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:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Teva

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Migraine Trust
   b. Association of British Neurologists - endorsed by Royal College of Physicians
   c. British Association for the Study of Headache

4. **Expert personal perspectives** from:
   a. David Kernick– clinical expert, nominated by British Association for the Study of Headache
   b. Chani Montaque – patient expert, nominated by Migraine Trust
   c. Scott Bruce– patient expert, nominated by OUCH UK

5. **Evidence Review Group documents** prepared by Peninsula Technology Assessment Group (PenTAG)
   a. ERG report
   b. Factual accuracy check
   c. Erratum

6. **Technical engagement response** from Teva

7. **Technical engagement response from consultees and commentators:**
   a. Association of British Neurologists
   b. British Association for the Study of Headache
   c. NHS England
   d. Allergan
   e. Novartis

8. **Evidence Review Group critique of company response to technical engagement** prepared by Peninsula Technology Assessment Group (PenTAG)

9. **Addenda to Evidence Review Group report** prepared by Peninsula

Technology Assessment Group (PenTAG)

10. Final Technical Report

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 chronic and episodic migraine [ID1368]

Document B

Company evidence submission

April 2019

File name	Version	Contains confidential information	Date
Fremanezumab evidence submission	**FINAL v3.0 with revised confidential information**	**No**	**31 October 2019**

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

B 1.1 Decision problem

This submission focusses on part of the technology's Marketing Authorisation, namely patients who have failed with three or more prior migraine preventive treatments (with failure defined as a lack of a clinically meaningful improvement, intolerance or contraindication/unsuitability). The proposed position in the treatment pathway is narrower than the Marketing Authorisation because:

- This is relevant to NHS clinical practice, as corroborated by clinical opinion; it is unlikely that fremanezumab would be used in place of current oral preventive therapies (such as topiramate, propranolol or amitriptyline) due to the low cost of these therapies
- This position allows fremanezumab treatment to be focussed on patients who do not respond sufficiently to other preventive therapies, and matches the population where onabotulinumtoxin A has been approved; these patients currently have a high unmet need with few treatment options available, especially for those with episodic migraine for whom onabotulinumtoxin A is not available.

A summary of how the decision problem is addressed by this submission is provided in Table 1. It can be seen that in most aspects the published scope from NICE is followed. This submission considers chronic migraine (CM) and episodic migraine (EM) as separate populations wherever possible; as these populations have different comparators (onabotulinumtoxin A is only recommended for use within CM). Fremanezumab is available in two different dosing regimens, as a monthly or as a quarterly subcutaneous injection(s). These two regimens deliver an equivalent dose of fremanezumab (225mg *per* month/675mg quarterly) and have equivalent efficacy. Data on the efficacy of the two dosing regimens are presented separately, as reported in the clinical trials. Whereas cost-effectiveness is reported for both regimens of fremanezumab together, based on the equivalence in dose, efficacy, safety and price of the two regimens.

The scope defines subgroups of interest as: chronic and episodic migraine; the number of previous preventive treatments; and defined by the frequency of episodic migraine. As mentioned above, chronic and episodic migraine are presented separately wherever possible and the main focus of this submission is patients who have failed three or more previous preventive treatments. This submission also considers high-frequency episodic migraine (HFEM) as a separate subgroup (defined as eight to fourteen monthly headache days). These patients have a high unmet need due to onabotulinumtoxin A being unavailable to them, whilst having a substantial burden of disease that has been found to be comparable to CM.[1]

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with chronic or episodic migraine	As *per* scope, with chronic and episodic migraine considered separately	As onabotulinumtoxin A is only recommended for use within chronic migraine populations, chronic and episodic migraine have different comparators; therefore, these populations were considered separately wherever possible.
Intervention	Fremanezumab	As *per* scope	
Comparator(s)	Established clinical management for migraine prevention without fremanezumab, including: • Oral preventive treatments (such as topiramate, propranolol, amitriptyline) • Onabotulinumtoxin A • Erenumab (subject to ongoing NICE appraisal) • Best supportive care	Established clinical management for migraine prevention without fremanezumab, including: • Onabotulinumtoxin A • Best supportive care	Other oral preventive treatments were not considered as relevant comparators for the proposed positioning of fremanezumab (after three prior preventive treatment failures). Erenumab was not considered as a relevant comparator as it is not currently approved by NICE and hence is not a part of current standard NHS practice
Outcomes	The outcome measures to be considered include: • Frequency of headache days *per* month • Frequency of migraine days *per* month • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days	As *per* scope	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Reduction in acute pharmacological medication • Adverse effects of treatment • Health-related quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost *per* quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	As *per* scope	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People with chronic or episodic migraine • Subgroups defined by the number of previous preventive treatments	As *per* scope	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Subgroups defined by the frequency of episodic migraine		

B 1.2 Description of the technology being appraised

Further regulatory details of fremanezumab are included within appendix C.

Table 2 Technology being appraised

UK approved name and brand name	Ajovy® (fremanezumab)
Mechanism of action	Fremanezumab is a humanised IgG2Δa/kappa monoclonal antibody derived from a murine precursor. Fremanezumab selectively binds the calcitonin gene-related peptide (CGRP) ligand and blocks both CGRP isoforms (α-and β-CGRP) from binding to the CGRP receptor. While the precise mechanism of action by which fremanezumab prevents migraine attacks is unknown, it is believed that prevention of migraine is obtained by its effect on modulating the trigeminal system. CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief
Marketing authorisation/CE mark status	Marketing Authorisation was granted on 28 March 2019
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Fremanezumab is indicated for the prophylaxis of migraine in adults who have at least four migraine days *per* month. Fremanezumab is contraindicated in patients with a hypersensitivity to the active substance or to any of the excipients within the medicine. Warnings and precautions for use: • The name and the batch number of the administered product should be clearly recorded to allow traceability • Hypersensitivity reactions were reported in less than 1% of patients in clinical trials; if a hypersensitivity reaction occurs, discontinuation of fremanezumab administration should be considered and appropriate therapy should be initiated • Patients with certain major cardiovascular diseases were excluded from clinical studies and so no safety data are available in these patients • This product contains less than 1 mmol sodium *per* dose and is essentially “sodium-free”.
Method of administration and dosage	Fremanezumab is administered by subcutaneous injection at a dose of 225mg monthly, or at a dose of 675mg (3x 225mg) every 3 months (quarterly). Patients can self-inject after instruction in subcutaneous self-injection technique by a healthcare professional
Additional tests or investigations	No additional tests or investigations are needed

List price and average cost of a course of treatment	£450 *per* 225mg injection £5,400 *per* year

Calcitonin gene-related peptide (CGRP) is a 37 amino acid pro-inflammatory neuropeptide which plays a key role in the underlying pathophysiology of migraine and is present in the central and peripheral nervous systems, including the trigeminal ganglion,[2] and has been proposed to contribute to pain transmission and vasodilation.[3] In particular, it appears to play a major role in migraine development, as CGRP levels have been found to be increased during migraine attacks;[4] and when symptoms improve, CGRP serum levels were found to decrease.[5]

Fremanezumab is a fully humanised anti-CGRP monoclonal antibody developed for the preventive treatment of migraine.[6] Fremanezumab potently and selectively binds to both isoforms of CGRP (α and β), whilst its design ensures that the antibody does not cross react with CGRPs' closely related family members.[6] Fremanezumab differs from erenumab, another monoclonal anti-CGRP developed for migraine prevention, in the fact that the latter targets the CGRP receptor, giving both antibodies differences in mechanism of action.[6,7]

During a migraine attack, it has been demonstrated that CGRP levels are elevated.[4] Fremanezumab sequesters CGRP thus interfering with the ligands ability to bind to its receptor and hence prevent downstream signaling induced by the receptor.[6] This in turn is thought to lead to the reduction in the frequency and severity of migraines experienced by individuals.

Patient safety was a key focus during the development of this novel therapy. The bioengineering of fremanezumab, an IgG2Δa antibody, enables the introduction of a non-natural, human-mimicking sequence that does not activate complement dependent lysis or trigger cytotoxic activities, whilst retaining the desirable IgG properties, and therefore fremanezumab is postulated to have reduced immunogenicity. This is demonstrated by the low rate of anti-drug antibodies in the pivotal Phase III studies.[6] Furthermore, fremanezumab has been developed with patient convenience in mind, and so offers two dosing regimens (monthly or quarterly), the only anti-CGRP therapy to do so.[6]

In the clinical trials of fremanezumab involving patients with CM, a loading dose of 675mg was used in the monthly regimen. However, the Marketing Authorisation has been granted without this loading dose in order to harmonise the dosing for fremanezumab to 675mg every three months or 225mg every month. This simplification of the dosing of fremanezumab was granted based on data demonstrating equivalence in efficacy of the monthly regimen without the loading dose to the quarterly regimen.[8] The first of these analyses was based on data from the HALO and Phase II studies of fremanezumab and compared efficacy between patients with EM who had ≥12 headache days *per* month (considered as a good surrogate for patients with CM) receiving monthly dosing (no loading dose) and patients with CM receiving quarterly dosing. Analysis of the primary endpoint of mean monthly migraine days in comparison to placebo showed a similar effect size between these two groups, with no clinically meaningful difference in effect size (least square mean difference *versus* placebo of [redacted] for monthly fremanezumab in patients with EM and [redacted] for quarterly fremanezumab in patients with CM). Furthermore, comparisons between all treatment groups in these patient populations (patients with EM with ≥12 headache days *per* month and patients with CM) showed no meaningful differences. A further analysis was conducted using exposure-response models (built using clinical data from Phase III and Phase IIb trials of fremanezumab), which were developed to characterise the relationship between plasma fremanezumab concentration and efficacy outcomes. This model was able to predict responses consistent with clinical results, and predicted a treatment effect of a comparable size in patients with CM receiving quarterly fremanezumab and monthly fremanezumab (with no loading dose). Furthermore, it was found that a single dose of 225mg or 675mg fremanezumab had very similar median times to maximum concentration (t_{max}) of 5 to 7 days. The removal of the loading dose has the advantage of simplifying the dosing of fremanezumab for both patients and clinicians, whilst decreasing the risk of incorrect dosing. These data were considered sufficient for the Marketing Authorisation to be granted without the loading dose in CM, and the license to be granted for 675mg every three months or 225mg every month.

B 1.3 Health condition and position of the technology in the treatment pathway

B 1.3.1 Disease overview

Migraine is a common neurological disorder that is ranked amongst the top ten causes of disability globally.[9] Additionally, migraine is recognised as the most burdensome disease amongst neurological conditions evaluated as well as being globally the sixth leading cause of years of life lost to disability.[10,11] Migraine is a complex condition that is characterised by recurrent attacks usually lasting for four to 72 hours and involving pulsating head pain of moderate to severe intensity.[12] Typically, the pain is unilateral, may be aggravated by normal physical activity and can be accompanied by other physical symptoms such as nausea or vomiting, photophobia and phonophobia.[12] Ninety percent of patients report experiencing moderate to severe pain during a migraine attack and 75% of patients experience reduced functional ability.[13] Some patients may experience a gradual development of visual, sensory or other central nervous system symptoms prior to the onset of the headache, this is described as a "migraine with aura".[12]

Migraine can be classified by frequency of attacks as either EM or CM. The definitions of the International Headache Society (IHS) (ICHD-3 criteria) are the most widely accepted, and these define EM as headaches occurring on less than 15 days *per* month.[12] Whereas CM comprises headache occurring on 15 or more days *per* month for more than three months, which exhibits migraine characteristics on at least eight days *per* month.[12] These guidelines define a migraine attack (without aura) as a headache lasting at least four hours that includes at least two of the following characteristics (unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity) and at least one of the following characteristics (nausea/vomiting, photophobia and phonophobia).[12] For classification as "migraine with aura" it is required that one or more aura symptoms has at least three of the following characteristics (at least one aura symptom spreads gradually over ≥5 minutes; two or more aura symptoms occur in succession; each individual aura symptom lasts 5-60 minutes; at least one aura symptom is unilateral; at least one aura symptom is positive; the aura is

accompanied, or followed within 60 minutes, by headache).[12] The British Association for the Study of Headache (BASH) guidelines refer to the IHS ICHD-3 guidelines as being the internationally recognised standards for diagnosis in migraine.[14]

The classification of HFEM applies to patients with EM at the upper end of attack frequency. In a comparative study involving 1,109 patients with migraine, patients with HFEM were found to have similar migraine characteristics as patients with CM and were notably different from other patients with EM.[1] This study demonstrated that the EM population of patients were not homogenous; statistically significant differences were observed across multiple variables when comparing HFEM and low-frequency EM (LFEM) patients. Such differences included migraine disability assessment (MIDAS) score, State/Trait Anxiety Inventory and Beck Depression Inventory, where HFEM patients are more severely affected compared to LFEM patients. Indeed, when HFEM was compared to CM, there was no statistical significance in any of these aforementioned parameters,[1] demonstrating that the reduced quality of life and unmet need in HFEM is comparable to that in CM patients.

In the study above, HFEM was defined as patients experiencing ten to fourteen headache days *per* month.[1] However, a definition of HFEM has not been set within the ICHD-3 guidelines,[12] and no clearly accepted definition has been consistently adopted within research literature. Therefore, based on the advice received from clinical experts and the definitions used within clinical trials of fremanezumab, Teva has considered HFEM to be those patients with eight to 14 monthly headache days.

Accurate classification of migraine can also be difficult in some patients as headache characteristics can be inconsistent over time;[12] patients can present with either episodic or chronic migraine and their condition can worsen or improve over the course of the disease with or without treatment intervention. Globally, it is recognised that around 3% of patients *per* year can progress from EM to CM,[15] and a similar or higher number revert from CM to EM.[16] Based on an adult population of 43.7 million in England in 2017 (latest available figures),[17] there are estimated to be over 6 million adults who experience migraine. As EM accounts for around 90% of

patients,[18,19] this it would mean that approximately 160,000 episodic migraine patients are at risk of progressing to CM every year. However, there is a lack of long-term data on the clinical course of migraine within patients and any possible reasons behind these changes.

Changes in migraine frequency over time can be driven by fluctuation in hormone levels (*e.g.* with the onset of menopause).[20] Poor management of migraine, due to ineffective acute treatment,[21] is also associated with an increased risk of migraine chronification. Particularly for CM patients, an increased risk of medication overuse headache is a substantial concern, with around half of patients reverting to EM once their acute medication overuse is stopped.[12] Other risk factors for CM include obesity (especially when in combination with insulin resistance or other symptoms of metabolic syndrome), craniomandibular disorders and psychological factors (such as depression or stressful life events).[22]

In summary, the relationship between headache frequency, levels of disability and quality of life is not linear. This is further complicated by the fact that migraine characteristics can change over the course of the disease, in terms of frequency and severity. Taken together, this highlights the need for effective and well-tolerated treatments that are available across the full migraine spectrum of EM and CM; especially as some EM patients have a level of disability and quality of life comparable to that of CM patients. Currently, EM patients are excluded from receiving onabotulinumtoxin A treatment, which is reserved for CM.

