disables me beyond belief. There is so little sympathy and understanding for migraine sufferers as everyone relates to their worst headache and calls it a migraine whether it is or not. I wouldn't wish this debilitating condition on my worst enemies. It seemed so very unfair that FINALLY there has been drugs developed specifically for chronic migraine sufferers yet we are being denied access to these life changing drugs because of our post code and the chance to function in a more normal state. Why have biological drugs been allowed for other conditions such as Crohns, Rheumatoid and psoriasis been allowed and people with those conditions have been able to have their lives changed but chronic migraine sufferers are being devised this opportunity and are stuck using outdated, ineffective drugs with horrendous side effects and are left to function in a zombie state. Unless you sufferer from chronic migraine you can never really appreciate how awful this condition is and what struggles we all go through to stay positive and continue our personal quests to be free. Please, please, please give us a chance to be able to access these drugs. The cost to th UK economy of chronic migraine is substantial and significant surely this would be weighted in the benefits of offering this drug. A £400 per month injection could literally change lives!

Name	[redacted]
Comments on the ACD:	
Has all of the relevant evidence been taken into account? Trials have proven its affectiveness	

General comment
Current medications do not help a high % of people with chronic migraine, including myself. The side effects of these drugs (which were not developed for chronic migraines - blood pressure and seizure drugs!) outweighs the benefit. Botox has a limited effect - reducing severity for many but not the number of attacks. Chronic migraine although not life limiting, it is LIFE CHANGING!!!
I personally no longer have a career, have limited social life, increased depression and anxiety. My children's lives are affected daily due to my condition. We need new and advancing treatments.

There is little support for those living with chronic migraine - we feel isolated and abandoned by the medical profession.

The chronic migraine community needs open access to these new CGRP meds. Scotland does, England now needs it.

Name	[redacted]
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? See below. Significant factors. **General comment** I believe that recommending this drug in selected patients would enable many more people to get substantive relief from disabling migraine. I know I am not alone in being unable to work or socialise because of this illness. I dread the next possible 20 or 30 years with this disability. Many of the preventive drugs are not suitable for people with other conditions or have side effects that also severely affect the quality of life e.g trying Amitriptyline left me housbound as I was concerned about driving. Propanolol didn't suit me and the suggestion of Topiramate for someone with dry eye and mucous membrane pemphigoid and osteopenia looks very unwelcome and liable to cause even more problems. Patients with CVD and those over 65 have no real acute attack options as NSAIDs and Aspirin are often contraindicated. I belive that your failure to recommend this drug deprives a significant, and mainly older subset of patients from migraine relief. I contend that this failure fails to take account of equalities legislation. There is nothing on offer for people in this group that is self administered. IF you can get Botox on the NHS this is very rare and not I understand offered on a repeated basis. Thank you for reading this comments. Please give the older, disabled population some hope for the future. Thank you	
Name	[redacted]
Comments on the ACD:	
Comment on the line 'Fremanezumab is not cost effective compared with best supportive care for people with episodic migraine after 3 preventive treatments have failed' This will change over time. **General comment**	

Does anyone on the committee have migraines and understand the pain and suffering they cause? Many patients suffering from migraines try 3 or more preventives in a year. I am currently on a antidepressant, Topiramate, magnesium and B2. Plus, the abortive. And I still have a migraine a week that lasts anywhere from a few hours to 3 days. Having an injectable as an option drastically cut down on time spent counting and sorting pills, collecting them from the pharmacy and remembering to take them, especially during an attack.

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
No because the consultation continues to claim other medications are more effective and cost sensitive

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No because repeatedly its claimed Botox is efficasous and cheaper when actually for many patients Botox actually triggers such a severe migraine attack they are bedbound for over a week with absolutely no benefit

Are the recommendations sound and a suitable basis for guidance to the NHS?
No they discrimate against the small group of patients for whom every single other form of medication or treatment has already been tried and for whom the side effects are so severe they cannot be continued

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
The recomendations totally discriminate against and deliberately penalise the small group of constant chronic severe migraine patients who are the innocent victims of a mild TBI

No other form of medication or treatment available including Botox are of any help to this group

General comment
I cannot find any recognition of the appalling plight of all those with constant chronic post traumatic migraine after a mild TBI who have already tried every single form of medications thrown at migraine all of which have caused such horrendous side effects without any effect on the pain they have to be discontinued, they have also tried TMS, Vagus Nerve stimulant, DHEinfusion , occipital nerve blocks, Botox not one of them has had any effect on their suffering which basically goes unrecognised by almost every neurologist in the UK ....for them there is no life , no future and no hope ....they cannot hope to gain or hold down a job no matter how highly intelligent they are ,so a life of constant pain disability and a fight for benefits results. To deprive this small sector of patients of the chance to try CGRP or any of the new medications in the pipeline is beyond cruel its totally inhumane My now 21 yr old Grandaughter is one such patient who with an intelligence quotient of top 1% in the Country has spent the last 6 yrs in hell ...her determination means she struggles on but it is tearing the entire family apart to see her suffering and to not be able to acheive her aim of being a Human Rights

lawyer is a travesty .The NHS have proved at every level especially locally to be utterly useless and inept and getting appointments alone takes many many months and hours of exhausting travel to the only Neurologist who has any clue
Hence to deny this small sector of patients any form of CGRP medications is a travesty .

I totally understand and condone the refusal of NICE to allow the prescribing of CGRP to all migraine sufferers especially when currently available treatments work for them but for those who experience what my Grandaughter does the chance to be free of pain and able to earn a living and pay tax is a basic Human Right which you are denying on extremely spurious and incorrect grounds

Name	[redacted]
Comments on the ACD:	

Dear NICE Appraisal Committee,
I was a full-time General Practitioner until 10years ago, when I was forced into early retirement aged 46 due to Chronic Migraine.
At that time, I was fortunate in that I was able to obtain a specialist diagnosis from Professor Goadsby at an early stage. What I did not have access to, was good, effective treatment options that, happily are now available- but not easily, timeously (I refer to the BoTox guidelines) and the mAbs, currently not on the NHS.
There are few medications and interventions I have not tried in my attempts to regain my health; but each trial of prophylactic medication takes a minimum of six months. Years of a formerly intelligent and productive life wasted. Beta blockers, Topiramate, Sodium Valproate, Flunarizine, GON blocks, TMS, and others did not work for me. Neither did BoTox.
I received 3 months Fremanezumab (after three months initial placebo) as part of the FOCUS trial at King's and have been taking Erenumab for the last 12 months as part of the free-access scheme. These medications have been MORE EFFECTIVE than any others for me, and have allowed me a significant reduction in pain and an increase in functional ability. I no longer want to die.
I urge you to consider allowing the use of Fremanezumab, not just for Chronic Migraine, but for frequent, episodic migraine too.
My firm belief is, that, if these medications had been available to me when I had first shown signs of disease progression, then my medical career and life would not have been destroyed.
It is unscientific and frankly cruel, as well as causing a burden of unnecessary debility to individual sufferers and society as a whole, to limit or deny use of these especially-designed, targeted, low side-effect profile drugs in the early stages of FEM and CM.
I urge you to consider these two groups; for them, I am sure the medication IS cost-effective.
Thank you.

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
Have the surveys done via the migraine trust and answered by 200 patients already on Aimovig been taken in to account? These are vitally important to understand the ACTUAL positive effects these drugs are having on desperate patients.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Are these costs compared to the costs saved when patients cease other medications or interventions?
I was suicidal before Aimovig and under 2nd tier mental health teams as well as on 3 other medications. I am now on just the trail if Aimovig having withdrawn other medications and come off the mental health system.

Are the recommendations sound and a suitable basis for guidance to the NHS?
There are many patients happy to talk to you who will be able to give a direct patient's view of the effectiveness of these drugs against ANYTHING we have been offered before. They are changing lives but we need access to them.

Comment on line 'The most relevant comparators are best supportive care for episodic migraine and botulinum toxin type A for chronic migraine.'
Many people with chronic migraine like myself have tried over 15 interventions with no success.

Name	[redacted]
Comments on the ACD:	
My chronic migraine meant having to give up my career in IT. Working part time even, wasn't sustainable. A CGRP medication like this could transform my life and get me back into the workforce again. I have tried all of the oral medications available and Botox and none have been of a sustainable benefit. My life is being wasted, given over to migraine, and to be told that £450 a month is not cost effective to take me out of this migraine hell and back into work is soul destroying.	

Name	[redacted]
Comments on the ACD:	
Has all of the relevant evidence been taken into account? Yes **Are the recommendations sound and a suitable basis for guidance to the NHS?** No **Migraine has a substantial effect on health-related quality of life** Migraine has a substantial effect on every part of my quality of life - my ability to be a mother to my children, a wife, a friend and severely impacts my ability to work. I am on the edge of having to give up working. I am unable to drive long distances and rely on family to drive me anywhere. I suffer from anxiety and depression and at my worst banged my head into the wall and feel suicidal. My migraines last from one day at a time to daily for considerable amounts of time. I am taking 2 preventatives and have Botox and take triptans 5 times a month.	

It is uncertain whether fremanezumab is more clinically effective than botulinum toxin type A
I have been having Botox injections for 5 years and am still not in control of my migraines.