B 1.3.2 Epidemiology

Migraine has an estimated global lifetime prevalence of 13%.[9] This disease is known to affect women more frequently than men, with migraine prevalence rates in Western Europe and North America of 5-9% for men and 12-25% for women.[23] In the UK, the lifetime prevalence of migraine has been reported based on a database analysis of the National Child Development Studies.[24] This study followed 17,415 individuals born in one week of March 1958, and found the lifetime prevalence of migraine was 11% for women and 5% for men (in the 5,799 participants analysed for migraine).[24] Figures from a systematic survey in England during the early 2000s reported the one-year prevalence of migraine at 14%, with a rate two times higher in

women than in men (18% *versus* 7%).[25] Migraine prevalence has been shown to rise through early adult life with a peak at 30 to 40 years.[25] The incidence of migraine has been less reported in the literature, but results from a UK study using the General Practice Research Database found an incidence rate of migraine of 3.7 *per* 1,000 person-years.[26] Again, this study showed a higher rate of migraine in women (5.2 *per* 1,000 person-years) than men (2.1 *per* 1,000 person-years).[26] Based on an adult population of 43.7 million in England in 2017 (latest available figures),[17] there are estimated to be over 6 million adults who experience migraine and over 150,000 new adult cases each year. Furthermore, it is recognised that the prevalence and frequency of migraine attacks decrease with age. Reports state that for two-thirds of migraine patients, frequency of attacks decrease with age. Specifically in females who have started their menopause, studies suggest that 20% of migraineurs lose their attacks *per* 10 years of life,[27] highlighting that migraine is not a lifelong disease. Taken together, it is clear that migraine is not only a prevalent disease but also one that impacts individuals during some of the most productive years of their lives.

There is a general lack of studies investigating the relative prevalence of EM and CM. Within the literature, two large studies from the USA have been identified which report that CM makes up 9-12% of adult migraine cases.[18,19] Therefore, EM can be reasoned to account for the remaining 88-91% of patients.[18,19]

When considering the population relevant to this appraisal it is notable that many patients with migraine will not be able to manage their migraine through non-pharmacological means or through acute treatment of migraine attacks. Data from the UK show that around 28% of patients with EM and 32% of patients with CM require preventive migraine therapies.[28] Only 9% of EM and 28% of CM patients have used more than three different preventive treatments.[29]

Based on the available evidence, migraine does not appear to substantially impact mortality, as was concluded in a meta-analysis conducted in 2011.[30] A population-based cohort study from 2015 in Norway gave similar results, with no significant difference in the adjusted hazard ratios for mortality between patients with migraine and those without.[31]

B 1.3.3 Disease burden

B 1.3.3.1 Clinical burden

Migraine can be a hugely disabling condition due to the attacks that characterise this condition. Globally migraine is recognised at the sixth leading cause of years of life lost to disability. Evidence also suggests that disability is not only associated with the migraine attack itself but also the periods in between attacks, the interictal period, where patients experience functional impairment, with physical, emotional, economic, and social ramifications.[32]

It is not surprising that CM causes higher migraine-related disability than EM.[28,29] The UK results from two large multinational surveys show that 88% of CM patients reported very severe disability, whereas for EM this was 20-24% (Table 3).[28,29]

Table 3: Reported disability of CM and EM in UK patients[28,29]

	2012		2013	
MIDAS score	**EM (n=1,013)**	**CM (n=57)**	**EM (n=107)**	**CM (n=50)**
Grade 1 (little disability)	28%	5%	29%	2%
Grade 2 (mild disability)	22%	2%	29%	4%
Grade 3 (moderate disability)	26%	5%	22%	6%
Grade 4 (severe/very severe disability)	24%	88%	20%	88%

However, it should be noted that the EM population of patients is not considered to be homogenous. In a clinical comparison of migraine types (n=1,109), there were clear differences in migraine-related disability between EM and CM with the latter exhibiting a greater burden.[1] However, patients with HFEM were more closely aligned to patients with CM regarding headache-related disability outcomes and impact on daily life than to patients with LFEM.[1] When LFEM was compared to HFEM, MIDAS score, State/Trait Anxiety Inventory and Beck Depression Inventory differed significantly, with patients with HFEM being more severely affected. However, when HFEM was compared to CM, there was no statistical significance in any of these parameters.[1] Based on these findings, the traditional way of classifying

migraine, based on numbers of headache days, may prevent patients with HFEM from accessing therapies that are available to patients with CM, even though the disability, reduced quality of life and unmet need between the two groups is comparable.

Patients with migraine are often affected by other conditions, with 79% of patients reporting at least one comorbidity and some reporting as many as seven.[33] Depression (33%) and anxiety (31%) were the most frequently listed conditions.[33] Notably, patients with CM are more likely to be affected by comorbidities than patients with EM.[28] Studies have also shown that patients with migraine have reduced quality of life (QoL).[34] In a population-based survey undertaken in England, patients with migraine scored lower in eight out of nine tested aspects in the Medical Outcomes Study Short Form 36-Item Health Survey (a generic instrument for measuring self-reported QoL in chronic conditions) compared to matched controls without migraine.[35]

Furthermore, migraine has been found to negatively impact the family lives of patients, from causing relationship difficulties and breakups to causing children and partners to miss out on school or social activities.[36] Almost half of migraine patients have reported that they miss family, social and leisure activities and almost a third of patients avoided planning future activities or events, in the fear that they may suffer from a migraine.[37]

B 1.3.3.2 Economic burden

Migraine causes a substantial economic burden on healthcare systems. In the UK, the annual direct costs *per* person with migraine have been estimated to be £736.58 for EM and £3,160.67 for CM in 2010.[28] Based on these figures, the annual direct cost of migraine on the NHS could be as high as £6 billion. While there appear to be clear differences regarding the economic burden between EM and CM, HFEM appears to be relatively similar to CM (Table 4).[38]

Table 4: Resource use of patients with high-frequency EM and CM[38]

Category	High-frequency EM (n=105)	CM (n=128)	p-value
Mean ER visits (SD)	1.0 (2.2)	1.0 (2.6)	NS
Mean hospitalisations (SD)	0.2 (1.0)	0.2 (1.5)	NS
Mean HCP visits (SD)	5.6 (5.7)	9.6 (11.4)	<0.05
Patients paying >$100 for migraine prescription therapies (%)	13 (12.4)	18 (14.1)	NS
Patients paying >$200 for migraine-related HCP visits (%)	9 (8.6)	9 (7.0)	-

The impact of migraine extends beyond its direct costs on healthcare systems and absenteeism is a common occurrence for many patients with migraine. This impact is particularly important for migraine due to its prevalence in adults of working age.[25] An international survey (n=8,271) reported that more than a quarter of people with migraine lost more than five days of work, household, family, social or leisure activities in the previous three months, with 10% of men and 16% of women losing more than 20 days.[36] A survey that compared the impact of EM and CM found that patients with EM missed a mean of four work/school days during a four-week period, whereas patients with CM missed a mean of nine days during the same period.[39] Patients with CM also reported more work/school days where they experienced headache symptoms compared to patients with EM (17 *versus* five days, respectively).[39] A UK-based study reported the number of days of absenteeism by MIDAS category, with higher grades of disability associated with more days of work missed.[33] Patients with severe disability (Grade 4) missed 48 days during a three-month period.[33] It is estimated that in the UK, over 100,000 people are absent due to migraine every day, leading to 25 million lost school or work days every year.[25] The economic burden caused by absenteeism and reduced productivity in migraine is very large and is estimated to be around €27 billion in Europe (€3.2 billion in the UK).[40] Overall, indirect costs (such as absenteeism) account for more than 90% of the total cost of migraine.[41] A more recent report, developed by the Work Foundation, reported that 43 million work days are lost to absenteeism every year in the UK and additional 43 million work days are lost due to presenteeism. Together, this was estimated to impose a total cost of just under £8.8 billion every year.[42]

In summary, migraine is a prevalent condition that impacts many individuals' lives, their families and friends. This neurological condition is disabling, during attacks and between attacks, and negatively impacts a patient's quality of life. Disease burden is higher in CM compared to EM; however, HFEM patients are thought to be comparable to CM in terms of disability, reduced quality of life and unmet need. Migraine patients not only contribute to an economic burden on healthcare systems but also on society as a whole, through loss of productivity.

B 1.3.4 Current guidelines for prophylaxis in migraine

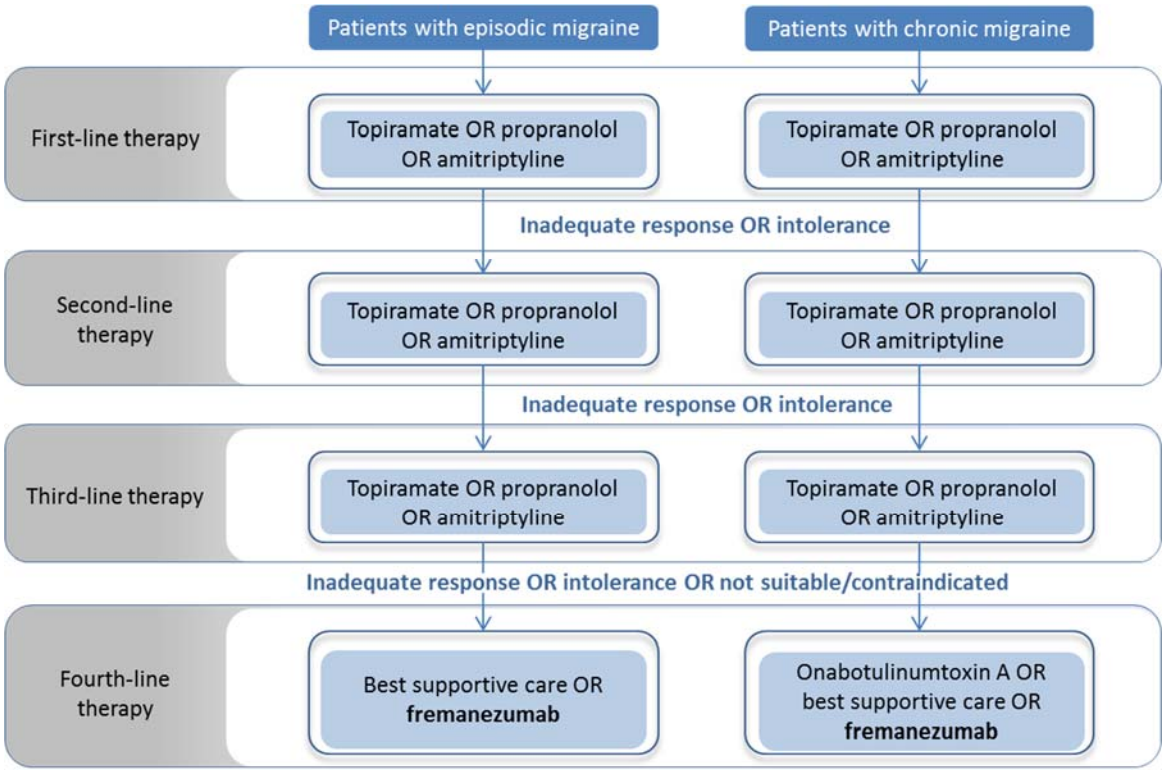
The following NICE guidelines and guidance are potentially relevant to this appraisal:

- Headaches in over 12s: diagnosis and management (CG150)[43]
- Headaches in over 12s (QS42)[44]
- Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (TA260)[45]
- Transcranial magnetic stimulation for treating and preventing migraine (IPG477)[46]
- Percutaneous closure of patent foramen ovale for recurrent migraine (IPG370)[47]
- Occipital nerve stimulation for intractable chronic migraine (IPG452)[48]
- Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine (IPG559)[49]
- Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552)[50]
- Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache (IPG527).[51]

The current treatment pathway for preventive therapies in patients with EM and CM based on NICE guidance is summarised in Figure 1. This pathway is based mainly on CG150, which recommends topiramate and propranolol as treatment options.[43] These guidelines also recommend considering amitriptyline and advising that riboflavin may be effective in reducing frequency and intensity of migraine attacks.[43] The guidelines also recommend offering a course of up to 10 sessions of acupuncture to patients for whom topiramate and propranolol are ineffective or not

suitable.[43] Within the guidance of CG150, there is also a recommendation that the need for preventive treatment is reviewed after 6 months.[43] For chronic migraine, TA260 adds onabotulinumtoxin A as an option for patients who have failed three other preventive therapies.[45] Anti-CGRP therapies, such as fremanezumab, are expected to fit as an alternative option to onabotulinumtoxin A.

Figure 1: NICE preventive treatment pathways for patients with migraine (including proposed positioning of fremanezumab)[43,45]



There are two other major UK guidelines related to migraine. The BASH guidelines differs from those of NICE in that they recommend topiramate as a second-line therapy in the prevention of migraine.[14] Amitriptyline and beta blockers (propranolol) are recommended as a first-line treatment options. Gabapentin, which is not recommended by NICE,[43] is included as a third-line treatment in the BASH guidelines.[14] In contrast, riboflavin, which is recommended for consideration by NICE,[43] is not recommended by BASH due to insufficient evidence.[14] BASH recommends that treatment is continued for six months before withdrawal is considered.[14]

The other guideline of interest is published by the Scottish Intercollegiate Guidelines Network (SIGN) and is generally in line with the recommendations made by NICE.[52] Notably, the SIGN guidelines recommend candesartan as a preventive treatment option, mainly due to it being an inexpensive drug with a well-established safety profile. Sodium valproate and flunarizine are also included as options for the prevention of migraine.[52] The SIGN guidelines include a recommendation that efficacy should be evaluated over at least three months and that the need for ongoing prevention should be considered after six to twelve months of treatment.[52]

In addition to the general guidelines on the treatment of migraine summarised above, the European Headache Federation (EHF) has recently published guidelines on the specific usage of anti-CGRP therapies.[53] These consensus guidelines summarise the current available evidence for the efficacy of anti-CGRP therapies and recommend that these treatments are used in patients who have failed two or more available migraine preventive therapies.[53] The EHF guidelines also recommend that continuation on treatment should be managed in the same way as for other preventive therapies; in that treatment should continue for at least 6-12 months in patients who have shown an adequate response before stopping is considered.[53]

Clinical experts consulted by Teva in preparation for this appraisal advised that a variety of clinical practice currently exists within the NHS regarding migraine prevention.[54] This tends to follow the above guidelines, but often with local variation in the treatments offered and the order in which treatments are likely to be prescribed. In addition, there was likely to be consideration of more invasive procedures (such as occipital nerve block and trigeminal nerve stimulation) should all other therapies fail.

The current treatment pathway highlights the need for new preventive therapies in the field of migraine that are specifically designed to target the underlying pathophysiology of the condition. There are currently very limited treatment options for those intolerant to the three first-line therapies and onabotulinumtoxin A.[43] Even for those patients where onabotulinumtoxin A is a treatment option, often it can be burdensome. Onabotulinumtoxin A treatment needs to be administered in a clinic by a trained healthcare professional,[45] meaning that clinic capacity may cause a delay

in receiving treatment cycles. In addition to this, this therapy is a relatively invasive technique, consisting of 31 injections in the head and neck region over approximately a 30 minute period.[45]

It has been shown that a subset of patients will fail to respond to at least three preventive therapies.[29] For example, 46% of patients may not respond to topiramate, 68% may not respond to propanolol and 54% may not respond to amitriptyline.[55,56,57,58] As demonstrated in the previous sections, these patients may face substantial disability and, currently, there are no further recommended treatment options available to them (except for onabotulinumtoxin A for patients with CM).[43]

B 1.4 Equality considerations

Migraine is a condition that is more common in women. In a survey conducted in England during the early 2000s, women had an approximately two times higher migraine prevalence compared to men (18% *vs* 7%).[25] Therefore, restricting access to migraine therapies will disadvantage women to a greater extent than men. There are no other equality factors that require consideration in this appraisal.

B.2 Clinical effectiveness

B 2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B 2.2 List of relevant clinical effectiveness evidence

There are three relevant randomised-controlled trials (RCTs) that have been conducted that provide evidence on the efficacy and safety of fremanezumab in patients with migraine. The key trials used to provide data within the application for a Marketing Authorisation are the HALO CM and EM trials. These trials investigated the efficacy and safety of fremanezumab in EM and CM patients (EM NCT02629861; CM NCT02621931). In addition, the FOCUS trial (NCT03308968) has recently been completed, which investigated the efficacy and safety of fremanezumab in patients with EM and CM who have had an inadequate response to two to four previous classes of preventive therapy (defined as a lack of a clinically meaningful improvement as *per* treating physician's judgement after at least 3 months of therapy at a stable dose, intolerance to the treatment or contraindication/unsuitability for a treatment). The FOCUS trial therefore provides data that are highly relevant to this appraisal and the expected place of fremanezumab in the migraine treatment pathway for patients with three or more treatment failures. No relevant non-RCT evidence for fremanezumab was identified through the systematic literature review conducted.

Table 5 Clinical effectiveness evidence – HALO EM trial

Study	HALO EM				
Primary study reference	Dodick *et al*. 2018[59]				
Study design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group trial				
Population	Adults with a history of migraine for at least 12 months and episodic migraine				
Intervention(s)	• Fremanezumab (225mg monthly) • Fremanezumab (675mg quarterly)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	*X*	Indicate if trial used in the economic model	Yes	
	No			No	*X*
Rationale for use/non-use in the model	The HALO EM trial does not provide data on the patient population (3+ previous therapies) included within the economic modelling				
Reported outcomes specified in the decision problem	• Mean change from baseline in monthly average number of migraine days (primary endpoint) • Mean change from baseline in monthly average number of days of use of any acute headache medication (secondary endpoint) • Migraine Disability Assessment (severity & HRQoL, secondary endpoint) • Migraine-Specific Quality of Life Questionnaire (HRQoL, exploratory endpoint) • Mean change from baseline in monthly average number of headache days (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of any severity (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of at least moderate severity (exploratory endpoint)				
All other reported outcomes	• Patients with at least 50% reduction from baseline in monthly average number of migraine days (secondary endpoint)				

Table 6 Clinical effectiveness evidence – HALO CM trial

Study	HALO CM				
Primary study reference	Silberstein *et al*. 2017[60]				
Study design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group trial				
Population	Adults with a history of migraine for at least 12 months and chronic migraine				
Intervention(s)	• Fremanezumab (675mg followed by 225mg monthly) • Fremanezumab (675mg quarterly)				
Comparator(s)	• Placebo				
Indicate if trial supports application for marketing authorisation	Yes	*X*	Indicate if trial used in the economic model	Yes	
	No			No	*X*
Rationale for use/non-use in the model	The HALO CM trial does not provide data on the patient population (3+ previous therapies) included within the economic modelling				
Reported outcomes specified in the decision problem	• Mean change from baseline in monthly average number of headache days of at least moderate severity (primary endpoint) • Mean change from baseline in monthly average number of migraine days (secondary endpoint) • Mean change from baseline in monthly average number of days of use of any acute headache medication (secondary endpoint) • Six-Item Headache Impact Test (severity & HRQoL, secondary endpoint) • Migraine-Specific Quality of Life Questionnaire (HRQoL, exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of any severity (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of at least moderate severity (exploratory endpoint)				
All other reported outcomes	• Patients with at least 50% reduction from baseline in monthly average number of migraine days (exploratory endpoint)				

Table 7 Clinical effectiveness evidence – FOCUS trial

Study	FOCUS				
Primary study reference	FOCUS results[61]				
Study design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group trial				
Population	Adults with migraine and inadequate response to 2 to 4 classes of prior preventive treatments				
Intervention(s)	• Fremanezumab (225mg monthly [EM patients] or 675mg followed by 225mg monthly [CM patients]) • Fremanezumab (675mg quarterly) [both EM and CM patients]				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes		Indicate if trial used in the economic model	Yes	*X*
	No	*X*		No	
Rationale for use/non-use in the model	The FOCUS trial includes only patients who have had an inadequate response to prior preventive treatments for migraine, which includes the most relevant data on the population of interest for this appraisal				
Reported outcomes specified in the decision problem	• **Mean change from baseline in monthly average number of migraine days (primary endpoint)** • Mean change from baseline in monthly average number of headache days of at least moderate severity (secondary endpoint) • Mean change from baseline in monthly average number of days of use of any acute headache medication (secondary endpoint) • Six-Item Headache Impact Test (severity & HRQoL, exploratory endpoint) • **Migraine-Specific Quality of Life Questionnaire (HRQoL, exploratory endpoint)** • Mean change from baseline in monthly average number of headache hours of at least moderate severity (exploratory endpoint)				
All other reported outcomes	• **Patients with at least 50% reduction from baseline in the monthly average number of migraine days (secondary endpoint)**				

B 2.3 Summary of methodology of the relevant clinical effectiveness evidence

B 2.3.1 Summary of clinical trial methodologies

The two HALO trials were 16-week RCTs that consisted of an initial screening visit to confirm eligibility and confirm enrolment; a 28-day run-in period (for establishment of baseline); and a 12-week (84-day) treatment period. Patients were seen at five scheduled clinic visits: at screening, baseline (dose 1), weeks 4 (dose 2) and 8 (dose 3), and week 12 (end of treatment), or at the time of withdrawal from the trial. Headache information was captured daily throughout study participation using an electronic headache diary device. Within the study, patients were randomised 1:1:1 between the three arms (monthly fremanezumab, quarterly fremanezumab and placebo), stratified by sex, country, and baseline preventive migraine medication use. Randomisation was performed using centrally located electronic interactive response technology. All patients and investigators were blinded to treatment assignments. Fremanezumab and placebo injection kits were identical in appearance and placebo was administered at the same volume as fremanezumab.

The FOCUS trial was a 16-week RCT that consisted of an initial screening visit to confirm eligibility and confirm enrolment; a 28-day run-in period; and a 12-week (84-day) treatment period. Patients were seen at five scheduled clinic visits: at screening, baseline (dose 1), weeks 4 (dose 2) and 8 (dose 3), and week 12 (end of treatment), or at the time of withdrawal from the trial. Headache information was captured daily throughout study participation using an electronic headache diary device. Within the study, patients were randomised 1:1:1 between the three arms (monthly fremanezumab, quarterly fremanezumab and placebo) stratified by sex, country, and baseline preventive migraine medication use. Randomisation was performed using centrally located electronic interactive response technology. All patients and investigators were blinded to treatment assignments. Placebo injections were designed to match fremanezumab injections and consisted of the same vehicle and excipients.

Table 8 Comparative summary of clinical trial methodology

Trial acronym	HALO EM	HALO CM	FOCUS	
			Episodic migraine	Chronic migraine
Location	International study in nine countries (USA, Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain)		International study in fourteen countries (USA, Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK)	
Trial design	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial		Phase IIIb, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial	
Eligibility criteria for participants	Have episodic migraine during the 28-day run-in period (headache on 6-14 days, with ≥4 days fulfilling ICHD-3 beta criteria for migraine with or without aura, probable migraine, or required use of triptans or ergot derivatives)	Have chronic migraine during the 28-day run-in period (headache on ≥15 days, with ≥8 days fulfilling ICHD-3 beta criteria for migraine with or without aura, probable migraine, or required use of triptans or ergot derivatives on)	Have episodic migraine during the 28-day run-in period (headache on 6-14 days, with ≥4 days fulfilling ICHD-3 beta criteria for migraine with or without aura, probable migraine, or required use of triptans or ergot derivatives)	Have chronic migraine during the 28-day run-in period (headache on ≥15 days, with ≥8 days fulfilling ICHD-3 beta criteria for migraine with or without aura, probable migraine, or required use of triptans or ergot derivatives on)
	Key inclusion criteria • Aged 18 to 70 years • History of migraine based on ICHD-3 beta criteria for at least 12 months prior to screening • Migraine onset at or prior to age 50 **Key exclusion criteria** • Use of onabotulinumtoxin A during previous four months before screening • Use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during previous two months prior to screening		**Key inclusion criteria** • Aged 18 to 70 years • History of migraine based on ICHD-3 beta criteria for at least 12 months prior to screening • Migraine onset at or prior to age 50 • Documented inadequate response to 2 to 4 classes of prior preventive migraine medications* within the past 10 years (defined as a lack of a clinically meaningful improvement after at least 3 months of therapy, intolerance to the treatment or contraindication/unsuitability for a treatment) **Key exclusion criteria**	

	• Use of opioid or barbiturate medications on more than four days during the 28-day run-in period • A lack of efficacy after ≥3 months of treatment of at least two of four classes of preventive medications Full inclusion and exclusion criteria are given in Appendix L		• Use of onabotulinumtoxin A during previous three months prior to screening • Use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during previous two months prior to screening • Use of opioids or barbiturate medications on more than four days during the 28-day run-in period • Use of preventive migraine medication for longer than 5 days prior to the screening visit • Use of triptans/ergots as preventive therapies Full inclusion and exclusion criteria are given in Appendix L	
Settings and locations where the data were collected	136 centres in nine countries (United States (n=88), Canada (n=5), Czech Republic (n=6), Finland (n=3), Israel (n=6), Japan (n=12), Poland (n=5), Russian Federation (n=7), Spain (n=4))	132 sites in nine countries (United States (n=87), Canada (n=4), Czech Republic (n=6), Finland (n=3), Israel (n=4), Japan (n=12), Poland (n=5), Russian Federation (n=7), Spain (n=4))	113 sites in nine countries (United States (n=30), Belgium (n=4), Czech Republic (n=10), Denmark (n=5), Finland (n=6), France (n=6), Germany (n=12), Italy (n=2), Netherlands (n=4), Poland (n=9), Spain (n=11), Sweden (n=5), Switzerland (n=3), United Kingdom (n=6))	
Trial drugs	Patients were randomised 1:1:1 (stratified by sex, country, and baseline preventive migraine medication use) to receive: • Fremanezumab monthly n=290 (one 225mg fremanezumab injection (1.5mL) and two 1.5mL placebo injections at baseline; one 225mg	Patients were randomised 1:1:1 (stratified by sex, country, and baseline preventive migraine medication use) to receive: • Fremanezumab monthly n=379 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 225mg fremanezumab injection (1.5mL) at weeks 4&8)	Patients were randomised 1:1:1 (stratified by gender, country, and special treatment failure defined as inadequate response to valproic acid and two to three other migraine preventive medication) to receive: • Fremanezumab monthly n=110 (one 225mg fremanezumab injection	Patients were randomised 1:1:1 (stratified by gender, country, and special treatment failure defined as inadequate response to valproic acid and two to three other migraine preventive medication) to receive: • Fremanezumab monthly n=173 (675mg (three 225mg injections

	fremanezumab injection (1.5mL) at weeks 4&8) • Fremanezumab quarterly n=291 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 1.5mL placebo injection at weeks 4&8) • Placebo n=294 (three 1.5mL placebo injections at baseline; one 1.5mL placebo injection at weeks 4&8) Administration of study drugs was conducted at study centres during scheduled study visits	• Fremanezumab quarterly n=376 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 1.5mL placebo injection at weeks 4&8) • Placebo n=375 (three 1.5mL placebo injections at baseline; one 1.5mL placebo injection at weeks 4&8) Administration of study drugs was conducted at study centres during scheduled study visits	(1.5mL) and two 1.5mL placebo injections at baseline; one 225mg fremanezumab injection (1.5mL) at weeks 4&8) • Fremanezumab quarterly n=107 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 1.5mL placebo injection) at weeks 4&8 • Placebo n=112 (three 1.5mL placebo injections at baseline; one 1.5mL placebo injection at weeks 4&8) Administration of study drugs was conducted at study centres during scheduled study visits	[1.5mL]) fremanezumab at baseline; one 225mg fremanezumab injection (1.5mL) at weeks 4&8) • Fremanezumab quarterly n=169 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 1.5mL placebo injection at weeks 4&8) • Placebo n=167 (three 1.5mL placebo injections at baseline; one 1.5mL placebo injection at weeks 4&8) Administration of study drugs was conducted at study centres during scheduled study visits
Permitted and disallowed concomitant medication	A subset of patients were allowed to continue use of one preventive migraine medication if dosing had been stable for ≥2 months Acute headache medications were permitted		At least five half-lives of prior preventive migraine therapies must have passed Acute medication to treat migraine and drugs to treat adverse events were permitted	
Primary outcome	Mean change from baseline in monthly average number of migraine days (defined as day with either at least 2 consecutive hours of a headache meeting criteria for migraine (with or without aura); probable migraine	Mean change from baseline in monthly average number of headache days of at least moderate severity (defined as day with headache pain that lasted at least 4 consecutive hours and had a peak severity of at least	Mean change from baseline in the monthly average number of migraine days (defined as a day with either at least four consecutive hours of a headache meeting criteria for migraine (with or without aura); probable migraine (only one migraine criterion missing); or headache of any duration treated with migraine-specific acute medication) during the 12-week period after the first dose	

	(only one migraine criterion absent); or day when acute migraine medication was required) during 12-week period after the first dose	moderate; or day when when acute migraine medication was required) during the 12-week period after the first dose		
Assessment methods for primary outcomes	Clinical data were derived from an electronic headache diary device used daily by study participants, which recorded headache durations, symptoms, severity and acute medication usage. Patients were seen at five scheduled visits for protocol-specified evaluations: at screening, baseline, weeks 4 and 8, and week 12, or at the time of early withdrawal from the trial		Clinical data were derived from an electronic headache diary device used daily by study participants, which recorded headache durations, symptoms, severity and acute medication usage. Patients were seen at scheduled visits for protocol-specified evaluations: at screening, baseline, weeks 4, 8, 12, 16 and week 20 or at the time of early withdrawal from the trial	
Other outcomes used in the economic model/specified in the scope	• Mean change from baseline in monthly average number of days of use of any acute headache medication (secondary endpoint) • Migraine Disability Assessment (secondary endpoint) • Patients with at least 50% reduction from baseline in monthly average number of migraine days (secondary endpoint) • Migraine-Specific Quality of Life Questionnaire (exploratory endpoint) • Mean change from baseline in monthly average number of	• Mean change from baseline in monthly average number of migraine days (secondary endpoint) • Mean change from baseline in monthly average number of days of use of any acute headache medication (secondary endpoint) • Six-Item Headache Impact Test (secondary endpoint) • Patients with at least 50% reduction from baseline in monthly average number of migraine days (exploratory endpoint)	• Mean change from baseline in monthly average number of days of use of any acute headache medication (secondary endpoint) • Migraine Disability Assessment (secondary endpoint) • Patients with at least 50% reduction from baseline in monthly average number of migraine days (secondary endpoint) • Migraine-Specific Quality of Life Questionnaire (exploratory endpoint) • Mean change from baseline in monthly average number of	• Mean change from baseline in monthly average number of days of use of any acute headache medication (secondary endpoint) • Six-Item Headache Impact Test (secondary endpoint) • Patients with at least 50% reduction from baseline in monthly average number of migraine days (secondary endpoint) • Migraine-Specific Quality of Life Questionnaire (exploratory endpoint) • Mean change from baseline in monthly average number of

	headache days (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of any severity (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of at least moderate severity (exploratory endpoint)	• Migraine-Specific Quality of Life Questionnaire (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of any severity (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of at least moderate severity (exploratory endpoint)	headache hours of any severity (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of at least moderate severity (exploratory endpoint)	headache hours of any severity (exploratory endpoint) • Mean change from baseline in monthly average number of headache hours of at least moderate severity (exploratory endpoint)
Pre-planned subgroups	Pre-planned subgroup analyses were carried out for the monthly average number of migraine days and the monthly average number of headache days of at least moderate severity for the following subgroups: • Patients receiving or not receiving concomitant preventive treatment • Patients with past topiramate use for migraine • Patients with past onabotulinumtoxin A use for migraine • Age groups (18-45 years; >45 years) • Race groups (Caucasian; non-Caucasian) • Sex		Pre-planned subgroup analyses were carried out for: • Special treatment failure group (patients with inadequate response to valproic acid plus two to three other migraine preventive medications) • Age groups (18-45 years; >45 years) • Sex • Region (North America; Europe) • Migraine classification (CM; EM) • Valproic acid failure (yes; no)	

*The classes included the following: beta-blockers (propranolol, metoprolol, atenolol, and bisopropol), anticonvulsants (topiramate), tricyclics (amitriptyline), calcium channel blocker (flunarizine), angiotensin II receptor antagonist (candesartan), onabotulinumtoxinA and valproic acid.