Some people will need fremanezumab to be administered for them
If you suffer the pain of migraine you would not be afraid of a needle. I gave birth to two children drug free and it was less painful than a migraine. I remember only being worried about having a migraine.

Fremanezumab is not recommended for use in the NHS
Surely this should be made available for patients with chronic migraine. I get 4 or 5 migraines a week, not a month.

Name	[redacted]
Comments on the ACD:	
For years daily' chronic migraine has left me almost bed bound, tried all preventatives, sTMS & botox, not helped. Started Aimovig privately a month ago and only had one migraine since, it helped instantly but can't afford it for more than 6 months as unable to work due to this debilitating condition. Please, please give chronic migraine sufferers a chance of their life back rather than just existing in misery. Surely with strict guidelines to follow you will help us PLEASE	

Name	[redacted]
Comments on the ACD:	
Having suffered from migraines from a young age I am completely baffled by this decision. My Neurologist believes I could benefit from this treatment, I currently am supposed to be on botulinum toxin every 3 months at the Royal Free Hospital, I last had this in July and was told the next free appointment would be February 2020! I have been trying to get a cancellation for 2 months now but all clinics are full. Surely if this treatment works on any % of patients it would free up valuable time for the clinics - I am now back to having headaches/migraines almost daily and I cannot get an appointment. I am not saying it would necessarily work for me, but if it did then great - I could self administer and not have to travel into London, if not it would work for others and free up clinic space so I could get an appointment every 3 months! Clearly the people who made this decision have never suffered from this debilitating condition. My six year old son asked my husband if 'mummy was going to die' the other day as more often than not I have to be in a dark room. Also why have NHS Scotland had this agreed?!!! again so unfair, I've even considered trying to register with an NHS doctor there. I would love to get a reply to this.	

Name	[redacted]
Comments on the ACD:	
As someone who suffers with Chronic Migraine and has tried 5 or more different oral preventative medications, as well as a number or Triptans that do not have an effect, I feel we should be given the option to choose between the two different medications of botulinum toxin type A and fremanezumab. Making the decision to have botulinum toxin type A is very difficult as it has several side effects - some of which can be physically seen (i.e. droopy eye). From what I	

have been told by both my GP and a private Neurologist, having this treatment carried out can be a unpleasant and painful experience which is off-putting and daunting, especially as I also suffer with a phobia of needles. Having a small injection (depending on what dosage was prescribed) over more than 30 would be my first choice.

Being told that my last option for treatment is botulinum toxin type A made my world come crashing down. I was told that there is basically a 50/50 chance that the treatment wouldn't make a difference. How is that meant to give me a positive outlook on life? The thought that the LAST treatment option as I was told could potentially make no difference made me feel worthless. Also being told that fremanezumab would not be an option for me due to funding made me feel like I was being told that my standard of life was not worth the cost and that I would have to fund it myself privately if I wanted it as a treatment option. If I am unable to work due to this agonizing condition, how am I meant to afford £500 every month to pay for this treatment?

Effectively I was told I must choose between living the rest of my life with this crippling condition or having a treatment that nobody of my age should even have be considering, and that it might not even help. To have another option would lift a huge weight off my shoulders and give some hope to my future.

At the age of 25 I have gone from being a bright bubbly person who was full of life and always smiling, to someone who no longer socialises, struggling to maintain relationships with not only friends but also family, suffers with depression and has recurring suicidal thoughts – especially during severe migraine attacks. It is rare that you see a genuine smile on my face…

I am lucky to have 4-5 days out of a month where I do not suffer with a headache or migraine. This is no way to live. I am lucky enough to have a supportive employer, but when I am having 10-15 days off sick in the space of a few months, you can only expect them to tolerate for this so long. I used to excel in my career but now I am limited as to what I can achieve.
I know I am not the first victim of migraine to feel this way, and I am sure I won't be the last, but this condition is so under studied considering the number of people who suffer in this day and age.

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
I feel the evidence is not wholly appropriate - in particular that related to comparing botox to CGRP drugs.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No - not taking into consideration wider costs to economy of chronic migraine patients. Cost to nhs for mental health related aspects (stress, anxiety, depression, suicide, CBT etc) and cost to economy of unemployment.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No - I do not support the recommendations.

General comment
As a chronic migraine patient currently taking botox and Aimovig combined I do not agree with the recommendation of to not allow CGRP drugs as they're not proven to be more effective than botox.

Firstly botox and CGRP drugs are targeting migraines in a completely different way - so those who responded well on the botox trial might not respond to CGRP drugs but likewise those who didn't respond to botox May well respond to CGRP drugs! So not allowing CGRP drugs is denying many chronic patients the chance at a considerable reduction in the frequency of their migraines.

Secondly I am using botox and CGRP drugs side by side. Botox gave me overall a 3% reduction in attack days where as adding Aimovig to my treatment has reduced my attack days by a further 11%. So combining botox and Aimovig has reduced my attack days by a total of 14%. Over a year that's giving me 50 days of my life back, 50 extra days with no pain. Without Aimovig it would be 10 extra days with out an atta m per year - seems nothing compared to 50.

My average duration of attack hours has decreased by combining botox and Aimovig, and my ratio of migraine to headache has dropped from 37% migraine and 68% headache on botox to 20% migraine and 80% headache on botox and Aimovig. Therefore I am having less attack days, but when I do get an attack is more often a headache (so much lower pain scales) and it last much less time. Overall for me combining the two drugs has hit a "sweet spot" - I have taken far less time off work, been able to participate in more social occasions, been able to do simple things like wear my hair in a pony tail etc. I feel like right now I live a much more "normal" life and my chronic illness is not defining me.

However, right now I am privately finding my Aimovig. I have nearly spent all my savings and have enough money left for three more rounds. I am not sure what I am going to do when the money runs out. The stress and anxiety I am suffering not knowing whether I can afford to keep taking this life changing drug is immense. I am in a vicious circle of needing to work to fund my medication and needing my medication to keep going to work. Having had the amazing 5 months I've had on Aimovig I really can't bear to think of not continuing, but also the detriment to others of not having the chance to take these CGRP drugs.

I understand the cost associated is high, but I firmly believe it should not be compared to botox and the economic implications of more migraine sufferers being able to live a more normal life, go back to work, less mental health requirements etc far outweigh the administration costs.
As a chronic migraine sufferer who feels like she has her life back I urge you to reconsider your recommendations on CGRP drugs and their use in nhs England.

Name	[redacted]
Comments on the ACD:	
Please reconsider the 3 year wait to either retrial this drug or to review its general use within the NHS. Fortunate are those indeed who were already on this drug and can now stay on it. Fortunate indeed those who can afford to obtain it privately from their consultant. It is for many of us a last line of hope, both for migraine sufferers and for their families.	

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
No, you haven't got a head to head study that would show the CGRPs are miles ahead of Botox.

And you haven't taken into account the benefits of getting people with migraine back to a full and contributing life.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No

Are the recommendations sound and a suitable basis for guidance to the NHS?
Absolutely not. They are shameful.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Yes. Migraine is a disorder that particularly affects women. You need to take into account that by not approving these medications you are demeaning the struggle of women, and that as there are more women in the prime of their lives removed from the workforce because of migraine than there are because of childbirth, you are actively contributing to the gender pay gap if you fail to approve these medications.

General
What other disease, in the world, are you forced to take medication for something else before you can be properly treated? You should be ashamed of the quite frankly unethical and pathetic reasons to reject both Ajovy and Aimovig. These are life changing medications, the very first specifically designed to prevent migraine attacks, and are in an entirely different league to Botox - which is dangerous, painful, and doesn't work very well. Neither do the other medications like beta blockers or anti-depressants. By the logic presented here, someone with a heart condition or depression should have to try a migraine medication and perhaps a pain killer and an asthma preventer before actually getting the medication they need. These are very cheap biologics, they will make an enormous difference to the health and wellbeing of *young* working age people, mostly women, who should be paying taxes rather than debilitated by illness. Any cost of providing the medications will be more than offset by increased productivity and tax revenue. Shame on you.

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
N/a

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

N/a

Are the recommendations sound and a suitable basis for guidance to the NHS?
N/a

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

Comment on line '1 Recommendations - Therefore, fremanezumab is not recommended'
Migraine is a debilitating condition which affects one in seven people. For many those one in seven of us, it's not 'just' a headache - it's a chronic condition which manifests itself several times a week. Migraine has a significant impact on the lives of sufferers, who in too many cases cannot do normal, everyday things, like going to the gym, eating certain foods, or staying up late, because it could trigger an attack.

If it does trigger an attack, then that can mean a couple of days in bed, nausea, time off work, sensitivity to light, smells, and noise - and an excruciating pain.

While there are some treatments which can help, they're cures for other things. Anti-depressants, beta blockers, epilepsy medication, arthritis pills, botulism. It's a happy accident if they work, but in many cases they're badly prescribed. They come with a litany of unwanted side effects, and they don't always work.

So medications link fremanezumab - created to treat migraine and showing positive results - really do seem like a game-changer. I've heard anecdotally about the huge difference it's had to the lives of sufferers, and I've read the results of studies into how they work. For one in seven of us, prescribing fremanezumab really is an acceptable use of resources.