B 2.3.2 Patient baseline characteristics

B 2.3.2.1 HALO EM

Baseline demographics and clinical characteristics were similar among all treatment groups in the HALO EM trial, with no significant differences observed (Table 9).

Table 9 Baseline characteristics of patients in HALO EM trial

HALO EM Baseline characteristic	Placebo (n=294)	Fremanezumab quarterly (n=291)	Fremanezumab monthly (n=290)
Age, years			
Mean (SD)	41.3 (12.0)	41.1 (11.4)	42.9 (12.7)
Median (range)	41.0 (18-70)	42.0 (18-69)	43.0 (18-70)
Sex, n (%)			
Male	47 (16)	40 (14)	46 (16)
Female	247 (84)	251 (86)	244 (84)
Weight, kg			
Mean (SD)	75.3 (16.0)	74.2 (15.4)	72.1 (15.8)
Median (range)	74.3 (43-118)	73.0 (45-120)	69.3 (45-119)
Time since initial migraine diagnosis, years			
Mean (SD)	19.9 (11.9)	20.0 (12.1)	20.7 (12.9)
Median (range)	17.5 (1-51)	19.0 (1-65)	19.0 (0-58)
Preventive medication use during run-in period, n (%)			
Yes	62 (21)	58 (20)	62 (21)
No	232 (79)	233 (80)	228 (79)
Previous topiramate use for migraine, n (%)			
Yes	53 (18)	51 (18)	64 (22)
No	241 (82)	240 (82)	226 (78)
Number of headache days of at least moderate severity during run-in period			
n	293	291	288
Mean (SD)	6.9 (3.1)	7.2 (3.1)	6.8 (2.9)
Median (range)	7.0 (0-15)	7.0 (0-16)	6.5 (0-15)
Number of migraine days during run-in period			
n	293	291	288
Mean (SD)	9.1 (2.7)	9.3 (2.7)	8.9 (2.6)
Median (range)	9.0 (4-15)	9.0 (4-17)	9.0 (3-16)
Number of days of use of any acute headache medications during run-in period			
n	293	291	288
Mean (SD)	7.7 (3.6)	7.8 (3.7)	7.7 (3.4)
Median (range)	8.0 (0-15)	8.0 (0-16)	7.7 (0-15)

HALO EM Baseline characteristic	Placebo (n=294)	Fremanezumab quarterly (n=291)	Fremanezumab monthly (n=290)
Number of days of use of migraine-specific acute headache medications during run-in period			
n	137	152	148
Mean (SD)	7.1 (3.0)	6.6 (3.1)	6.1 (3.1)
Median (range)	7.0 (1-14)	7.0 (1-14)	6.0 (1-14)
Migraine Disability Assessment (MIDAS) total score			
n	290	287	287
Mean (SD)	37.3 (27.6)	41.7 (33.0)	38.0 (33.2)
Median (range)	32.5 (0-156)	33.0 (0-206)	33.0 (0-306)

B 2.3.2.2 HALO CM

Baseline demographics and clinical characteristics were similar among all treatment groups in the HALO CM trial, with no significant differences observed (Table 10).

Table 10 Baseline characteristics of patients in HALO CM trial

HALO CM Baseline characteristic	Placebo (n=375)	Fremanezumab quarterly (n=376)	Fremanezumab monthly (n=379)
Age, years			
Mean (SD)	41.4 (12.0)	42.0 (12.4)	40.6 (12.0)
Median (range)	41.0 (19-70)	43.0 (18-71)	40.0 (18-70)
Sex, n (%)			
Male	45 (12)	45 (12)	49 (13)
Female	330 (88)	331 (88)	330 (87)
Weight, kg			
Mean (SD)	72.6 (15.6)	72.4 (15.8)	72.5 (16.4)
Median (range)	71.2 (45-119)	70.5 (45-132)	69.8 (44-119)
Time since initial migraine diagnosis, years			
Mean (SD)	19.9 (12.9)	19.7 (12.8)	20.1 (12.0)
Median (range)	17.0 (1-57)	18.0 (1-61)	18.0 (1-55)
Preventive medication use during run-in period, n (%)			
Yes	77 (21)	77 (20)	85 (22)
No	298 (79)	299 (80)	294 (78)
Previous topiramate use for migraine, n (%)			
Yes	117 (31)	106 (28)	117 (31)
No	258 (69)	270 (72)	262 (69)

HALO CM Baseline characteristic	Placebo (n=375)	Fremanezumab quarterly (n=376)	Fremanezumab monthly (n=379)
Previous onabotulinumtoxin A use for migraine, n (%)			
Yes	49 (13)	66 (18)	50 (13)
No	326 (87)	310 (82)	329 (87)
Any acute headache medication use during run-in period, n (%)			
Yes	358 (95)	359 (95)	360 (95)
No	17 (5)	17 (5)	19 (5)
Total number of headache days of any duration and any severity during run-in period			
Mean (SD)	20.3 (4.2)	20.4 (3.9)	20.3 (4.3)
Median (range)	19.3 (11-28)	20.0 (13-28)	19.0 (8-28)
Number of headache days of at least moderate severity during run-in period			
Mean (SD)	13.3 (5.8)	13.2 (5.5)	12.8 (5.8)
Median (range)	12.6 (0-28)	13.0 (1-28)	12.0 (0-28)
Number of migraine days during run-in period			
Mean (SD)	16.4 (5.2)	16.2 (4.9)	16.0 (5.2)
Median (range)	15.5 (7-28)	15.9 (7-28)	15.4 (5-28)
Number of days of use of any acute headache medications during run-in period			
Mean (SD)	13.0 (6.9)	13.1 (6.8)	13.1 (7.2)
Median (range)	13.5 (0-28)	14.0 (0-28)	13.6 (0-28)
Number of days of use of migraine-specific acute headache medications during run-in period			
n	192	208	187
Mean (SD)	10.7 (6.3)	11.3 (6.2)	11.1 (6.0)
Median (range)	10.0 (1-28)	11.0 (1-28)	10.3 (1-27)
Headache Impact Test (HIT-6) Disability score			
n	373	370	377
Mean (SD)	64.1 (4.8)	64.3 (4.7)	64.6 (4.4)
Median (min, max)	64.0 (48-78)	65.0 (42-78)	64.0 (50-78)

B 2.3.2.3 FOCUS

Baseline demographics and clinical characteristics were similar among all treatment groups within the FOCUS trial, with no significant differences observed (Table 11).

Table 11 Baseline characteristics of patients in FOCUS trial

FOCUS Baseline characteristic	Placebo (n=279)	Fremanezumab quarterly (n=276)	Fremanezumab monthly (n=283)
Age, years			
Mean (SD)	46.8 (11.1)	45.8 (11.0)	45.9 (11.1)
Median (range)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	46 (16)	47 (17)	45 (16)
Female	233 (84)	229 (83)	238 (84)
Weight, kg			
Mean (SD)	71.4 (13.7)	70.7 (13.4)	71.0 (13.7)
Median (range)	[redacted]	[redacted]	[redacted]
Time since initial migraine diagnosis, years			
Mean (SD)	24.3 (13.6)	24.3 (12.8)	24.0 (13.7)
Median (range)	[redacted]	[redacted]	[redacted]
Number of migraine days during run-in period			
Mean (SD)	14.3 (6.1)	14.1 (5.6)	14.1 (5.6)
Median (range)	[redacted]	[redacted]	[redacted]
Number of headache days of at least moderate severity during run-in period			
Mean (SD)	12.8 (5.9)	12.4 (5.8)	12.7 (5.8)
Median (range)	[redacted]	[redacted]	[redacted]
Number of days of use of any acute headache medications during run-in period			
Mean (SD)	12.3 (6.3)	12.8 (6.2)	12.2 (6.0)
Median (range)	[redacted]	[redacted]	[redacted]
Number of days of use of migraine-specific acute headache medications during run-in period			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Migraine Disability Assessment (MIDAS) total score			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
HIT-6 total score			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

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

Statistical considerations related to the two HALO studies and the FOCUS study are summarised in Table 12, and CONSORT diagrams providing a full summary of the participant flow in both trials are provided in Appendix D.

Table 12 Summary of statistical analyses in included studies

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
HALO EM	Null hypothesis: change from baseline in the monthly average number of migraine days is the same between treatment groups. Alternative hypothesis: change from baseline in the monthly average number of migraine days is not the same between treatment groups.	Pre-specified comparisons between treatment groups were conducted by ANCOVA of the change from baseline. The least-square means (LSM), corresponding 95% CIs and associated p-value were calculated. The Wilcoxon rank-sum test was performed if there was deviation from normality as assessed by the Shapiro-Wilk test. A mixed-effects repeated-measures (MMRM) analysis was implemented as a sensitivity analysis. A fixed-sequence (hierarchical) testing procedure was implemented to control the type 1 error rate at 0.05	The target sample size for this trial was calculated to be at least 768 total patients (256 patients *per* treatment group); based on having at least 90% power to detect a 1.6 difference in migraine days between active and placebo arms and assuming a common SD of 5.2 days and a 12% discontinuation rate	All efficacy analyses were conducted on the full analysis set (FAS) (patients who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessments). Safety analyses were conducted on all patients who received treatment (only one randomised patient in monthly fremanezumab group did not receive treatment). For withdrawals or patients with missing e-diary data, data was either prorated (≥10 days data) or considered as missing (<10 days data). A multiple imputation method was conducted as a sensitivity analysis

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
HALO CM	Null hypothesis: change from baseline in the monthly average number of headache days of at least moderate severity is the same between treatment groups. Alternative hypothesis: change from baseline in the monthly average number of headache days of at least moderate severity is not the same between treatment groups.	Pre-specified comparisons between treatment groups were conducted by ANCOVA of the change from baseline. LSM, corresponding 95% CIs and associated p-value were calculated. The Wilcoxon rank-sum test was performed if there was deviation from normality as assessed by the Shapiro-Wilk test. A mixed-effects repeated-measures (MMRM) analysis was implemented as a sensitivity analysis. A fixed-sequence (hierarchical) testing procedure was implemented to control the type 1 error rate at 0.05.	The target sample size for this trial was calculated to be at least 1020 total patients (340 patients *per* treatment group); based on having at least 90% power to detect a 1.7 difference in migraine days between active and placebo arms and assuming a common SD of 6.3 days and a 15% discontinuation rate.	All efficacy analyses were conducted on the FAS (patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment). Safety analyses were conducted on all patients who received treatment (only one randomised patient in monthly fremanezumab group did not receive treatment). For withdrawals or patients with missing e-diary data, data were either prorated (≥10 days data) or considered as missing (<10 days data). A multiple imputation method was conducted as a sensitivity analysis.
FOCUS	Null hypothesis: change from baseline in the monthly average number of migraine days for the fremanezumab treatment group and the placebo group is the same. Alternative hypothesis: change from baseline in the	Pre-specified comparisons between treatment groups were conducted by ANCOVA of the change from baseline. LSM, corresponding 95% CIs and associated p-value were calculated. A mixed-effects repeated-measures (MMRM) analysis was implemented as a sensitivity analysis. A fixed-sequence (hierarchical) testing procedure was	The target sample size for this trial was calculated to be at least 804 total patients (268 patients *per* treatment group); based on having at least 90% power to detect a 1.8 difference in migraine days between active and placebo arms and assuming a common SD of 6.0 days and a	All efficacy analyses were conducted on the modified intention-to-treat (mITT) cohort (patients who received at least one dose of study drug and had at least 10 days post-baseline efficacy assessment). Safety analyses were conducted on all patients who received at least one dose of study drug during the open-label phase (ITT cohort). For withdrawals or patients with missing e-diary data, data were

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	monthly average number of migraine days for the fremanezumab treatment group and the placebo group is not the same.	implemented to control the type 1 error rate at 0.05.	12% discontinuation rate.	either prorated (≥10 days data for monthly variables and ≥3 days data for weekly variables) or considered as missing (<10 days data for monthly variables and <3 days data for weekly variables). A multiple imputation method was conducted as a sensitivity analysis.

B 2.4.1 HALO EM

B 2.4.1.1 Sample size

The HALO EM required sample size was calculated based on having at least 90% power to detect a difference of 1.6 in migraine days between active and placebo arms, at an alpha level of 0.05, and assuming a common SD of 5.2 days. Based on these assumptions, it was calculated that a sample size of 675 patients (225 patients *per* treatment group) was required. With the discontinuation rate assumed to be 12%, a target sample size of at least 768 patients was therefore set (256 patients *per* treatment group).

B 2.4.1.2 Analyses sets

All 875 randomised patients were included in the intention-to-treat (ITT) cohort. Only one patient (in the monthly fremanezumab group) did not receive treatment. The full analysis set (FAS) included all randomised patients who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessments for the primary endpoint. There were four randomised patients in the placebo group, three patients in the quarterly fremanezumab group and three patients in the monthly fremanezumab group not included in the FAS. All efficacy analyses were conducted on the FAS and safety analyses were conducted on all patients who received treatment.

B 2.4.1.3 Withdrawals and discontinuations

Withdrawals or patients with missing diary data were managed in the following way:

- If patient had ≥10 days of data for a month, number of days/hours was prorated to 28 days for that month, and a multiple imputation method was also conducted as a sensitivity analysis
- If patient had <10 days data for a month, the monthly number of days of efficacy variables was considered missing before the multiple imputation procedure

Patients in active treatment groups who discontinued because of adverse events or lack of efficacy were assigned to the placebo group.

There were no interim analyses planned for this trial, but following completion of the trial, patients had the option to enter an extension to evaluate the long-term safety and efficacy of fremanezumab. There were no formal rules for early termination of this trial. All serious adverse events were reviewed as they were reported; patients were able to discontinue participation at any time for any reason and the investigator and/or sponsor could withdraw a patient at any time for any reason.

B 2.4.1.4 Statistical analysis

This trial aimed to demonstrate the efficacy of fremanezumab compared to placebo in reducing the monthly average number of migraine days. Statistical analysis of the primary outcome was conducted by analysis of covariance (ANCOVA) of the change from baseline. The ANCOVA model included treatment, sex, region, and baseline preventive migraine medication use as fixed effects and the baseline number of migraine days and years since onset of migraine as covariates. The least square means (LSM) and corresponding 95% confidence intervals (CI) for the treatment differences and associated p-value were calculated. The Wilcoxon rank-sum test was performed as the primary analysis if there was deviation from normality as assessed by the Shapiro-Wilk test. A mixed-effects, repeated-measures (MMRM) analysis was implemented as a sensitivity analysis to estimate the mean change from baseline in the monthly average number of migraine days for the overall 3-month treatment period and for each month.

An ANCOVA method similar to that used for the primary outcome analysis was used for all relevant secondary outcomes and a Cochran Mantel-Haenszel test stratified by baseline preventive migraine medication use was used for analysing the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days. A fixed-sequence (hierarchical) testing procedure was implemented to control the type 1 error rate at 0.05. Pre-defined subgroup analyses (see Table 8 for details) were conducted using the ANCOVA and MMRM methods described above.

B 2.4.2 HALO CM

B 2.4.2.1 Sample size

The HALO CM required sample size was calculated based on having at least 90% power to detect a difference of 1.7 in headache days between active and placebo arms, at an alpha level of 0.05, and assuming a common SD of 6.3 days. Based on these assumptions, it was calculated that a sample size of 867 patients (289 patients *per* treatment group) was required. With the discontinuation rate assumed to be 12%, a target sample size of at least 1020 patients was therefore set (340 patients *per* treatment group).

B 2.4.2.2 Analyses sets

All 1130 randomised patients were included in the ITT cohort and received at least one dose of treatment. The FAS included all randomised patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment for the primary endpoint. There were four randomised patients in the placebo group, one patient in the quarterly fremanezumab group and four patients in the monthly fremanezumab group not included in the FAS. All efficacy analyses were conducted on the FAS and safety analyses were conducted on the ITT cohort (all patients who received treatment).

B 2.4.2.3 Withdrawals and discontinuations

Withdrawals or patients with missing diary data were managed in the following way:

- If patient had ≥10 days of data for a month, number of days/hours was prorated to 28 days for that month, and a multiple imputation method was also conducted as a sensitivity analysis
- If patient had <10 days data for a month, the monthly number of days of efficacy variables was considered missing before the multiple imputation procedure.

Patients in active treatment groups who discontinued because of adverse events or lack of efficacy were assigned to the placebo group.

There were no interim analyses planned for this trial, but following completion of the trial, patients had the option to enter an extension to evaluate the long-term safety and efficacy of fremanezumab. There were no formal rules for early termination of this trial. All serious adverse events were reviewed as they were reported; patients were able to discontinue participation at any time for any reason and the investigator and/or sponsor could withdraw a patient at any time for any reason.

B 2.4.2.4 Statistical analysis

This trial aimed to demonstrate the efficacy of fremanezumab compared to placebo in reducing the monthly average number of headache days of at least moderate severity. Statistical analysis of the primary outcome was conducted by ANCOVA of the change from baseline. The ANCOVA model included treatment, sex, country, and baseline preventive migraine medication use as fixed effects and the baseline number of headache days and years since onset of migraine as covariates. The LSM and corresponding 95% CIs for the treatment differences and associated p-value were calculated. The Wilcoxon rank-sum test was performed as the primary analysis if there was deviation from normality as assessed by the Shapiro-Wilk test. A MMRM analysis was implemented as a sensitivity analysis to estimate the mean change from baseline in the monthly average number of headache days for the overall 3-month treatment period and for each month.

An ANCOVA method similar to that used for the primary outcome analysis was used for all relevant secondary outcomes and a Cochran Mantel-Haenszel test stratified by baseline preventive migraine medication use was used for analysing the proportion of patients reaching at least 50% reduction in the monthly average number of headache days. A fixed-sequence (hierarchical) testing procedure was implemented to control the type 1 error rate at 0.05. Pre-defined subgroup analyses (see Table 8 for details) were conducted using the ANCOVA and MMRM methods described above.

B 2.4.3 FOCUS

B 2.4.3.1 Sample size

The sample size required in the FOCUS trial was calculated based on having at least 90% power to detect a difference of 1.8 in migraine days between active and placebo arms, at an alpha level of 0.05, and assuming a common SD of 6.0 days. Based on these assumptions, it was calculated that a sample size of 705 patients (235 patients *per* treatment group) was required. With the discontinuation rate assumed to be 12%, a target sample size of at least 804 patients was therefore set (268 patients *per* treatment group).

B 2.4.3.2 Analyses sets

All 838 patients were included in the ITT cohort and received at least one dose of treatment. The modified intention-to-treat (mITT) cohort included all randomised patients who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessment for the primary endpoint. There was a single patient with EM in the placebo group who was not included in the mITT cohort. All efficacy analyses were conducted on the mITT and safety analyses were conducted on the ITT cohort (all patients who received treatment).

B 2.4.3.3 Withdrawals and discontinuations

Withdrawals or patients with missing diary data were managed in the following way:

- If patient had ≥10 days of data for a month, number of days/hours was prorated to 28 days for that month, and a multiple imputation method was also conducted as a sensitivity analysis
- If patient had <10 days data for a month, the monthly number of days of efficacy variables was considered missing before the multiple imputation procedure.

In terms of weekly variables, patients with three or more days of electronic headache diary data for a week had their number of days of efficacy variables prorated to seven days for that week. For patients with less than three days of data, these variables were considered as missing for that week. For patients who withdrew from

the trial, their safety data at the early termination visit was excluded from the by-visit summaries but was included in the last assessment summaries.

There were no interim analyses planned for this trial, but the trial does include a pre-planned open-label extension. There were no formal rules for early termination of this trial. All serious adverse events were reviewed as they were reported; patients were able to discontinue participation at any time for any reason and the investigator and/or sponsor could withdraw a patient at any time for any reason.

B 2.4.3.4 Statistical analysis

This trial aimed to demonstrate the efficacy of fremanezumab compared to placebo in reducing the monthly average number of migraine days in patients who had previously had an inadequate response to two to four previous classes of migraine preventive treatments. Statistical analysis of the primary outcome was conducted by ANCOVA of the change from baseline. The ANCOVA model included treatment, sex, region, inadequate response to valproic acid (and 2 to 3 other classes of migraine preventive medications), migraine classification (CM or EM), and treatment-by-migraine classification interaction as fixed effects and the baseline number of migraine days and years since onset of migraine as covariates. The LSM difference and corresponding 95% CIs for the treatment differences and associated p-value were calculated. A MMRM analysis was implemented as a sensitivity analysis to estimate the mean change from baseline in the monthly average number of migraine days for the overall 3-month treatment period and for each month.

An ANCOVA method similar to that used for the primary outcome analysis was used for all relevant secondary outcomes and a logistic regression model was used for analysing the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days, with the following effects: treatment, sex, region, inadequate response to valproic acid (and two to three other classes of migraine preventive medications) and migraine classification (CM or EM). A fixed-sequence (hierarchical) testing procedure was implemented to control the type 1 error rate at 0.05. Pre-defined subgroup analyses (see Table 8 for details) were conducted using the ANCOVA and MMRM methods described above.

B 2.5 Quality assessment of the relevant clinical effectiveness evidence

The HALO clinical trials were prospective, multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase III trials in episodic and chronic migraine patients. The FOCUS clinical trial, also conducted in both chronic and episodic migraine patients, was a prospective, multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase IIIb trial. A summary of the quality assessment of these trials is presented in Table 13 and further details are given in Appendix D. These trials were conducted in accordance with the International Conference for Harmonisation Guidelines for Good Clinical Practice, the Declaration of Helsinki, and all relevant national and local regulations. Randomisation and blinding methods were appropriate and described in detail. There were no significant differences in the baseline characteristics of the study groups, and there was no obvious difference in drop-out rates between groups for either trial. There was no evidence that other endpoints beyond those described were investigated. The safety analysis was conducted on the intention-to-treat cohort (as long as they had received at least one dose of study drug), and the efficacy analyses were conducted on all patients who received at least one dose of study drug and had post-baseline efficacy assessment (which excluded only small numbers of patients from each group). The use of this group for efficacy analyses can be considered appropriate as this group had the minimum requirements needed in order for a meaningful assessment of efficacy to be conducted. The methodology for dealing with missing data can also be considered appropriate, with a sensitivity analysis conducted to assess this assumption.

In addition to the above, the design of the CM studies fulfilled the recommendations produced by the International Headache Society in the Guidelines for controlled trials of preventive treatment of chronic migraine in adults (2018) across multiple domains; including, but not limited to, duration of the observation period, primary and secondary endpoints, inclusion of patients with medication overuse, duration and age of onset of disease, use of concomitant preventive medications, and acute medication use.[62]

The patient population that was included in the FOCUS study reflected the UK patient population in consideration for this appraisal and included UK clinical trial centres. Over 95% of the study participants were aged between 18-65 years,[61] which reflects the population of people that are most commonly affected by migraine in the UK[25] – the age group that reflects the period of peak economic productivity. In addition to this, as found globally and in the UK,[23,24] over 80% of trial participants were women.[61] The majority of participants had a diagnosis of migraine for over 20 years and experienced [redacted] or [redacted] migraine days at baseline for EM and CM, respectively. In addition, at baseline, patients reported using acute headache medication on [redacted] days and [redacted] days for EM and CM, respectively, with disability scores for HIT-6 and MIDAS in the [redacted] category.[61] These characteristics suggest that the patients enrolled within the FOCUS study had a high disease burden, for several years, that was substantially impacting their quality of life. This reflects the population of patients that are not achieving meaningful benefit to a number of preventives and are seen in UK headache clinics; as confirmed by clinical experts.

Patients enrolled into the study were able to continue to use their acute headache medications due to the fact that it is recognised that often patients need both acute and preventive treatment to manage their migraines.[61,63] Furthermore, headache guidelines written by BASH recommend that, when indicated, preventive therapy is used in addition to acute treatment and not in place of it.[14] This highlights that the FOCUS study, not only included patients with baseline demographics that reflected the UK migraine population, but also patients were able to continue managing their condition with acute therapy as they would do in the real-world.

The FOCUS study enrolled EM and CM patients whom had failed 2 to 4 classes of prior preventives. The number of treatment failures were based on classes rather than individual drugs, to ensure that patients within the study had failures on medications that have distinct mechanisms of action. This highlights the robust design of the FOCUS trial, as patients recruited had tried several different medication classes that have distinct mechanisms in reducing migraine frequency; just as the NICE treatment pathway for migraine recommends patients to be offered

preventive treatment with medications from different classes.[43] Additionally, preventive medications classes, considered for failures, included NICE recommended treatments for migraine prevention.[43]

The FOCUS trial consisted of patients whom had an inadequate response to two to four classes of preventive therapy; therefore, further *post-hoc* subgroup analyses on the most relevant population for this submission were conducted (inadequate response to three or more previous preventive therapies). This data therefore provides the best available data in a group that it is very similar to those expected to receive this therapy in UK practice. Therefore, these data should be considered to be generalisable to the population considered in this appraisal. The comparator of placebo was chosen to demonstrate the efficacy and safety in a straightforward manner and consistent with other trials conducted in this area. These trials were funded by Teva.

Table 13 Quality assessment results for parallel group RCTs

Trial acronym	HALO EM	HALO CM	FOCUS
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

B 2.6 Clinical effectiveness results of the relevant trials

B 2.6.1 HALO trials

B 2.6.1.1 Episodic migraine

All efficacy outcomes of the HALO EM trial were assessed in the FAS, which included 290 patients who received placebo, 288 who received the quarterly dose of fremanezumab and 287 who received the monthly dose of fremanezumab.

Adherence to study medication was very high in all groups, with six placebo (2.0%), three quarterly fremanezumab (1.0%) and five monthly fremanezumab patients (2.0%) having noncompliance with the study medication. A summary of the key efficacy results are included below in Table 14. For all outcomes, fremanezumab (in both dosing regimens) was significantly more effective than placebo (p<0.0001).

Table 14 Summary of main efficacy outcomes in HALO EM trial

	Placebo (n=290)	**Fremanezumab quarterly (n=288)**	**Fremanezumab monthly (n=287)**
Mean monthly migraine days			
Baseline (SD)	9.1 (2.7)	9.3 (2.7)	8.9 (2.6)
LSM change (95% CI)	-2.2 (-2.68 to -1.71)	-3.4 (-3.94 to -2.96)	-3.7 (-4.15 to -3.18)
Difference *vs* placebo (95% CI)		-1.3 (-1.79 to -0.72)	-1.5 (-2.01 to -0.93)
P-value *vs* placebo		<0.0001	<0.0001
Patients with at least 50% reduction in monthly average migraine days			
Number achieving endpoint (%)	81 (27.9%)	128 (44.4%)	137 (47.7%)
Difference *vs* placebo (95% CI)		16.5 (8.9 to 24.1)	19.8 (12.0 to 27.6)
P-value *vs* placebo		<0.0001	<0.0001
Mean monthly days of use of any acute headache medication			
Baseline (SD)	7.7 (3.6)	7.8 (3.7)	7.7 (3.4)
LSM change (95% CI)	-1.6 (-2.04 to -1.20)	-2.9 (-3.34 to -2.48)	-3.0 (-3.41 to -2.56)
Difference *vs* placebo (95% CI)		-1.3 (-1.76 to -0.82)	-1.4 (-1.84 to -0.89)
P-value *vs* placebo		<0.0001	<0.0001

	Placebo (n=290)	Fremanezumab quarterly (n=288)	Fremanezumab monthly (n=287)
Migraine Disability Assessment score			
Baseline (SD)	37.3 (27.6)	41.7 (33.0)	38.0 (33.2)
LSM change (95% CI)	-17.5 (-20.62 to -14.47)	-23.0 (-26.10 to -19.82)	-24.6 (-27.68 to -21.45)
Difference *vs* placebo (95% CI)		-5.4 (-8.90 to -1.93)	-7.0 (-10.51 to -3.53)
P-value *vs* placebo		<0.0001	<0.0001

B 2.6.1.1.a) Change in monthly average number of migraine days (primary endpoint)

Fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 (p<0.0001 for both dosing regimens). Placebo treatment provided a median change of -2.7 monthly migraine days ([IQR -4.7, -0.5; mean change -2.2 migraine days, 95% CI -2.68, -1.71). In comparison, the median overall change from baseline for quarterly fremanezumab was -4.0 migraine days (IQR -6.4, -1.9; mean change -3.4 migraine days, 95% CI -3.94, -2.96); and for monthly fremanezumab was -4.2 migraine days (IQR -6.2, -2.0; mean change -3.7 migraine days, 95% CI -4.15, -3.18). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -1.3 migraine days (95% CI -1.79, -0.72, p<0.0001 Wilcoxon rank-sum test) for quarterly fremanezumab and -1.5 migraine days (95% CI -2.01, -0.93, p<0.0001 Wilcoxon rank-sum test) for monthly fremanezumab.

The MMRM sensitivity analysis supported the above results, with a LSM difference *versus* placebo of -1.2 migraine days (95% CI -1.74, -0.69, p<0.0001) for quarterly fremanezumab and -1.4 migraine days (95% CI -1.96, -0.90, p<0.0001) for monthly fremanezumab. The MMRM analysis also showed that fremanezumab treatment resulted in a greater reduction from baseline in the average number of migraine days compared to placebo throughout the study period (up to 12 weeks, p=0.0013 and p=0.0002 for quarterly and monthly fremanezumab, respectively).

The results of the primary outcome demonstrate the efficacy of fremanezumab and its ability to reduce the number of migraine days experienced by patients. Further confidence in these results can be taken from the fact that the two separate analysis techniques used produced very similar overall results for the treatment effect.