Please, reconsider your recommendation.

Name	[redacted]
Comments on the ACD:	
As a migraine patient who has been suffering for the last 11 years .. I want to say due to many of the side effects of the following medications- beta-blockers, antidepressants and epilepsy medications, such as causing breathing difficulties, foggy thoughts and anxiety, etc, I have not been able to try these preventative drugs with doctors advice. As I am in the category who has had history of asthma in the past/ migraine causes severe fog to me/ I already suffer from severe anxiety due to the impact migraine has had on me. I feel more needs to be done for patient like myself, where I am not able to try these as it will make my condition worse. Only to be left in the dark to suffer the pain, I get over 11 attacks a month! I really hope NICE will be considering options that will benefit everyone! [redacted]	

Name	[redacted]
Comments on the ACD:	
Dear Sirs, I am a chronic migraine sufferer having up to 3 migraines per week and daily headaches. I have tried numerous preventative medications including Botox all of which I have had varying degree of intolerance to. I have also tried cranial osteopathy, reflexology, acupuncture and treatment from a chiropractor and also tried various supplements. none of which have helped with my migraines. I am therefore desperate for Fremanezamab or another new preventative drug to be approved for use on the NHS in order to improve my quality of life. Yours gratefully, [redacted]	

Name	[redacted]
Comments on the ACD:	
I participated in the Frenenuzamab trial and the impact on my life was nothing short of a miracle. I had and now have post-trial no quality of life without such a drug. I am trying to find a way to access the drugs I require privately but this will take my life savings and I'm concerned at what happens when they run out. Do I sell my home? To me this is literally a life saving drug as I have no life without it. Please do help by approving this drug for chronic sufferers. I believe it's cheaper than botox and, for me, much much more effective. Kind regards. [redacted]	

Name	[redacted]
Comments on the ACD:	
I sincerely wish this is available in England easily to patients. Numerology waiting list to have Botox is one year. Hoping the threshold for having Aimovig and Botox is lowered and those with chronic migraine benefit with these on time rather wait for decades to see if other prophylactics fail.	

Name	[redacted]
Comments on the ACD:	
Has all of the relevant evidence been taken into account? I don't know. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I don't know. **Are the recommendations sound and a suitable basis for guidance to the NHS?** I don't know **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group**	

of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
I don't know.

Comment on line 'Appraisal consultation - Fremanezumab for preventing migraine'

I've suffered from migraine since 1998. I have tried all of the preventative treatment - antidepressants, blood pressure and epilepsy meds. Topiramate and Venlafaxine left me suicidal. I tried botox with no improvement. I changed my diet (caffeine, dairy, ketogenic) with limited improvement. I had to leave my job as I was no longer reliable. I was so sad.

I've now been on Aimovig for the last 6 months and all I can say is that it's been life changing. I no longer live in fear of the next migraine and I no longer have a permanent headache. Gone is the gastroparesis and the nausea. Gone is my hyperosmia. I no longer have debilitating fatigue. Bright lights no longer bother me and I can drive at night. I've started to volunteer with a view to returning to work. It's amazing. I would hope that NICE could approve CGRP antibody so that other migraineurs could benefit too and start to live again.

Name	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
Evidence gathered by the migraine trust surveyed over 200 migraine patients taking CGRP drugs between October and November 2019 and found that 80% had seen an improvement to the quality of their life as a result of taking the medication.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
On a personal basis and for many chronic migraine sufferers who have failed on other drugs it is cost effetive as we can continue to work and contrbute as tax payers and not have to claim benifits.

Comment on line 'Fremanezumab for preventing migraine'
I am a chronic migraine sufferer and before taking a CGRP drug I had failed to respond to amitriptaline, topiramate, candesartan, epilim, propranolol, dosulepin, fluarizine, Gammacore, multiple cranial nerve blocks and Botox. Before starting the CGRP in June 2019 I was only having between 7 and 8 migraines free days a month and this was having a massive impact on my life. Now, not only have my migraine free days increased to up to 20, but the average pain has reduced from a scale of 7 to 5 on a scale of 1 to 10 with 10 being the highest pain. With reduced pain my mental state has improved which, although had not yet become a major issue, was something I was starting to struggle with.

Before starting on the CGRP drug I was in danger of losing my job due to sickness absence which would have had a knock on cost implication as I would no longer be able to contribute significantly as a tax payer but would potentially become dependent on the welfare state.

These CGRP drugs are giving a quality of life to chronic migraine sufferers who have struggled for years and who have not responded to other drugs and treatments. Chronic migraine does not only affect the sufferer but also their family,

friends and colleagues. I work as a Teaching Assistant and my chronic migraine has had an effect on the children I work with as due of my illness as they have not had the support they needed. These CGRP drugs have not just improved my health and family life but made me a functioning person again who can contribute to society.

Name	[redacted]
Comments on the ACD:	
I truly believe Fremanezumab should be made available on the NHS again. It doesn't make sense to me that it is available on the Scottish NHS but not in England anymore. I have read how patients in Scotland an America have had their lives greatly improved by this medicine and now that this isn't available in England, migraine sufferers are limited in choice to mitigate migraine pains. Botox is an alternative, but this obviously has many implications. Chronic Migraine's are very hard to treat, but that shouldn't mean that funding for a treatment that has had amazing reviews should simply be stopped leaving few other options for sufferers to turn to. I urge you to reconsider funding Fremanezumab again, lives can be changed with this drug. Thank you.	

Name	[redacted]
Comments on the ACD:	
Fremanezumab for preventing migraine **Comment on chapter - "1 Recommendations"** **Comment on Chapter, 1 Recommendations** I am the creator of a group of over 120 migraine sufferers, who have come together on social media (**Provide Aimovig for migraine on the NHS** and **@PutAimovigonNHS**). Some of us have tried Aimovig or other CGRPs either prior to the NICE rejection or privately. Many of us have been too unwell to speak out as much as we would like to explain how desperately we want our doctors to have this class of drugs in their arsenal. This is especially so due to the often tight or uncertain timeframes in which consultation periods occur – the minimum criterion for chronic migraine is 15 days/month but many of us, myself included have continuous migraine states for months at a time that are totally debilitating, and make it hard for us to have our voices heard when timeframes are shorter than our periods of illness. I mention this partly as this is not the impression of migraine's duration, or level of debility, that a casual reader would get from the description in this report. In all my comments I am commenting in my own name but I will also refer to the concerns and experiences of members of the group named above. **Fremanezumab for preventing migraine** **Comment on subsection - "1.2"** All of the migraine patients in our group who are by their own description getting their lives back on CGRPs belong to one of two groups. Either they have - Tried everything - including botox - for years, and often decades, with no relief, having lost jobs, relationships, independence, the chance to have a family, and meaning and purpose in their lives. During this time they will have spent enormous amounts of time and NHS money pursuing relief, made extensive use of	

emergency services in desperation living without relief, and suffered hospitalisations and even surgeries as a result of often serious side effects of other preventatives that failed to help the migraines.

Or

- Received significant relief only from the *combined* use of a CGRP and botox.

From this I would argue strongly that while indirect evidence and patient survey data (plus vast supportive anecdotal data from online support groups) already indicate that CGRPs are, as it happens, more effective than botox, basing the decision to approve on a requirement for CGRPs to be more effective than botox seems antithetical to providing the best care for a significant number of the patients most likely to benefit most from the availability of CGRPs.

It means that the large group of patients who do not respond at all to botox are left stranded with no recourse - when they could be getting back on their feet, able to live and work again.

Due to a lack of suitable medical options and the cuts to social welfare budgets, please know from our bitter experience that following failure of other preventatives, 'best supportive care' in real life for non-responsive chronic migraine most resembles one of the circles of hell in Dante's Inferno. We don't appreciate the way this phrase glosses over the experience to which many have lost all quality of life. Throughout the document, the difficulty obtaining accurate quality of life data is shown to be a direct result of the level of devastation migraine wreaks on quality of life itself. We feel language throughout is not an accurate reflection of the level of suffering and the burden of migraine on individuals, society and the economy.

For the second group - those finding significant relief only through a *combination* of botox and CGRPs, this is evidence fremanezumab needs to be available for neurologists to use as part of an integrated treatment plan, not just as a single silver bullet of last resort. Just as you would not offer surgery for cancer without adjuvant chemotherapy, or amputate a limb but not also offer rehab, so we feel offering botox alone to patients who could have much better or even (we know a large number of cases) perfect outcomes with the addition of a CGRP is an irresponsible approach that has real life consequences of a huge burden of suffering as well as the absence of contribution (including £8.8 billion a year economically) of those same people to the country.

CGRPs' unique mechanism of action mean they must be part of our neurologists' armoury, and considered both for their capacity to work for a distinct segment of the patient population where all else fails *and* to function as a component of a complete therapy where inadequate partial response is achieved with one treatment alone.

Fremanezumab for preventing migraine
Comment on chapter - "2 Information about fremanezumab"
Comment on Chapter, 2 Information about fremanezumab

All those who voiced an opinion in our group stated that they felt the MIA must, if necessary, be restricted to recalcitrant chronic migraine only rather than rejected for all. As patients, we don't fully understand the logistics of how this more restricted MIA would be achieved – perhaps that is in the drug company's hands, in which case, we hope they are can be made aware of this and consider our

suffering along with the bottom line. But we do (reluctantly) support (at least initially) restricting the prescription to chronic migraine alone, due to the extreme severity of disability this causes.

We further agree that other cheaper preventatives should typically be tried first as sometimes excellent relief is achieved with these. However, we notice that the reason for rejection here hinges on controversy between neurologists over whether trying a fourth preventative is worthwhile or whether at that point the likelihood of response dwindles to nothing. We wish to point out here that we are not a set of shelves you are trying to stop from falling down, where another nail in the wrong place is no harm done. The lived experience of patients trialling ineffective preventatives, aside from the agony of continued migraine and the real life effects of this continuing illness (in the form of lost jobs, partners walking out, children neglected or carers for their parent, and couples missing the chance to have children) include many intolerable side effects. The following is not from the packet inserts but represent the lived experiences fed back to me by just from those patients I'm speaking for:

> spleen/gallbladder damage – screaming in pain, liver damage, diabetes, weight gain, low blood pressure and resting heart rate, numb mouth, hands, feet and face, loss of use of hands and feet, anxiety, fatigue, cognitive impairment, decreased awareness – so many say 'like a zombie', night terrors, panic attacks, anaphylaxis, nausea, insomnia, gastritis, vertigo (preventing some from driving and making others housebound), behaviour changes, rage, absent libido, hospitalisation for breathing difficulties, hospitalisation for chest pains, constant kidney stones, depression, fainting, weight loss, hair loss, aphasia, memory loss (including working 'like I had dementia' and episodic -- of all her childhood memory), suicidal thoughts.

Of course, I could have given you the statistical breakdown of side effects across all the different preventatives: instead I have given you a series of 'anecdotes'. I chose to do this not because I lack awareness of the limitations and distortions of anecdotal evidence, but because I think it is important to underscore that trying four different preventatives *not designed to target the pathology of migraine* but established to effectively *hit a different biochemical target* is going to result in life stories like the above. Because taking effective modifiers of the pathologies of blood pressure, mental illness and epileptic conditions *will* modify healthy areas of patients' biology. CGRP antagonists are different because their on-target effect is the pathology of migraine. We know of course they will not be side-effect free, though so far the side-effect profile is much better than other preventatives – but they will be *on-label-effect free*.

Above all, the report reads to me like it raises the controversy because it wishes for a fourth preventative to be tried, as if there is no downside – but the effect of increasing the time delay between onset of illness and reaching an effective treatment is to cost many patients the best years of their lives, their careers, their savings, their families. This also creates an enormous indirect cost of untreated migraine to the NHS through continued appointments (across a vast array of departments), hosptialisations, and wasted prescriptions.

Fremanezumab for preventing migraine
Comment on subsection - "3.1"

We feel that the language used here is very understated compared to the reality of in particular chronic migraine.

- While migraine does usually last 4-72 hours, many sufferers of chronic migraine have migraines lasting much longer than this. Personally, mine last months at a time without let up. Weeks at a time is very common too, among the patient group most in need of this drug.

- 'Can adversely affect quality of life' sounds relatively benign compared to what the people I represent are experiencing. 'Can affect concentration' sounds like it's a bit distracting. Accurate is: can't move, can't think, can't speak, can't see, can't listen. Like death but with pain worse than childbirth day after day. Like total deprivation of the senses but instead of darkness, blinding light, instead of silence endless crashing cymbals. 'Difficulty concentrating' doesn't really describe quite how 'adverse' the impact on quality of life is.

- We would prefer you explicitly use the phrase 'severe disability' to identify chronic migraine, because that's what it is.

- We would like you to cite the WHO, who have classed migraine as more disabling than blindness, paraplegia and acute psychosis and on the same level of disability as quadriplegia and dementia.

Fremanezumab for preventing migraine
Comment on subsection - "3.11"

We agree that measuring quality of life would have been compromised by doing so on days patients were well enough to attend appointments.

However, on days they were not well enough to attend I would suggest they would also not have been well enough to accurately complete such a self-report measure. Cognitive impairment and aphasia are common migraine symptoms that together with sound and light aversion, restrict communication. A member of our group joined and told her story – it was clear she was suffering but her words were all over the place. She then began CGRP injections. Eight days later it was like a different person was writing - she sounded extremely bright and articulate, so incisive in her explanations. I mention this because even providing patients with surveys for days they can't leave their beds is hindered by the fact thinking clearly through a migraine is such extremely hard work.

However, I also consider that this *in itself* is evidence of the extreme effect on quality of life of migraine. The report sounded as if it was dismissing the evidence as inconclusive, but the very reason it was inconclusive is evidence of extreme debility and suffering.

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Questions
Has all of the relevant evidence been taken into account?

We are not in a position to answer this fully as a patient group. However, I feel one area in which evidence does not appear to have been correctly assessed is in to what extent the panel have properly recognised chronic migraine as a disability, let alone (as I mentioned in the comments) as a disability classified by the WHO as more debilitating than blindness, paraplegia and acute psychosis, and at the same level of disability as quadriplegia.

While the report acknowledges at one point that the patient expert highlighted that chronic migraine 'can be a disability' (the phrasing of which, in the context of severity highlighted above, appears to be soft peddled), in more careless moments, I note that the panel designated 'patients with disabilities' as a separate sub-section, indicating that, like most of the general public, they are prone to forgetting that chronic migraine patients already *are* patients with disabilities.

By way of illustrating the reason for my assessment that the panel do not demonstrate a clear understanding of the severity of the condition, I would liken the way in which migraine is generally described throughout the consultation document to a description of a tsunami. I might define a tsunami as 'a phenomenon in which the sea can become choppy, which may cause interference with objects on the land'. While this is accurate, it fundamentally misrepresents the situation – and, in terms of correctly assessing the burden on patients and society, more profoundly than if it were factually incorrect. I don't mean that it is missing emotive language. I mean that it markedly avoids existing technical language that would capture the severity of what it refers to. If my description of a tsunami were in a document assessing cost-effectiveness of better sea defences, you would not expect it to yield a correct assessment of how desperately these were needed. I suggest the muted language used to describe migraine may have allowed predominant ableist societal misconceptions that migraine is 'a bit of a headache' to creep into the panel's decision making, and cause a similar level of forgetfulness and apathy that this is one of the world's most severe, and most costly, disabilities.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, we think this has been approached incorrectly as the methodology for assessing cost is not the right one. As made clear in the report of the All-Party Parliamentary Group on Primary Headache Disorders 2014, headache is not only wrongly 'bottom of the pile' in terms of priorities but the NHS has been inefficient in its spending as a result of erroneously trying to save on direct costs, when, as the National Audit Office has confirmed, greater savings can be made by averting indirect costs of patients accessing services in an emergency setting. You can stop thousands of us making frequent agonizing and expensive trips to A&E for a 'migraine cocktail' or for yet another horrendous side-effect of other preventatives by giving us this medicine.

On a finer point, while we agree that ideally, more high quality trial evidence would be available to understand how botox and CGRPs differ, we are aware both of evidence around mechanism of action and data from the increasingly large numbers of patients responding to treatments that suggest a head to head comparison of fremanezumab with botox is not the fundamental question that should decide whether it is available for neurologists to use.

The mechanism of action of botox is entirely distinct from CGRPs and what we know about migraine pathology clearly suggests that three patient groups will emerge. Those who respond to botox alone, those who respond to CGRPs alone, and those who only get significant relief with both agents used together. This is the pattern being reported by thousands of patients currently using CGRPs with or without botox. Therefore, the lack of direct data on CGRPs being superior to botox should be irrelevant to whether they are required in neurologists' toolkits for best treatment in specific patient groups.

Therefore, while we do believe these studies should have been available – both to assess relative rates of effectiveness AND to understand if specific patient populations respond better to one than the other, or and when/how often combined therapy yields best outcomes – we don't believe a decision about prescription should be based on a lack of head to head while there is good data on CGRPs' effectiveness itself.

From our standpoint as patients unaware of all the procedural conventions, we had hoped the drug companies would have conducted them in readiness for the appraisal so that cost-effectiveness could better be projected. However, we also cannot envisage a scenario in which data on this topic should lead to a situation where fremanezumab is *never* available for prescription on the NHS.

*

Regarding administration costs: I am not in possession of statistics to dispute the panel's claim that administration costs needed to be increased from the company's estimate by 10% due to a perceived need for NHS staff to administer the injections of disabled (by which the panel surely mean disabled in additional ways than by migraine), elderly and needle phobic patients. However, this claim suggested to me that the panel may also not be relying on the best information to obtain a clear understanding either of the access needs of chronic migraine patients or of the needs of chronic migraine patients with dexterity impairments.