B 2.6.1.1.b) Patients with at least 50% reduction in monthly average number of migraine days

The reduction of at least 50% in the average monthly migraine days with fremanezumab was investigated as a secondary outcome for the HALO EM trial. With fremanezumab, significantly more patients experienced a reduction of at least 50% in the average monthly number of migraine days compared to placebo ($p<0.0001$ for both dosing regimens). Overall, 128 patients (44.4%) treated with quarterly fremanezumab and 137 patients (47.7%) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compared to 81 patients (27.9%) in the placebo group. Analysis through the trial period demonstrated that fremanezumab resulted in a higher proportion of patients reaching at least 50% reduction in monthly migraine days at months one, two, and three compared to placebo treatment (Table 15). Furthermore, similar results were seen in an analysis of cumulative reduction of at least 75% in monthly migraine days; this was achieved in 25.8% and 27.2% of patients for the quarterly and monthly fremanezumab groups, respectively, compared to 15.4% of patients in the placebo group.

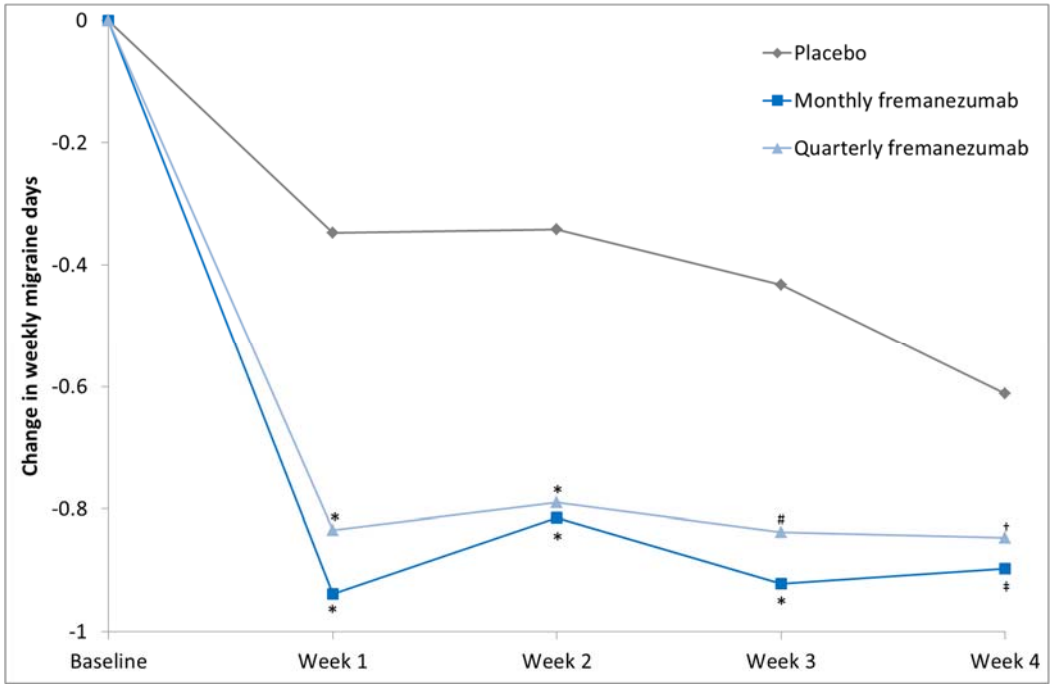
Table 15 Proportion of patients with 50% or greater reduction in average monthly migraine days

Time point statistic	Placebo N/n (%)	Fremanezumab quarterly N/n (%)	p-value quarterly *vs* placebo	Fremanezumab monthly N/n (%)	p-value monthly *vs* placebo
Month 1	73/290 (25.2)	127/288 (44.1)	<0.0001	135/287 (47.0)	<0.0001
Month 2	101/274 (34.8)	135/274 (46.9)	0.0032	139/274 (48.4)	0.0010
Month 3	108/268 (37.2)	141/269 (49.0)	0.0048	147/263 (51.2)	0.0003
Overall	81/290 (27.9)	128/288 (44.4)	<0.0001	137/287 (47.7)	<0.0001

B 2.6.1.1.c) Mean change in weekly average number of migraine days during the 4-week period after first dose of study drug

The reduction in weekly number of migraine days over the first month of treatment was another secondary outcome in the HALO trial. This analysis helps to provide information about speed of onset of fremanezumab. These results are shown in Figure 2 and demonstrate that there was a statistically significant difference between placebo and fremanezumab from the first time point of one week ($p<0.0001$ for both dosing regimens). The efficacy of fremanezumab remains almost constant throughout the first month. These results demonstrate that fremanezumab has a rapid onset of action, with clinically significant effects seen within a week of initiating therapy.

Figure 2 Change in weekly migraine days over time (MMRM analysis)



*p<0.0001; #p=0.0003; †p=0.04; ‡p=0.01 *vs* placebo

B 2.6.1.1.d) Mean change in monthly average number of days of use of any acute headache medication

Overuse of acute headache medication is a concern in migraine, therefore, one of the goals of preventive therapy is to reduce the need for acute medication. The HALO trials investigated the change in monthly average number of days where any

acute headache medication was used. Fremanezumab (in both dosing regimens) reduced the average monthly number of days with acute headache medication use to a significantly greater degree than was seen with placebo treatment ($p<0.0001$ for both dosing regimens). Placebo treatment provided a median change of -1.7 days with acute headache medication use (IQR -4.0, 0.0; mean change -1.6 days, 95% CI -2.04, -1.20). In comparison, the median overall change from baseline for quarterly fremanezumab was -3.0 medication days (IQR -5.6, -0.8; mean change -2.9 days, 95% CI -3.34, -2.48); and for monthly fremanezumab was -3.2 medication days (IQR -5.2, -1.2; mean change -3.0 days, 95% CI -3.41, -2.56). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -1.3 medication days (95% CI -1.76, -0.82, $p<0.0001$ Wilcoxon rank-sum test) for quarterly fremanezumab and -1.4 medication days (95% CI -1.84, -0.89, $p<0.0001$ Wilcoxon rank-sum test) for monthly fremanezumab. The MMRM sensitivity analysis supported the above results, with a LSM difference *versus* placebo of -1.3 medication days (95% CI -1.76, -0.82, $p<0.0001$) for quarterly fremanezumab and -1.4 medication days (95% CI -1.84, -0.89, $p<0.0001$) for monthly fremanezumab.

These results show a similar efficacy to that seen in the primary trial outcome, and demonstrate that fremanezumab is able to reduce medication usage in patients with migraine to a significant degree.

B 2.6.1.1.e) Quality of life measures

The quality of life for patients with migraine is a key measure by which to judge the overall impact of a treatment. A number of HRQoL measures were investigated in the HALO trials, and results from the MIDAS and Migraine-Specific Quality of Life Questionnaire (MSQoL) are presented herein.

Fremanezumab (in both dosing regimens) reduced the average MIDAS score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment ($p=0.0023$ and $p=0.0021$ for quarterly and monthly fremanezumab, respectively). Placebo treatment provided a median change of -12.5 (IQR -29.5, -2.0; mean change -17.5, 95% CI -20.62, -14.47). In comparison, the median overall change from baseline for quarterly fremanezumab was -18.0 (IQR -39.0, -6.0; mean change -23.0, 95% CI -26.10, -19.82); and for monthly

fremanezumab was -19.0 (IQR -36.0, -7.0; mean change -24.6, 95% CI -27.68, -21.45). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -5.4 (95% CI -8.90, -1.93, p=0.0023 Wilcoxon rank-sum test) for quarterly fremanezumab and -7.0 (95% CI -10.51, -3.53, p=0.0021 Wilcoxon rank-sum test) for monthly fremanezumab.

Analysis of the mean change from baseline in the MSQoL scores at four weeks after final dose showed differences from placebo in favour of fremanezumab for all three domains (role function – restrictive, role function – preventive and emotional state). The LSM differences with placebo for role function – restrictive domain were 4.1 and 7.0 for quarterly and monthly fremanezumab, respectively (p<0.01).

B 2.6.1.1.f) Other outcomes

Further outcomes in the HALO EM trial investigated other aspects of disease impact and severity and results for relevant outcomes are summarised below.

Mean change in monthly average number of headache days of at least moderate severity during the 12-week trial period showed a significant difference from placebo in favour of fremanezumab (p<0.0001 for both dosing regimens). The LSM difference *versus* placebo was -1.5 headache days (95% CI -1.96, -1.04, p<0.0001) for quarterly fremanezumab and -1.5 headache days (95% CI -1.92, -0.99, p<0.0001) for monthly fremanezumab.

Mean change in monthly average number of headache hours of any severity during the 12-week trial period showed a significant difference from placebo in favour of fremanezumab (p=0.0007 and p<0.0001 for quarterly and monthly fremanezumab, respectively). The LSM difference *versus* placebo was -8.8 headache hours (95% CI -13.28, -4.32, p=0.0001) for quarterly fremanezumab and -12.5 headache hours (95% CI -16.99, -8.03, p<0.0001) for monthly fremanezumab. When headache hours of at least moderate severity were considered, the LSM difference *versus* placebo was -6.4 headache hours for quarterly fremanezumab and -7.4 headache hours for monthly fremanezumab (p<0.0001 for both dosing regimens).

B 2.6.1.2 Chronic migraine

All efficacy outcomes in the HALO CM trial were assessed in the FAS, which included 375 who received the quarterly dose of fremanezumab, 375 who received the monthly dose of fremanezumab and 371 patients who received placebo.

Adherence to study medication was very high in all groups, with two quarterly fremanezumab (0.5%), six monthly fremanezumab (1.6%) and eight placebo (2.1%) patients having noncompliance with the study medication. A summary of the key efficacy results are included below in Table 16. Across all outcomes, fremanezumab (in both dosing regimens) was significantly more effective than placebo treatment ($p<0.001$).

Table 16 Summary of main efficacy outcomes in HALO CM trial

	Placebo (n=371)	**Fremanezumab quarterly (n=375)**	**Fremanezumab monthly (n=375)**
Mean monthly headache days of at least moderate severity			
Baseline (SD)	13.3 (5.8)	13.2 (5.5)	12.8 (5.8)
LSM change (95% CI)	-2.5 (-3.06 to -1.85)	-4.3 (-4.87 to -3.66)	-4.6 (-5.16 to -3.97)
Difference *vs* placebo (95% CI)		-1.8 (-2.46 to -1.15)	-2.1 (-2.76 to -1.45)
P-value *vs* placebo		<0.0001	<0.0001
Mean monthly migraine days			
Baseline (SD)	16.4 (5.2)	16.2 (4.9)	16.0 (5.2)
LSM change (95% CI)	-3.2 (-3.86 to -2.47)	-4.9 (-5.59 to -4.20)	-5.0 (-5.70 to -4.33)
Difference *vs* placebo (95% CI)		-1.7 (-2.48 to -0.97)	-1.8 (-2.61 to -1.09)
P-value *vs* placebo		<0.0001	<0.0001
Patients with at least 50% reduction in monthly average migraine days			
Number achieving endpoint (%)	74 (19.9%)	115 (30.7%)	125 (33.3%)
P-value *vs* placebo		0.0008	<0.0001
Mean monthly days of use of any acute headache medication			
Baseline (SD)	13.0 (6.9)	13.1 (6.8)	13.1 (7.2)
LSM change (95% CI)	-1.9 (-2.48 to -1.28)	-3.7 (-4.25 to -3.06)	-4.2 (-4.79 to -3.61)
Difference *vs* placebo (95% CI)		-1.8 (-2.43 to -1.12)	-2.3 (-2.97 to -1.67)

	Placebo (n=371)	Fremanezumab quarterly (n=375)	Fremanezumab monthly (n=375)
P-value *vs* placebo		<0.0001	<0.0001
Headache Impact Test score			
Baseline (SD)	64.1 (4.8)	64.3 (4.7)	64.6 (4.4)
LSM change (95% CI)	-4.5 (-5.38 to -3.60)	-6.4 (-7.31 to -5.52)	-6.8 (-7.71 to -5.97)
Difference *vs* placebo (95% CI)		-1.9 (-2.90 to -0.96)	-2.4 (-3.32 to -1.38)
P-value *vs* placebo		<0.0001	<0.0001

B 2.6.1.2.a) Mean change in monthly average number of headache days of at least moderate severity (primary endpoint)

The HALO CM trial used monthly average number of headache days as its primary endpoint rather than monthly average number of migraine days as in the HALO EM trial. Therefore, headache days are reported here as the primary outcome and migraine days are reported in the section below.

Fremanezumab (in both dosing regimens) reduced the average monthly number of headache days of at least moderate severity to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ($p<0.0001$ for both dosing regimens). Placebo treatment provided a median change of -2.5 monthly headache days (interquartile range [IQR] -5.6, 0.0; mean change -2.5 headache days, 95% CI -3.06, -1.85). In comparison, the median overall change from baseline for quarterly fremanezumab was -4.2 headache days (IQR -7.7, -1.7; mean change -4.3 headache days, 95% CI -4.87, -3.66); and for monthly fremanezumab was -4.5 headache days (IQR -7.8, -1.7; mean change -4.6 headache days, 95% CI -5.16, -3.97). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -1.8 headache days (95% CI -2.46, -1.15, $p<0.0001$ Wilcoxon rank-sum test) for quarterly fremanezumab and -2.1 headache days (95% CI -2.76, -1.45, $p<0.0001$ Wilcoxon rank-sum test) for monthly fremanezumab.

The MMRM sensitivity analysis supported the above results, and showed a significant greater reduction in headache days of at least moderate severity for fremanezumab (both dosing regimens) compared to placebo ($p<0.0001$ Wilcoxon rank-sum test). The MMRM analysis also showed that fremanezumab treatment resulted in a greater reduction from baseline in the average number of headache days of at least moderate severity compared to placebo treatment throughout the study period (up to 12 weeks, $p=0.0007$ and $p=0.0001$ for quarterly and monthly fremanezumab, respectively).

The results of the primary outcome demonstrate the efficacy of fremanezumab and its ability to reduce the number of headache days of at least moderate severity experienced by patients, with this result confirmed by two separate analysis techniques.

B 2.6.1.2.b) Mean change in monthly average number of migraine days

Fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ($p<0.0001$ for both dosing regimens). Placebo treatment provided a mean change of -3.2 monthly migraine days (95% CI -3.86, -2.47). In comparison, the mean overall change from baseline for quarterly fremanezumab was -4.9 migraine days (95% CI -5.59, -4.20); and for monthly fremanezumab was -5.0 migraine days (95% CI -5.70, -4.33). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -1.7 migraine days (95% CI -2.48, -0.97, $p<0.0001$) for quarterly fremanezumab and -1.8 migraine days (95% CI -2.61, -1.09, $p<0.0001$) for monthly fremanezumab. The MMRM analysis supported the above results, with fremanezumab treatment demonstrating a greater reduction from baseline in the average number of migraine days compared to placebo treatment as early as one month after administration of the first dose (first analysis point, $p<0.0001$ for both dosing regimens). This difference was maintained through the rest of the trial (up to 12 weeks, $p=0.0063$ and $p=0.0004$ for quarterly and monthly fremanezumab, respectively).

These results are more directly relevant to this submission than headache days, as the economic model is driven by monthly migraine days. The results clearly

demonstrate the efficacy of fremanezumab and its ability to reduce the number of migraine days experienced by patients. This reduction in migraine days was rapidly achieved and persisted throughout the study period.