Speaking as someone with grip and tremor issues as well as migraine, the barriers for independently getting to medical appointments (mobility, dexterity as well as lights/sounds/smell triggers) are infinitely greater than employing the same strategies as I do if I want a cup of tea. From what those in the disabled community say, this is widely generalisable to other disabilities, though of course not universally. In my case, a carer or friend could be trained to administer at the same time as me. If a patient's care needs are being so insufficiently met that they can't home administer this medicine, there is a much bigger social services problem to address – and the answer is not in the NHS budget. Certainly not if it results in the medicine then becoming too expensive to give anyone. Further, only the most extreme needle phobia is likely to prevent patients using an injection that stops chronic migraine. Members of our group note they have significant phobias and would willingly expose themselves to them to get relief.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. We believe that the concept of sound and suitable is not commensurate with recommendations that will result in extreme, preventable suffering, as well as the continued high rate of suicide and suicide attempts by people who now could have been returned to health and returned to work and society. We are not aware if the financial burden of migraine on the UK economy is taken into account, and suspect that perhaps the financial burden on the NHS is the only factor considered.

However, the utilitarian relevance of the burden on the economy is starkly apparent and ignoring the significance of this can only work on paper. Migraine costs the UK economy £8.8 billion per year and a total of 86 million workdays. 75% of migraineurs are women, and a similar number, 80% of healthcare workers are women, meaning migraine disproportionately affects NHS workdays lost to migraine. Not treating migraine is outrageously expensive and damaging to our

country and costs the NHS more than just in its neurology budget and in the wide array of other departments such as A&E picking up the slack for the under-treatment of this condition in more appropriate patient pathways. And that vast economic loss is supervenient on the vast personal loss of all those people.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I could not make sense of the fact that the report acknowledges that migraine disproportionately affects women, and, as the report phrases it, 'can be' considered a disability – yet states nothing needed to be done differently as a result of this? What does this mean? I wanted to elaborate on the wider implications and context, beyond the nod to the impact on our careers, of the disproportionate impact of this decision on women and disabled people.

Migraine is *long overdue* research focus of the calibre that has brought the role of CGRPs in its pathology to light. This long delay is in large part due to the fact that migraine affects women three times more often than it does men. Women's health is, as I'm sure you know, systematically under-researched, and chronic migraine is a good example of a disability primarily affecting women that has suffered as a result of academic disinterest. This academic apathy is reflected in apathy all the way along the chain from research to treatment, with recognition within the NHS that GPs are grudging in their willingness to take migraine seriously or to refer to a specialist when necessary. Migraine accounts for 45% of disability due to a neurological condition but takes a fraction of the budget. It is the acknowledged 'Cinderella' of neurological disorders – and this is related, directly, to the fact it is a 'women's condition', and to sexism and the neglect of women's pain within our society -something that NICE has a commitment to fight against.

The pattern of understating the case of migraine shouldn't be perpetuated in healthcare too, and sadly this is what you are doing. If you don't think you are, imagine for a moment opening your report on quadriplegia by mentioning that it 'can be disabling'.

This lack of priority is also related – directly – to the fact migraine is an invisible disability. I personally have chronic migraine as a part of a larger disorder that affects my mobility and as such I frequently use mobility aids. It is extremely marked how much more sympathy I get for these aids than I do for my migraines. This is not to say that visible disabilities do not receive their own equally shameful amount of discrimination – but not being believed, considered to be 'a drama queen', 'a wimp', even a liar etc, and offered no understanding or concern – that's more the fate of those with invisible disabilities, and that is what has happened to migraine. Increasingly, the DWP is refusing benefits to those with severe disabilities, and those with migraine are especially vulnerable both to being rejected because their disability is unseen and, due to chronic migraine's unusually high incidence of suicide attempts relative to other disabilities, to becoming one of the 90 people per month dying shortly after being declared fit for work.

I highlight this here because, while the fault is spread across a number of different domains, nowhere in the report do you appear to factor in that *there will be deaths* as a result of refusing to provide fremanezumab and other CGRPs. And those deaths will be as a result of discrimination against women and disabled people. The availability of CGRPs privately at hundreds of pounds per injection will also

have a greater impact on those on low incomes (though class discrimination appears not to be considered in this question), which women and disabled people are also relatively more likely to be.

This is the very first class of drugs to specifically target the pathology of migraine and the result of using drugs for other conditions, though sometimes effective, is an unsurprising host of horrendous side effects and lack of response to treatment. If migraine is the acknowledged Cinderella of neurology, then Fremanezumab is her Prince Charming. You need to step up and be the fairy godmother.

Name	[redacted]
Comments on the ACD:	

To whom it may concern

I hope this email is not too late to consider for the consultation about Fremanezumab. I have been unwell for the past 3 weeks, as I believe is a common occurrence for migraine sufferers. I could not make out how to comment on the initial consultation (appeal) via my phone, as the method of comment made very little sense to me.

I am a migraine patient, with between 12 and 25 days of headache/migraine a month (at least 10 days of which are migraine). I have tried numerous, if not all, preventatives available to me on the NHS with little success.

I have undergone 4 doses of Botox treatment, which, when it's working, is great. But it has changed my migraines so although I have fewer long migraines I now have more headache days, as well as a few longer, non-responsive migraines.

I would welcome the chance to try something different. I know that you see Fremanezumab as not being cost-effective compared to Botox, but when a patient is on Botox, is not getting the type of recovery required to live a healthy and satisfactory life, let alone being unable to go to work, and still needs triptans, this is not a cost-effective way to live or to treat the disease.

If there is any chance of this drug being available for those who do not see improvement with Botox, it would be a potential godsend. At present my life is only worth living for about 1 month in 3, when the Botox is doing its job. Other than that it is a miserable existence. And there are so many people like me, who could be able to work and live properly if given suitable preventatives.

Fremanezumab for preventing migraine [ID1368]: a single technology appraisal

Addendum #5

ERG response to company new evidence appendix

(Post AC1)

18 December 2019

1 Introduction

The purpose of this addendum is to address evidence presented by Teva in respect of the positioning of fremanezumab as a fifth-line treatment after three oral prophylactics and onabotulinum toxin A (OBA), alongside expanded cost-effectiveness modelling addressing committee assumptions expressed in the ACD. The ERG's commentary comprises of a brief critique of the clinical evidence presented, a discussion of the modifications made to the economic model by Teva, and a validation of the ICERs presented.

2 Clinical evidence

The focus of the company's clinical evidence to support a fifth-line positioning draws on three clinical subgroups from the FOCUS trial:

- patients with chronic migraine who have experienced an inadequate response to three oral preventive treatments and OBA;
- patients with chronic migraine who have experienced an inadequate response to at least three prior preventive treatments, of which one was OBA; and
- patients with chronic migraine who have experienced an inadequate response to OBA, regardless of the total number of treatments.

Evidence for patients with episodic migraine was not submitted. As expected, the sample size available for analysis increases as included study populations increase in breadth. While a potential weakness of the most restrictive population is that it has the smallest sample size (n=[redacted] for placebo, n=[redacted] for quarterly fremanezumab, n=[redacted] for monthly fremanezumab), the ERG believes that this is the most probative subgroup analysis and thus focuses its critique on these specific results. This subgroup most closely matches the proposed fifth-line positioning of fremanezumab.

The analytic methods used to generate this subgroup analysis appear to match the methods used to generate the original estimates in the FOCUS trial, though this is not consistently clear. Results are presented both for the two active fremanezumab arms separately as well as for the pooled fremanezumab arms.

Findings for the estimates per three trial arms are presented in Table 1, and for estimates with pooled active arms in
Abbreviations: CI, confidence interval; LSM, least squares mean; MSQoL, migraine-specific quality of life; OBA, onabotulinumtoxin A; SD, standard deviation; vs, versus

Table 2. Unsurprisingly, findings compared to placebo are inconsistently significant. However, findings from the pooled active arms suggest that fremanezumab reduced mean monthly migraine days ([redacted]) and increased the odds of achieving at least 30% reduction in mean migraine days (OR=[redacted]). These estimates were comparable to estimates presented for the larger subgroup in the company's original submission, which comprised patients with chronic migraine who had failed three or more classes of preventive therapy.

Table 1. Efficacy results from FOCUS for patients chronic migraine and inadequate response to three oral preventive treatments and OBA.

	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Mean monthly migraine days			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Patients with at least 30% reduction in monthly average migraine days			
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Mean headache days of at least moderate severity			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]
Mean monthly days of use of any acute headache medication			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Headache Impact Test score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Migraine Disability Assessment score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]

	Placebo (n=[redacted])	Fremanezumab quarterly (n=[redacted])	Fremanezumab monthly (n=[redacted])
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Role function – Restrictive			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Role function – Preventive			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
MSQoL Emotional function			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]

Abbreviations: CI, confidence interval; LSM, least squares mean; MSQoL, migraine-specific quality of life; OBA, onabotulinumtoxin A; SD, standard deviation; vs, versus

Table 2. Efficacy results from FOCUS for patients chronic migraine and inadequate response to three oral preventive treatments and OBA, pooled across active trial arms.