B 2.6.1.2.c) Patients with at least 50% reduction in monthly average number of migraine days

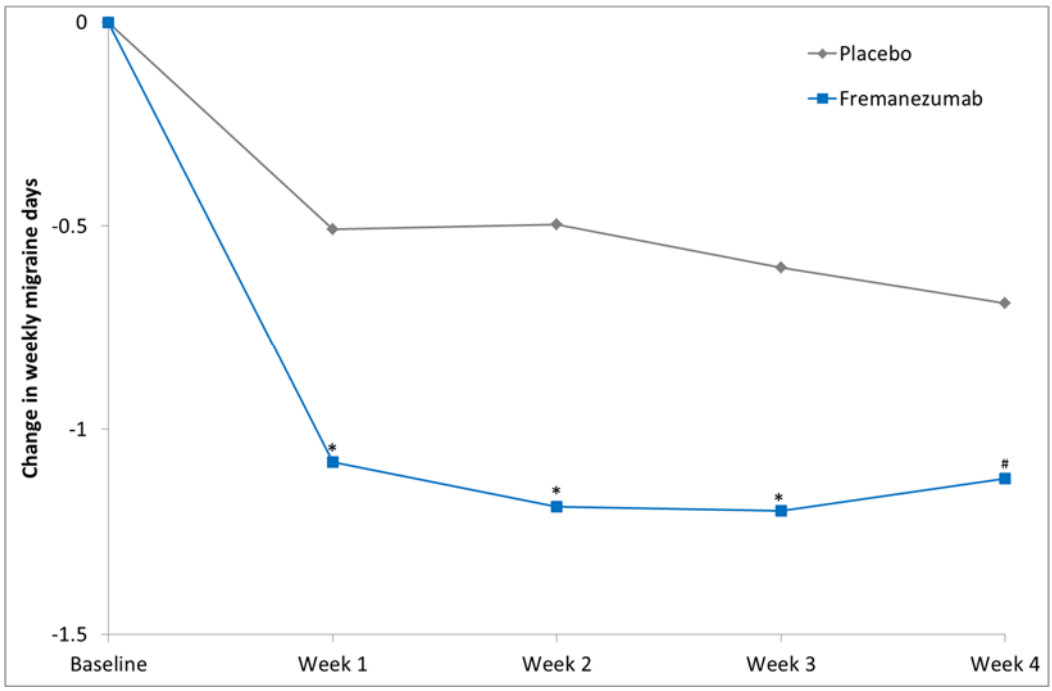
Significantly more patients experienced a reduction of at least 50% in the average monthly number of migraine days with fremanezumab compared to placebo treatment ($p=0.0008$ and $p<0.0001$ for quarterly and monthly fremanezumab, respectively). Overall, 115 patients (30.7%) treated with quarterly fremanezumab and 125 patients (33.3%) treated with monthly fremanezumab reached this threshold of migraine days reduction, compared to 74 patients (19.9%) in the placebo group. Analysis through the trial period demonstrated that fremanezumab resulted in a higher proportion of patients reaching at least 50% reduction in monthly migraine days at months one, two, and three compared to placebo treatment.

These results show that a substantial proportion of fremanezumab patients achieve a highly relevant level of reduction in monthly migraine days, and this is significantly greater than the proportion treated with placebo.

B 2.6.1.2.d) Mean change in weekly average number of migraine days over first month of treatment

Another secondary outcome for the HALO CM trial was the reduction in weekly number of migraine days over the first month of treatment. These results are shown in Figure 3 for the combined fremanezumab dosing regimens and demonstrate that there was a statistically significant difference between placebo and fremanezumab from the first time point of one week ($p<0.0001$). The efficacy of placebo gradually increased after this time point, whilst the efficacy of fremanezumab remained almost constant. Overall, this led to a reduction in p-values for fremanezumab, with a p-value of 0.01 at week 4. These results demonstrate the rapid onset of action with fremanezumab.

Figure 3 Change in weekly migraine days over time (MMRM analysis)



*p<0.0001; #p<0.001 *vs* placebo

B 2.6.1.2.e) Mean change from baseline in monthly average number of days of use of any acute headache medication

Fremanezumab (in both dosing regimens) reduced the average monthly number of days from baseline with acute headache medication use to a significantly greater degree than was seen with placebo treatment (p<0.0001 for both dosing regimens). Placebo treatment provided a median change from baseline of -2.0 days with acute headache medication use (IQR -5.3, 0.2; mean change -1.9 days, 95% CI -2.48, -1.28). In comparison, the median overall change from baseline for quarterly fremanezumab was -3.6 medication days (IQR -7.3, -0.7; mean change -3.7 days, 95% CI -4.25, -3.06); and for monthly fremanezumab was -4.2 medication days (IQR -7.6, -1.1; mean change -4.2 days, 95% CI -4.79, -3.61). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -1.8 medication days (95% CI -2.43, -1.12, p<0.0001 Wilcoxon rank-sum test) for quarterly fremanezumab and -2.3

medication days (95% CI -2.97, -1.67, p<0.0001 Wilcoxon rank-sum test) for monthly fremanezumab. The MMRM sensitivity analysis supported the above results, with a significantly greater reduction for fremanezumab (both dosing regimens) compared to placebo (p<0.0001 for both dosing regimens). These results show that fremanezumab is able to reduce medication usage in patients with migraine to a significant degree.

B 2.6.1.2.f) Quality of life measures

A number of HRQoL measures were investigated in the two HALO trials, and results from the 6-item Headache Impact Test (HIT-6) and MSQoL will be presented here.

Fremanezumab (in both dosing regimens) reduced the average HIT-6 score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment (p=0.0004 and p<0.0001 for quarterly and monthly fremanezumab, respectively). Placebo treatment provided a median change from baseline of -4.0 (IQR -7.0, 0.0; mean change -4.5, 95% CI -5.38, -3.60). In comparison, the median overall change from baseline for quarterly fremanezumab was -5.0 (IQR -10.0, -2.0; mean change -6.4, 95% CI -7.31, -5.52); and for monthly fremanezumab was -6.0 (IQR -11.0, -2.0; mean change -6.8, 95% CI -7.71, -5.97). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -1.9 (95% CI -2.90, -0.96, p=0.0004 Wilcoxon rank-sum test) for quarterly fremanezumab and -2.4 (95% CI -3.32, -1.38, p<0.0001 Wilcoxon rank-sum test) for monthly fremanezumab.

Analysis of the mean change from baseline in the MSQoL scores at four weeks after final dose showed differences from placebo in favour of fremanezumab for all three domains (role function – restrictive, role function – preventive and emotional state). The LSM differences with placebo for role function – restrictive domain were 6.1 and 6.9 for quarterly and monthly fremanezumab, respectively (p<0.0001).

B 2.6.1.2.g) Other outcomes

Further outcomes in the HALO CM trial investigated other aspects of disease impact and severity and results for relevant outcomes are summarised below.

Mean change from baseline in monthly average number of headache hours of any severity during the 12-week trial period showed a significant difference from placebo

in favour of fremanezumab (p=0.0003 and p<0.0001 for quarterly and monthly fremanezumab, respectively). The LSM difference *versus* placebo was -13.7 headache hours (95% CI -21.10, -6.31, p=0.0003) for quarterly fremanezumab and -18.6 headache hours (95% CI -25.96, -11.17, p<0.0001) for monthly fremanezumab. When headache hours of at least moderate severity were considered, fremanezumab demonstrated similar relative efficacy; the LSM difference *versus* placebo was -10.3 headache hours for quarterly fremanezumab (p=0.0001) and -12.3 headache hours for monthly fremanezumab (p<0.0001).

B 2.6.2 FOCUS trial

The FOCUS trial was designed and conducted as a single trial that covered both chronic and episodic migraine. Results for the FOCUS trial were reported separately for both chronic and episodic migraine populations, but its primary outcomes were reported in the overall migraine population and so these will be summarised first.

All efficacy outcomes were assessed in the modified intention to treat cohort (mITT), which included 278 patients who received placebo, 276 who received the quarterly dose of fremanezumab and 283 who received the monthly dose of fremanezumab. A summary of the key efficacy results are included below in Table 17, which shows that fremanezumab (in both dosing regimens) was significantly more effective than placebo treatment (p≤0.0002) in all areas.

Table 17 Summary of main efficacy outcomes in FOCUS clinical trial

	Placebo (n=278)	**Fremanezumab quarterly (n=276)**	**Fremanezumab monthly (n=283)**
Mean monthly migraine days			
Baseline (SD)	14.3 (6.1)	14.1 (5.6)	14.1 (5.6)
LSM change (95% CI)	-0.6 (-1.25 to 0.07)	-3.7 (-4.38 to -3.05)	-4.1 (-4.73 to -3.41)
Difference *vs* placebo (95% CI)		-3.1 (-3.84 to -2.42)	-3.5 (-4.19 to -2.78)
P-value *vs* placebo		<0.0001	<0.0001
Patients with at least 50% reduction in monthly average migraine days			
Number achieving endpoint (%)	24 (8.6%)	95 (34.4%)	97 (34.3%)
Odds ratio *vs* placebo (95% CI)		5.84 (3.57 to 9.55)	5.82 (3.56 to 9.51)

	Placebo (n=278)	Fremanezumab quarterly (n=276)	Fremanezumab monthly (n=283)
P-value *vs* placebo		<0.0001	<0.0001
Mean monthly days of use of any acute headache medication			
Baseline (SD)	12.3 (6.3)	12.8 (6.2)	12.2 (6.0)
LSM change (95% CI)	-0.6 (-1.21 to 0.04)	-3.7 (-4.30 to -3.03)	-3.9 (-4.58 to -3.32)
Difference *vs* placebo (95% CI)		-3.1 (-3.75 to -2.41)	-3.4 (-4.03 to -2.69)
P-value *vs* placebo		<0.0001	<0.0001
Migraine Disability Assessment score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	-7.0 (-13.39 to -0.66)	-19.7 (-26.19 to -13.30)	-24.7 (-31.09 to -18.38)
Difference *vs* placebo (95% CI)		-12.7 (-19.48 to -5.95)	-17.7 (-24.45 to -10.97)
P-value *vs* placebo		0.0002	<0.0001
Headache Impact Test score			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	-2.2 (-3.31 to -1.17)	-5.2 (-6.29 to -4.13)	-6.1 (-7.12 to -4.99)
Difference *vs* placebo (95% CI)		-3.0 (-4.10 to -1.83)	-3.8 (-4.95 to -2.69)
P-value *vs* placebo		<0.0001	<0.0001

B 2.6.2.1 Mean change in monthly average number of migraine days (primary endpoint)

Fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 (p<0.0001 for both dosing regimens). Placebo treatment provided a mean change of -0.6 monthly migraine days (95% CI -1.25, 0.07). In comparison, the mean overall change from baseline for quarterly fremanezumab was -3.7 migraine days (95% CI -4.38, -3.05); and for monthly fremanezumab was -4.1 migraine days (95% CI -4.73, -3.41). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -3.1 migraine days

(95% CI -3.84, -2.42, p<0.0001) for quarterly fremanezumab and -3.5 migraine days (95% CI -4.19, -2.78, p<0.0001) for monthly fremanezumab.

The MMRM analysis of the treatment effect supported the above results, with a LSM difference *versus* placebo of -3.1 migraine days (95% CI -3.84, -2.42, p<0.0001) for quarterly fremanezumab and -3.5 migraine days (95% CI -4.17, -2.77, p<0.0001) for monthly fremanezumab.

The results of the primary outcome demonstrate the efficacy of fremanezumab and its ability to reduce the number of migraine days experienced by patients who have had at least two previous preventive treatment failures. Further confidence in these results can be taken from the fact that the two separate analysis techniques used produced overall results for the treatment effect that were similar.

B 2.6.2.2 Patients with at least 50% reduction in monthly average number of migraine days

The proportion of patients who achieved a reduction of at least 50% in average monthly migraine days was investigated as a secondary outcome. It was found that significantly more patients experienced a reduction of at least 50% in the average monthly number of migraine days with fremanezumab compared to placebo treatment (Table 18, p<0.0001 for both dosing regimens). Overall, 95 patients (34.4%) treated with quarterly fremanezumab and 97 patients (34.3%) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compares to 24 patients (8.6%) in the placebo group. Analysis through the trial period demonstrated that fremanezumab resulted in a higher proportion of patients reaching at least 50% reduction in monthly migraine days at months one, two, and three compared to placebo treatment.

Table 18 Proportion of patients with 50% or greater reduction in average monthly migraine days

Time point statistic	Placebo (n=278) N (%)	Fremanezumab quarterly (n=276) N (%)	p-value quarterly *vs* placebo	Fremanezumab monthly (n=283) N (%)	p-value monthly *vs* placebo
Month 1	28 (10.1)	105 (38.0)	<0.0001	101 (35.7)	<0.0001
Month 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	24 (8.6)	95 (34.4)	<0.0001	97 (34.3)	<0.0001

B 2.6.2.3 Mean change in weekly average number of migraine days over first month of treatment

The reduction in weekly number of migraine days over the first month of treatment helps to show the speed of onset of treatment effect with fremanezumab. These results (Figure 4) demonstrate that there was a statistically significant difference between placebo and fremanezumab from the first time point of one week ($p<0.0001$ for both dosing regimens). This efficacy is maintained throughout the first month ($p<0.0001$ for both dosing regimens at all time points).

Figure 4 Change in weekly migraine days over time (MMRM analysis)

*[redacted] *vs* placebo

B 2.6.2.4 Mean change in monthly average number of days of use of any acute headache medication

Fremanezumab (in both dosing regimens) reduced the average monthly number of days with acute headache medication use to a significantly greater degree than was seen with placebo treatment ($p<0.0001$ for both dosing regimens). Placebo

treatment provided a mean change of -0.6 days with acute headache medication use (95% CI -1.21, 0.04). In comparison, the mean overall change from baseline for quarterly fremanezumab was -3.7 medication days (95% CI -4.30, -3.03); and for monthly fremanezumab was -3.9 medication days (95% CI -4.58, -3.32). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -3.1 medication days (95% CI -3.75, -2.41, p<0.0001) for quarterly fremanezumab and -3.4 medication days (95% CI -4.03, -2.69, p<0.0001) for monthly fremanezumab. The MMRM sensitivity analysis supported the above results, with a LSM difference *versus* placebo of [redacted] medication days (95% CI [redacted]) for quarterly fremanezumab and [redacted] medication days (95% CI [redacted]) for monthly fremanezumab.

B 2.6.2.5 QOL measures

A number of HRQoL measures were investigated in the FOCUS trial, and results from the MIDAS, HIT-6 and MSQoL will be presented here.

Fremanezumab (in both dosing regimens) reduced the average MIDAS score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment (p=0.0002 and p<0.0001 for quarterly and monthly fremanezumab, respectively). Placebo treatment provided a mean change of -7.0 (95% CI -13.39, -0.66). In comparison, the mean overall change from baseline for quarterly fremanezumab was -19.7 (95% CI -26.19, -13.30); and for monthly fremanezumab was -24.7 (95% CI -31.09, -18.38). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -12.7 (95% CI -19.48, -5.95, p=0.0002) for quarterly fremanezumab and -17.7 (95% CI -24.45, -10.97, p<0.0001) for monthly fremanezumab.