	Placebo (n=[redacted])	Fremanezumab (n=[redacted])
Mean monthly migraine days		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
Patients with at least 30% reduction in monthly average migraine days		
Number achieving endpoint (%)	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
Mean headache days of at least moderate severity		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]
P-value vs placebo		[redacted]
Mean monthly days of use of any acute headache medication		
Baseline (SD)	[redacted]	[redacted]

	Placebo (n=[redacted])	**Fremanezumab (n=[redacted])**
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
Headache Impact Test score		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
Migraine Disability Assessment score		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
MSQoL Role function – Restrictive		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
MSQoL Role function – Preventive		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]
MSQoL Emotional function		
Baseline (SD)	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]

Abbreviations: CI, confidence interval; LSM, least squares mean; MSQoL, migraine-specific quality of life; OBA, onabotulinumtoxin A; SD, standard deviation; vs, versus

While the new clinical evidence presented aligns closely with the proposed fifth-line positioning, the company notes several weaknesses with which the ERG agrees. Specifically, FOCUS was not powered to detect a difference in the specific subgroup presented here; nor are the presented *post hoc* analyses strictly randomised in the sense that OBA use, for example, was not used as a trial stratification factor. The ERG further notes that evidence of covariate balance was not presented, nor analysis methods presented in sufficient depth to ensure comparability of methods with prior clinical evidence submitted. In sum, the ERG regards that while there is some evidence of effectiveness for the proposed fifth-line positioning, the evidence is tenuous and should be treated with caution.

3 Changes to cost-effectiveness modelling

As part of additional evidence submitted, Teva included a response to the ACD. This response included additional modifications to the ERG's original modelling and proposed a new base case that departed significantly from committee's preferred assumptions in the ACD. Below the ERG discusses these modifications.

3.1 Population

Teva presents an additional population to approximate a fifth-line positioning of fremanezumab. This population consists of patients with chronic migraine who have had an inadequate response to any four preventive treatments. The company's rationale for using this subgroup instead of the most directly probative subgroup included above is that the presented subgroup includes a greater number of patients. While this is an intuitively appealing reason, there is only cursory regard to covariate balance within this subgroup or even similarity to the subgroups for which new clinical evidence was presented. However, cost-effectiveness findings for both subgroups are presented.

3.2 Value proposition

Teva includes a new patient access scheme, which is currently under review. This would result in a price of [redacted] per 225mg injection and was implemented in all analyses.

3.3 Modifications to ERG analyses

Three areas of departure from the ERG's modelling approach were highlighted. First, Teva implemented a change to standardise the use of on and off treatment utilities between fremanezumab and OBA. Second, Teva standardised reversion in monthly migraine days after treatment discontinuation across treatments, though this was combined with a larger concern with the committee's preferred assumptions relating to residual benefit, discussed below. Third, response rates were recoded to accommodate multiple subgroups. While the ERG disagreed with Teva's larger point on the reversion in monthly migraine days, it accepted that the substance of the changes was acceptable.

3.4 Updated OBA administration costs

The company updated the administration cost of OBA in the model to align with the budget impact analysis conducted by NICE and NHS England. The company noted that this analysis assumed £218 for the first appointment and £125 for subsequent appointments (based on the use of the treatment function code 400 for neurology), but utilised the value of £125 in the

economic model. The ERG noted that the company had updated this cost in the “Demographics & Costs” worksheet (Cell E33).

3.5 Utilities

ERG modelling as part of its original report noted that the use of on-treatment and off-treatment utilities was potentially specious and had important implications for understanding the effectiveness of the intervention. This was subsequently raised at committee and reflected in the ACD. However, in the additional evidence presented, the company commented that the inclusion of separate on- and off-treatment utilities was clinically valid and accepted practice within migraine modelling. The company’s rationale was that the utility data presented were based on clinical trial data from the FOCUS trial which demonstrated that quality of life was higher when participants were on fremanezumab treatment, and that similar on-treatment effects in terms of quality of life have been observed. The company referenced a prior NICE TA which had concluded that the most plausible ICER included separate on- and off-treatment utilities. The ERG maintains its original views relating to the use of on-treatment and off-treatment utilities, however the ERG maintained the company’s utilities in validating the proposed ICERs.

The company proposed an alternative scenario using a ‘blend’ of on-treatment and off-treatment utilities, where the treatment benefit in terms of utilities is reduced by 50%. The ERG did not regard that there was a principled basis for this scenario and thus did not consider it further, especially as this scenario was not empirically led.

3.6 Residual fremanezumab effect in non-responders

An additional change made by Teva includes the restoration of effect in monthly migraine days experienced by non-responders to fremanezumab. The basis for this change was the clinical trial evidence and perceived challenges in interpretation of model results. The ERG regards that the change as implemented by Teva was accurately produced, while noting the position of the ACD on this issue.

3.7 Positive stopping rule

Picking up another key issue from the ACD, the company notes that positive stopping rules are based on tenuous data. Teva suggest a 15% annual positive stop rate is reasonable given the little evidence relating to positive stopping in OBA from a single-centre study. In addition, Teva did not agree with the use of treatment waning and restarting as implemented by the ERG, though accepted that data to counter the ERG’s proposed scenarios were scarce. Teva implemented in their base case an annual, permanent stop of 15%, with scenario analyses of

10% permanent stop annually and of 50% resuming treatment once half the effect had been lost. This last scenario analysis, which was intended to incorporate the ERG's previous modelling strategy, lacks for empirical basis.

At the crux of this issue remains that the original model submitted by Teva did not adequately account for natural history of migraine, in which many patients spontaneously remit e.g. after menopause. This was discussed in depth in the ERG's original report. Given this suboptimal situation in both model structure and data availability, the ERG agrees that a range of scenario analyses is useful to consider. However, it remains the case that the assertion that 50% of patients would restart, which Teva describes as 'conservative', may or may not in fact overestimate how many patients with positive stopping eventually restart. Thus, the ERG's original modelling strategy remains a viable scenario analysis.

3.8 Efficacy compared to OBA

The company maintained that the assumption of equal efficacy between fremanezumab and OBA, which was a committee preference expressed in the ACD, was inappropriate given the network meta-analysis estimates suggested superior efficacy of fremanezumab as compared to OBA. The ERG maintains that the many issues with the network meta-analysis, including concerns relating to transitivity, conduct of the analysis, transparency of reporting and sparseness of evidence networks, cast serious doubt on the trustworthiness of any claim of clinical superiority.

4 Updated cost-effectiveness results

4.1 Revised company base case results

Teva noted that the updated base case was based on the committee's preferred assumptions as outlined in the ACD and ERG Addendum #3, with the following changes made:

- Standardisation of approach across active treatments (see Section 3.3)
- New PAS price for fremanezumab included.
- Updated OBA administration costs (£125 per administration).
- Restoring fremanezumab (and OBA) efficacy in non-responder patients.
- Restoring treatment impact on utilities using separated on- and off-treatment utilities.

- Updated positive stopping rule where 15% of patients stop treatment after each annual assessment and treatment effect wanes to baseline over one year after treatment cessation.

- Restoration of OBA efficacy as based on network meta-analysis results.

Teva's base case considered three populations: (1) adults with chronic migraine who have had an inadequate response to three or more preventive migraine treatments; (2) adults with episodic migraine who have had an inadequate response to three or more preventive migraine treatments; and (3) adults with chronic migraine who receive fremanezumab post-PBA. The ERG noted that the latter was a new patient group not considered in the main CS (refer to Table 3).

Table 3: Company scenario analyses

Scenario	Explanation of scenario
A – Updated costs	All assumptions set to the committee's preferences with updated PAS price for fremanezumab, updated onabotulinumtoxin A administration costs and onabotulinumtoxin A efficacy based on the NMA results
B – Updated costs plus original utilities	As scenario A but with the original on- and off-treatment utilities restored
C – Updated costs plus blended utilities	As scenario B but with treatment effect of on-utilities reduced by half
D – Updated costs plus restoring fremanezumab effect	As scenario A but with fremanezumab effectiveness in non-responder patients restored (also restores efficacy in onabotulinumtoxin A to reverse change of coding correction)
E – Updated costs plus PSR (15% stop) and no restart	As scenario A but with inclusion of an updated positive stopping rule whereby 15% of treated patients permanently stop treatment each year
F – Updated costs plus PSR (10% stop) and no restart	As scenario A but with inclusion of an updated positive stopping rule whereby 10% of treated patients permanently stop treatment each year
G – Updated costs plus PSR (15%) with restart	As scenario A but with inclusion of an updated positive stopping rule whereby 15% of treated patients stop treatment each year and 50% of patients restart treatment after half of treatment effect is lost

4.2 Chronic migraine

Table 4 provides the updated base case results based on the changes referenced in Section 4.1 and Table 5 provides the additional scenario analyses exploring the impact of the changes from the committee preferred assumptions. The ERG was able to validate the ICERs successfully.

Table 4: Base case results in chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

	Total		Incremental		ICER vs BSC (£/QALY)	Incremental vs OBA ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs		
BSC	[redacted]	[redacted]				
OBA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost-effectiveness ratio; OBA, onabotulinumtoxin A; QALY, quality-adjusted life year

Table 5: Scenario analyses in chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

	ICER vs OBA	ICER vs BSC
A – updated costs	[redacted]	[redacted]
B – updated costs plus original utilities	[redacted]	[redacted]
C – Updated costs plus blended utilities	[redacted]	[redacted]
D – Updated costs plus restoring frem effect	[redacted]	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]	[redacted]
G – Updated costs plus PSR (15% stop) with restart	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; OBA, onabotulinumtoxin A; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

4.2.1 Three prior preventive migraine treatments and OBA

Table 6 provides base case results for post-OBA chronic migraine patients who have had an inadequate response to three prior preventive migraine treatments and OBA, and Table 7 provides the additional scenario analyses exploring the impact of the changes from the committee preferred assumptions.

Table 6: Base case results for post-OBA chronic migraine patients who have had an inadequate response to three prior preventive migraine treatments and OBA

	Total		Incremental		ICER vs BSC (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
BSC	[redacted]	[redacted]			
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 7: Scenario analyses for post-OBA chronic migraine patients who have had an inadequate response to three prior preventive migraine treatments and OBA

	ICER vs BSC
A – updated costs	[redacted]
B – updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring frem effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15% stop) with restart	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

4.2.2 Four prior preventive migraine treatments

Table 6 provides base case results for chronic migraine patients who have had an inadequate response to four prior preventive migraine treatments, and Table 7 provides the additional scenario analyses exploring the impact of the changes from the committee preferred assumptions.

Table 8: Base case results for chronic migraine patients who have had an inadequate response to four prior preventive migraine treatments

	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER vs BSC (£/QALY)
BSC	[redacted]	[redacted]			
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 9: Scenario analyses for chronic migraine patients who have had an inadequate response to four prior preventive migraine treatments

	ICER vs BSC
A – updated costs	[redacted]
B – updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring frem effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15% stop) with restart	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

4.3 Episodic migraine

Table 10 provides the updated base case results based on the changes referenced in Section 4.1 and Table 11 provides the additional scenario analyses exploring the impact of the changes from the committee preferred assumptions. The ERG was able to validate the ICERs successfully.

Table 10: Base case results in episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER vs BSC (£/QALY)
BSC	[redacted]	[redacted]			
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 11: Scenario analyses in episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

	ICER vs BSC
A – updated costs	[redacted]
B – updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring frem effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15% stop) with restart	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; OBA, onabotulinumtoxin A; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

Fremanezumab for preventing migraine [ID1368]: a single technology appraisal

Addendum #6

Committee's preferred assumptions alongside the Company's preferred assumptions (Post AC1)

31 January 2020

Summary of amendments:

Date	Amendment
31-Jan-2020	ERG updated Table 5 to include incremental costs. A footnote was added to Table 4 and Table 5 to explain the negative QALY values following discussion in the pre-meeting briefing call

1 Introduction

The purpose of this addendum is to address a request for the presentation of additional ICERs based on the Committee's preferred assumptions from NICE. To enable comparison of the ICERs, the Company ICERs are also provided.

2 Company and Committee preferred assumptions

Three populations were considered: (1) adults with chronic migraine who have had an inadequate response to three or more preventive migraine treatments; (2) adults with episodic migraine who have had an inadequate response to three or more preventive migraine treatments; and (3) adults with chronic migraine who receive fremanezumab post-OBA. The latter was a new patient group presented as additional evidence (refer to Addendum #5 for details) not considered in the main CS.

The Company preferred base case has also been provided in the tables to enable comparison of results (Table 1). Key differences between the Company's and Committee's preferred assumptions include: removal of the utility premium; application of positive stopping rule (15% of patients stop treatment after each annual assessment and treatment effect wanes to baseline over one year after treatment cessation); and, restoration of fremanezumab (and OBA) efficacy in non-responder patients.

Table 1: Comparison of Company vs Committee preferred base case

Base case assumptions	Company	Committee
Utility calculation fixes	✓	✓
Increase fremanezumab assessment period from 2 to 3 cycles	✓	✓
Increase OBA assessment period from 2 to 3 cycles (CM only)	✓	✓
Correction of company waning code (CM and waning scenarios only)	✓	✓
Lifetime modelling horizon (58 years, 754 model cycles)	✓	✓
On prophylaxis treatment utility equal to no treatment (premium removed)	X	✓
PSR removed (incl. no off-treatment period for observation)	X	✓
PSR restart	0%	0%
10% of frem patients require support to administer (30 mins Band 5 nurse)	✓	✓
Baseline migraine frequency for all prophylaxis users upon drop-out	✓	✓
Linear wane to baseline of BSC effect (responders)	✓	✓
Removal of residual frem effect in non-responders	X	✓
5 year wane in frem positive stoppers (frem vs. BSC in CM only)	✓	X
5 year wane in frem positive stoppers with re-start at 50% MMDs vs BL	✓	X

Abbreviations: BL, baseline; BSC, best supportive care; CM, chronic migraine; frem, fremanezumab; mins, minutes; MMDs, mean monthly migraine days; OBA, onabotulinumtoxin A; PSR, positive stopping rule; vs, versus

2.1 Chronic migraine

Table 2 provides the updated base case results for the Committee and Company preferred assumptions outlined in Table 1.

Note! The Company base case is included in the tables to enable comparison of results with the Committee base case

Table 2: Base case results in chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments (assumption of OBA efficacy based on network meta-analysis results) (probabilistic ICER in italics in parentheses)

CM	Committee Base Case							
	Total		Incr vs BSC			Incr vs OBA		
	Costs	QALYs	iCosts	iQALYs	ICER (£/QALY)	iCosts	iQALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	.	.	.	.	.	.
OBA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM	**Company Base Case**							
	Total		**Incr vs BSC**			**Incr vs OBA**		
	Costs	**QALYs**	**iCosts**	**iQALYs**	**ICER (£/QALY)**	**iCosts**	**iQALYs**	**ICER (£/QALY)**
BSC	[redacted]	[redacted]	.	.	.	.	.	.
OBA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost-effectiveness ratio; OBA, onabotulinumtoxin A; QALY, quality-adjusted life year

The Company conducted a number of scenario analyses exploring the impact of the changes from the Committee preferred assumptions. Note Scenario A is the Committee base case.

Table 3: Scenario analyses in chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

	Company	
	ICER vs OBA	ICER vs BSC
A – Updated costs (Committee base case settings)	[redacted]	[redacted]
B – Updated costs plus original utilities	[redacted]	[redacted]
C – Updated costs plus blended utilities	[redacted]	[redacted]
D – Updated costs plus restoring frem effect	[redacted]	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]	[redacted]

	Company	
	ICER vs OBA	**ICER vs BSC**
G – Updated costs plus PSR (15% stop) with restart	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; OBA, onabotulinumtoxin A; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

In addition, the ERG conducted a scenario analysis whereby the response rate for OBA was assumed to be equivalent to fremanezumab. For both the Committee and the Company preferred assumptions, fremanezumab was both more costly and generated fewer health outcomes than OBA (Table 4).

Table 4: Scenario analyses in chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments (assumption that OBA response rate is equivalent to frem)

CM	**Committee Base Case**				
	Total		**Incr vs OBA**		
	Costs	**QALYs**	**iCosts**	**iQALYs[a]**	**ICER (£/QALY)**
OBA	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM	**Company Base Case**				
	Total		**Incr vs OBA**		
	Costs	**QALYs**	**iCosts**	**iQALYs**	**ICER (£/QALY)**
OBA	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost-effectiveness ratio; iCosts, incremental costs; iQALYs, incremental QALYs; incr, incremental; OBA, onabotulinumtoxin A; QALY, quality-adjusted life year; vs, versus

Notes:

[a] Negative values for QALYs due to the difference in assessment period for OBA vs frem (24 weeks vs 12 weeks, respectively). At 12 weeks frem non-responders discontinue and revert to their baseline MMD and individuals treated with OBA accrue treatment benefit for an additional 12 weeks

The Company scenario analyses were conducted exploring the impact of the changes from the Committee preferred assumptions assuming equivalence in response for OBA and fremanezumab (Table 5).

Table 5: Scenario analyses in chronic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments (assumption that OBA response rate is equivalent to frem)

OBA response rate equivalent to Frem	**iCosts**	**iQALYs[a]**	**ICER vs OBA**	**ICER vs BSC**
A – Updated costs (Committee base case settings)	[redacted]	[redacted]	[redacted]	[redacted]
B – Updated costs plus original utilities	[redacted]	[redacted]	[redacted]	[redacted]

OBA response rate equivalent to Frem	iCosts	iQALYs[a]	ICER vs OBA	ICER vs BSC
C – Updated costs plus blended utilities	[redacted]	[redacted]	[redacted]	[redacted]
D – Updated costs plus restoring frem effect	[redacted]	[redacted]	[redacted]	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]	[redacted]	[redacted]	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]	[redacted]	[redacted]	[redacted]
G – Updated costs plus PSR (15% stop) with restart	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; OBA, onabotulinumtoxin A; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

Notes:

[a] Negative values for QALYs due to the difference in assessment period for OBA vs frem (24 weeks vs 12 weeks, respectively). At 12 weeks frem non-responders discontinue and revert to their baseline MMD and individuals treated with OBA accrue treatment benefit for an additional 12 weeks

2.1.1 Chronic migraine: post-OBA (3 prior preventive migraine treatments and OBA)

Table 6 provides base case results for post-OBA chronic migraine patients who have had an inadequate response to three prior preventive migraine treatments and OBA, and Table 7 provides the additional scenario analyses exploring the impact of the changes from the committee preferred assumptions.

Note! Comparison with OBA is not relevant as the population is post-OBA.

Table 6: Base case results in chronic migraine patients post-OBA (i.e. patients who have had an inadequate response to three prior preventive migraine treatments and OBA)

CM	Committee Base Case				
	Total		Incr vs BSC		
	Costs	QALYs	iCosts	iQALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM	**Company Base Case**				
	Total		**Incr vs BSC**		
	Costs	**QALYs**	**iCosts**	**iQALYs**	**ICER (£/QALY)**
BSC	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost-effectiveness ratio; OBA, onabotulinumtoxin A; QALY, quality-adjusted life year

Table 7: Scenario analyses for post-OBA chronic migraine patients who have had an inadequate response to three prior preventive migraine treatments and OBA

	ICER vs BSC
A – Updated costs (Committee base case settings)	[redacted]
B – Updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring frem effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15% stop) with restart	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

Notes:

[a] ERG validation of the ICERs reported by the Company for the scenarios identified minor discrepancies vs the ICERs reported in the additional evidence submitted by the Company which were as follows: Scenario A [redacted]; Scenario B [redacted]; Scenario C [redacted]; Scenario D [redacted]; Scenario E [redacted]; Scenario F [redacted]; Scenario G [redacted]. ICERs reported in the table are ERG corrected values.

2.1.2 Chronic migraine: post-OBA (4 preventive migraine treatments)

Table 8 provides base case results for post-OBA chronic migraine patients who have had an inadequate response to four prior preventive migraine treatments, and Table 9 provides the additional scenario analyses exploring the impact of the changes from the committee preferred assumptions.

Table 8: Base case results in chronic migraine patients post-OBA (i.e. patients who have had an inadequate response to four prior preventive migraine treatments)

CM	**Committee Base Case**				
	Total		**Incr vs BSC**		
	Costs	**QALYs**	**iCosts**	**iQALYs**	**ICER (£/QALY)**
BSC	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM	**Company Base Case**				
	Total		**Incr vs BSC**		
	Costs	**QALYs**	**iCosts**	**iQALYs**	**ICER (£/QALY)**
BSC	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost-effectiveness ratio; OBA, onabotulinumtoxin A; QALY, quality-adjusted life year

Table 9: Scenario analyses for post-OBA chronic migraine patients who have had an inadequate response to four prior preventive migraine treatments and OBA

	ICER vs BSC
A – Updated costs (Committee base case settings)	[redacted]
B – Updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring frem effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15% stop) with restart	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

Notes:

[a] ERG validation of the ICERs reported by the Company for the scenarios identified minor discrepancies vs the ICERs reported in the additional evidence submitted by the Company which were as follows: Scenario B [redacted] and Scenario G [redacted]. ICERs reported in the table are ERG corrected values.

2.2 Episodic migraine

Table 10 provides the updated base case results for the committee and Company preferred assumptions outlined in Table 1, and Table 11 provides the additional scenario analyses exploring the impact of the changes from the committee preferred assumptions.

Table 10: Base case results in episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments (assumption of OBA efficacy based on network meta-analysis results) (probabilistic ICER in italics in parentheses)

EM	Committee Base Case				
	Total		Incr vs BSC		
	Costs	QALYs	iCosts	iQALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EM	**Company Base Case**				
	Total		**Incr vs BSC**		
	Costs	**QALYs**	**iCosts**	**iQALYs**	**ICER (£/QALY)**
BSC	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; OBA, onabotulinumtoxin A; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

Table 11: Scenario analyses in episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments

	ICER vs BSC
A – Updated costs	[redacted]
B – Updated costs plus original utilities	[redacted]
C – Updated costs plus blended utilities	[redacted]
D – Updated costs plus restoring frem effect	[redacted]
E – Updated costs plus PSR (15% stop) and no restart	[redacted]
F – Updated costs plus PSR (10% stop) and no restart	[redacted]
G – Updated costs plus PSR (15% stop) with restart	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; OBA, onabotulinumtoxin A; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

Fremanezumab for preventing migraine [ID1368]: a single technology appraisal

Addendum #6: Erratum

Committee's preferred assumptions alongside the Company's preferred assumptions (Post AC1)

18 February 2020

Summary of amendments:

The following changes were made in response to factual inaccuracies highlighted by the Company at AC2 (7 February 2020) – new text highlighted ***bold italic*** and deleted text indicated with strikethrough in the table below. Clean copies of the corrected pages have been provided.

Date	Amendment
Page 3, Table 1:	The ERG removed the following 2 rows from the table: • 5 year wane in frem positive stoppers (frem vs. BSC in CM only) • 5 year wane in frem positive stoppers with re-start at 50% MMDs vs BL These rows had been incorrectly transferred from the model to the Addendum. (Note that implementation of the linear wane to baseline [over one year] in the model was correct.) "1 year" was added to the row "Linear wane to baseline of BSC effect (responders) –" to clarify.
Page 8, Table 9:	The ERG corrected the footnote as follows: "…Scenario B [redacted] and Scenario G [redacted]. ICERs reported in the table are ERG corrected values."
Page 8, Table 10:	The ERG corrected table caption to remove the reference to OBA as this is not relevant to the EM population: "Base case results in episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments ~~(assumption of OBA efficacy based on network meta-analysis results)~~ (probabilistic ICER in italics in parentheses)"

1. Introduction

The purpose of this addendum is to address a request for the presentation of additional ICERs based on the Committee's preferred assumptions from NICE. To enable comparison of the ICERs, the Company ICERs are also provided.

2. Company and Committee preferred assumptions

Three populations were considered: (1) adults with chronic migraine who have had an inadequate response to three or more preventive migraine treatments; (2) adults with episodic migraine who have had an inadequate response to three or more preventive migraine treatments; and (3) adults with chronic migraine who receive fremanezumab post-OBA. The latter was a new patient group presented as additional evidence (refer to Addendum #5 for details) not considered in the main CS.

The Company preferred base case has also been provided in the tables to enable comparison of results (Table 1). Key differences between the Company's and Committee's preferred assumptions include: removal of the utility premium; application of positive stopping rule (15% of patients stop treatment after each annual assessment and treatment effect wanes to baseline over one year after treatment cessation); and, restoration of fremanezumab (and OBA) efficacy in non-responder patients.

Table 1: Comparison of Company vs Committee preferred base case

Base case assumptions	Company	Committee
Utility calculation fixes	✓	✓
Increase fremanezumab assessment period from 2 to 3 cycles	✓	✓
Increase OBA assessment period from 2 to 3 cycles (CM only)	✓	✓
Correction of company waning code (CM and waning scenarios only)	✓	✓
Lifetime modelling horizon (58 years, 754 model cycles)	✓	✓
On prophylaxis treatment utility equal to no treatment (premium removed)	X	✓
PSR removed (incl. no off-treatment period for observation)	X	✓
PSR restart	0%	0%
10% of frem patients require support to administer (30 mins Band 5 nurse)	✓	✓
Baseline migraine frequency for all prophylaxis users upon drop-out	✓	✓
Linear wane to baseline of BSC effect (responders) – 1 year	✓	✓
Removal of residual frem effect in non-responders	X	✓

Abbreviations: BL, baseline; BSC, best supportive care; CM, chronic migraine; frem, fremanezumab; mins, minutes; MMDs, mean monthly migraine days; OBA, onabotulinumtoxin A; PSR, positive stopping rule; vs, versus

PAGE 8

Table 9: Scenario analyses for post-OBA chronic migraine patients who have had an inadequate response to four prior preventive migraine treatments and OBA

	ICER vs BSC
A – Updated costs (Committee base case settings)	[redacted][a]
B – Updated costs plus original utilities	[redacted][a]
C – Updated costs plus blended utilities	[redacted][a]
D – Updated costs plus restoring frem effect	[redacted][a]
E – Updated costs plus PSR (15% stop) and no restart	[redacted][a]
F – Updated costs plus PSR (10% stop) and no restart	[redacted][a]
G – Updated costs plus PSR (15% stop) with restart	[redacted][a]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus

Notes:

[a] ERG validation of the ICERs reported by the Company for the scenarios identified minor discrepancies vs the ICERs reported in the additional evidence submitted by the Company which were as follows: Scenario B [redacted] and Scenario G [redacted]. ICERs reported in the table are ERG corrected values.

1.1 Episodic migraine

Table 10 provides the updated base case results for the Committee and Company preferred assumptions outlined in Table 1, and Table 11 provides the additional scenario analyses exploring the impact of the changes from the committee preferred assumptions.

Table 10: Base case results in episodic migraine patients who have had an inadequate response to three or more prior preventive migraine treatments (probabilistic ICER in italics in parentheses)

EM	**Committee Base Case**				
	Total		**Incr vs BSC**		
	Costs	**QALYs**	**iCosts**	**iQALYs**	**ICER (£/QALY)**
BSC	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EM	**Company Base Case**				
	Total		**Incr vs BSC**		
	Costs	**QALYs**	**iCosts**	**iQALYs**	**ICER (£/QALY)**
BSC	[redacted]	[redacted]	.	.	.
Frem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; frem, fremanezumab; ICER, incremental cost effectiveness ratio; OBA, onabotulinumtoxin A; PSR, positive stopping rule; QALY, quality-adjusted life year; vs, versus