Fremanezumab (in both dosing regimens) reduced the average HIT-6 score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment (p<0.0001 for both dosing regimens). Placebo treatment provided a mean change from baseline of -2.2 (95% CI -3.31, -1.17). In comparison, the mean overall change from baseline for quarterly fremanezumab was -5.2 (95% CI -6.29, -4.13); and for monthly fremanezumab was -6.1 (95% CI -7.12, -4.99). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -3.0 (95% CI -4.10, -

1.83, p<0.0001) for quarterly fremanezumab and -3.8 (95% CI -4.95, -2.69, p<0.0001) for monthly fremanezumab.

Analysis of the mean change from baseline in the MSQoL scores at four weeks after final dose showed differences from placebo in favour of fremanezumab for all three domains (role function – restrictive, role function – preventive and emotional state, p<0.0001), see Table 19 for full results. The LSM differences with placebo for role function – restrictive domain were [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 19 MSQoL results from FOCUS trial

	Placebo (n=278)	**Fremanezumab quarterly (n=276)**	**Fremanezumab monthly (n=283)**
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]
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]
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]

B 2.6.2.5.a) Other outcomes

Further outcomes in the FOCUS trial investigated other aspects of disease impact and severity and results for relevant outcomes are summarised below.

Mean change in monthly average number of headache days of at least moderate severity during the 12-week trial period showed a significant difference from placebo in favour of fremanezumab (p<0.0001 for both dosing regimens). The LSM difference *versus* placebo was -3.2 headache days (95% CI -3.93, -2.52, p<0.0001) for quarterly fremanezumab and -3.6 headache days (95% CI -4.30, -2.91, p<0.0001) for monthly fremanezumab.

Mean change in monthly average number of headache hours of at least moderate severity during the 12-week trial period showed a significant difference from placebo in favour of fremanezumab (p<0.0001 for both dosing regimens). The LSM difference *versus* placebo was -14.4 headache hours (95% CI -20.93, -7.89, p<0.0001) for quarterly fremanezumab and -16.6 headache hours (95% CI -23.07, -10.08, p<0.0001) for monthly fremanezumab.

B 2.6.3 Long-term efficacy data from HALO extension

Patients who completed the HALO trials were eligible to participate in a multicentre, randomised, double-blind, parallel-group extension to evaluate the long-term efficacy of fremanezumab over 12 months. In addition, a group of new patients were recruited for this extension following the same eligibility criteria as used in the main study. Patients who participated in the original double-blind, placebo-controlled trials and who received fremanezumab continued on the same dosing schedule; while placebo patients and new patients were randomly assigned to either monthly or quarterly fremanezumab (monthly fremanezumab in CM used a 675mg loading dose, as was used in the main trial). There was no placebo group within this extension, but patients were blinded as to the dosing schedule of fremanezumab that they were receiving. The same clinical measures of efficacy were used in this extension as were used within the main trial and are defined in the same manner.

There were [redacted] patients with EM and [redacted] patients with CM who rolled over from the main HALO trials, with [redacted] new patients recruited ([redacted] with EM and [redacted] with CM); and there were [redacted] screening failures. This gave a total population of [redacted] patients who were randomised or rolled over into this study. Within the patients with EM, there were [redacted] who were received quarterly fremanezumab and [redacted] who received monthly fremanezumab. Within the patients with CM, there were [redacted] who

were received quarterly fremanezumab and [redacted] who received monthly fremanezumab. All patients randomised received at least one dose of study drug and were included in the safety analysis population; except for [redacted] who did not receive a dose of study drug. The FAS (patients who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessments) included [redacted] patients with EM receiving quarterly fremanezumab, [redacted] patients with EM receiving monthly fremanezumab, [redacted] patients with CM receiving quarterly fremanezumab, and [redacted] patients with CM receiving monthly fremanezumab. There were a total of [redacted] patients ([redacted]) who discontinued from the study for all causes. The baseline characteristics of these patients are summarised in Appendix M.

As there was no placebo arm to evaluate the relative efficacy, the results are presented as the mean changes compared to baseline. Efficacy results are presented in the FAS, and are presented based on the timeframes of this extension study, *i.e.* active rollover patients have already received 12 weeks of treatment during the main trial. Therefore efficacy data for these patients at month one is after four months of treatment, at month 3 is at six months of treatment and at month 12 is after 15 months of treatment.

B 2.6.3.1 Episodic migraine

A summary of the key efficacy results within patients with EM are included below in Table 20. These results demonstrate that for the key measure of monthly migraine days, the newly treated patients achieved a response in the first month of treatment similar in magnitude to that seen in the rollover patients (who had already received three months of treatment at this point). The reduction in migraine days was then maintained throughout the duration of the extension trial, with no evidence of any waning in treatment effect or any difference in efficacy between the dosing regimens of fremanezumab. Similar results were also seen in other efficacy outcomes, with a relatively consistent proportion of patients showing at least a 50% reduction in mean migraine days at each time point. Overall, these results provide evidence of the efficacy of fremanezumab for up to 15 months of treatment.

Table 20 Summary of main efficacy outcomes in HALO clinical trial extension for EM

	Fremanezumab quarterly		Fremanezumab monthly	
	Newly treated patients (n=[redacted])	Active rollover patients (n=[redacted])	Newly treated patients (n=[redacted])	Active rollover patients (n=[redacted])
Mean monthly migraine days				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean headache days of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least a 50% reduction in monthly migraine days				
Number in month 1 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 3 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 6 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 12 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean monthly days of use of any acute headache medication				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

	Fremanezumab quarterly		Fremanezumab monthly	
	Newly treated patients (n=[redacted])	**Active rollover patients (n=[redacted])**	**Newly treated patients (n=[redacted])**	**Active rollover patients (n=[redacted])**
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Headache hours of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

B 2.6.3.2 Chronic migraine

A summary of the key efficacy results within patients with CM are included below in Table 21. These results demonstrate that for the key measure of monthly migraine days, the newly treated patients achieved a response in the first month of treatment similar in magnitude to that seen in the rollover patients (who had already received three months of treatment at this point). The reduction in migraine days was then maintained throughout the duration of the extension trial, with no evidence of any waning in treatment effect or any difference in efficacy between the dosing regimens of fremanezumab. Similar results were also seen in other efficacy outcomes, with a relatively consistent proportion of patients showing at least a 50% reduction in mean migraine days at each time point. Overall, these results provide evidence of the efficacy of fremanezumab for up to 15 months of treatment.

Table 21 Summary of main efficacy outcomes in HALO clinical trial extension for CM

	Fremanezumab quarterly		Fremanezumab monthly	
	Newly treated patients (n=[redacted])	**Active rollover patients (n=[redacted])**	**Newly treated patients (n=[redacted])**	**Active rollover patients (n=[redacted])**
Mean monthly migraine days				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean headache days of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least a 50% reduction in monthly migraine days				
Number in month 1 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 3 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 6 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 12 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean monthly days of use of any acute headache medication				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

	Fremanezumab quarterly		Fremanezumab monthly	
	Newly treated patients (n=[redacted])	**Active rollover patients (n=[redacted])**	**Newly treated patients (n=[redacted])**	**Active rollover patients (n=[redacted])**
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Headache hours of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

B 2.7 Subgroup analysis

The HALO clinical trials included the following predefined subgroup analyses: patients receiving or not receiving concomitant preventive treatment; patients with or without past topiramate use for migraine; patients with or without past onabotulinumtoxin A use for migraine; age (18-45 years; >45 years); race (Caucasian; non-Caucasian); sex. A summary of results from these subgroups is included in Appendix E.

The FOCUS trial included the following predefined subgroup analyses: special treatment failure group (patients with inadequate response to valproic acid plus two to three other migraine preventive medications); valproic acid failure (yes; no); age (18-45 years; >45 years); sex; region (North America; Europe). A summary of results from these subgroups is included in Appendix E.

The FOCUS trial also included a predefined subgroup analysis based on migraine classification (CM or EM). The results of this analysis are summarised below and demonstrate that fremanezumab has comparable efficacy in both CM and EM patient populations.

B 2.7.1 Episodic migraine

Baseline characteristics of the patients with EM within the FOCUS trial are summarised in Appendix M. Efficacy outcomes were assessed in this group which included 111 patients who received placebo, 107 who received the quarterly dose of fremanezumab and 110 who received the monthly dose of fremanezumab.

The results for EM (Table 22) show that fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ($p<0.0001$ for both dosing regimens). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -3.1 migraine days (95% CI -3.93, -2.19, $p<0.0001$) for quarterly fremanezumab and -3.1 migraine days (95% CI -4.00, -2.25, $p<0.0001$) for monthly fremanezumab. The MMRM analysis supported the above results, with a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]

[redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. Similar results were also seen for changes in mean headache days of at least moderate severity.

A significantly greater proportion of patients experienced a reduction of at least 50% in the average monthly number of migraine days with fremanezumab compared to placebo treatment ([redacted] for both dosing regimens). Overall, [redacted] patients ([redacted]) treated with quarterly fremanezumab and [redacted] patients ([redacted]) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compares to [redacted] patients ([redacted]) in the placebo group. Within these patients with at least a 50% response, fremanezumab was able to provide a mean change in monthly migraine days of [redacted] for quarterly dosing and [redacted] for monthly dosing compared to baseline, with mean monthly migraine days at 12 weeks after baseline of [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 22 Summary of main efficacy outcomes for patients with episodic migraine in FOCUS clinical trial

	Placebo (n=111)	**Fremanezumab quarterly (n=107)**	**Fremanezumab monthly (n=110)**
Mean monthly migraine days			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	-0.7 (-1.50 to 0.19)	-3.7 (-4.59 to -2.84)	-3.8 (-4.66 to -2.90)
Difference *vs* placebo (95% CI)		-3.1 (-3.93 to -2.19)	-3.1 (-4.00 to -2.25)
P-value *vs* placebo		<0.0001	<0.0001
Patients with at least 50% 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]

B 2.7.2 High-frequency episodic migraine

Baseline characteristics of the patients with HFEM within the FOCUS trial are summarised in Appendix M. Efficacy outcomes were assessed in this group which included [redacted] patients who received placebo, [redacted] who received the quarterly dose of fremanezumab and [redacted] who received the monthly dose of fremanezumab.

For the purposes of this submission, HFEM has been defined as EM patients who have between eight and 14 monthly headache days. This is the subgroup of interest for this appraisal as the high frequency of headaches mean that the impact of the disease in this group can be as significant as for those patients with CM.[1]

The results for HFEM (Table 23) show that fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ([redacted] for both dosing regimens). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. The MMRM analysis supported the above results, with a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab.

A significantly greater proportion of patients experienced a reduction of at least 50% in the average monthly number of migraine days with fremanezumab compared to placebo treatment ([redacted] for dosing regimens). Overall, [redacted] patients ([redacted]) treated with quarterly fremanezumab and [redacted] patients ([redacted]) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compares to [redacted] patients ([redacted]) in the placebo group. In these patients with at least a 50% response, fremanezumab was able to provide a mean change in monthly migraine days of [redacted] for quarterly dosing and [redacted] for monthly dosing compared to baseline; monthly migraine days at 12 weeks after baseline were [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 23 Summary of main efficacy outcomes for patients with high-frequency episodic migraine 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 50% 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]

B 2.7.3 Chronic migraine

Baseline characteristics of the patients with CM within the FOCUS trial are summarised in Appendix M. Efficacy outcomes were assessed in this group which included 167 patients who received placebo, 169 who received the quarterly dose of fremanezumab and 173 who received the monthly dose of fremanezumab.

The results for CM (Table 24) show that fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ($p<0.0001$ for both dosing regimens). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of -3.2 migraine days (95% CI -4.16, -2.18, $p<0.0001$) for quarterly fremanezumab and -3.8 migraine days (95% CI -4.76, -2.80, $p<0.0001$) for monthly fremanezumab. The MMRM analysis supported the above results, with a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. Similar results were also seen for changes in mean headache days of at least moderate severity.

A significantly greater proportion of patients experienced a reduction of at least 30% in the average monthly number of migraine days with fremanezumab compared to placebo treatment ([redacted] for dosing regimens). Overall, [redacted] patients ([redacted]) treated with quarterly fremanezumab and [redacted] patients ([redacted]) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compares to [redacted] patients ([redacted]) in the placebo group. In these patients with at least a 30% response, fremanezumab was able to provide a mean change in monthly migraine days of [redacted] for quarterly dosing and [redacted] for monthly dosing compared to baseline; with monthly migraine days at 12 weeks after baseline of [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 24 Summary of main efficacy outcomes for patients with chronic migraine in FOCUS clinical trial

	Placebo (n=167)	**Fremanezumab quarterly (n=169)**	**Fremanezumab monthly (n=173)**
Mean monthly migraine days			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	-0.7 (-1.64 to 0.20)	-3.9 (-4.79 to -2.99)	-4.5 (-5.39 to -3.61)
Difference *vs* placebo (95% CI)		-3.2 (-4.16 to -2.18)	-3.8 (-4.76 to -2.80)
P-value *vs* placebo		<0.0001	<0.0001
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]

B 2.7.4 Patients who have failed three or more classes of preventive migraine treatment

The main subgroup of interest is patients who have failed three or more prior preventive migraine treatments as these patients are the focus of this submission. Therefore, the efficacy in this group of patients is highly relevant.

The FOCUS trial defined treatment failure by class of treatment and not simply by number of treatments, *i.e.* patients could not have just failed three different beta blockers. In theory, this makes the study design more robust and more in line with UK clinical practice and guidelines, *e.g.* NICE guidelines (Headaches in over 12s: diagnosis and management [CG150]). In practice, [redacted]. All results presented here are based on the FOCUS defined criteria of classes of treatments split by type of migraine (EM/HFEM or CM).

B 2.7.4.1 Episodic migraine

Baseline characteristics of the patients with EM who have failed three or more classes of preventive therapy within the FOCUS trial are summarised in Appendix M. Baseline characteristics were similar between groups. Efficacy outcomes were assessed in this group which included [redacted] patients who received placebo, [redacted] who received the quarterly dose of fremanezumab and [redacted] who received the monthly dose of fremanezumab.

The results for EM (Table 25) show that fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ([redacted] for both dosing regimens). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]

[redacted]) for monthly fremanezumab. The MMRM analysis supported the above results, with a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. Similar results were also seen for changes in mean headache days of at least moderate severity.

A significantly greater proportion of patients experienced a reduction of at least 50% in the average monthly number of migraine days with fremanezumab compared to placebo treatment ([redacted] for quarterly and monthly fremanezumab, respectively). Overall, [redacted] patients ([redacted]) treated with quarterly fremanezumab and [redacted] patients ([redacted]) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compares to [redacted] patients ([redacted]) in the placebo group. Within these patients with at least a 50% response, fremanezumab was able to provide a mean change in monthly migraine days of [redacted] for quarterly dosing and [redacted] for monthly dosing compared to baseline, with mean monthly migraine days at 12 weeks after baseline of [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 25 Summary of main efficacy outcomes for patients with episodic migraine who have failed three or more classes of preventive therapy 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 50% 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]

	Placebo (n=[redacted])	Fremanezumab quarterly (n=[redacted])	Fremanezumab monthly (n=[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]
Mean monthly headache hours 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]

Further outcomes within this patient group were also investigated. Fremanezumab (in both dosing regimens) reduced the average monthly number of days with acute headache medication use to a significantly greater degree than was seen with placebo treatment ([redacted] for both dosing regimens). The LSM difference *versus* placebo was [redacted] medication days (95% CI [redacted]) for quarterly fremanezumab and [redacted] medication days (95% CI [redacted]) for monthly fremanezumab.

Mean change from baseline in monthly average number of headache hours of at least moderate severity during the 12-week trial period showed a significant difference from placebo in favour of fremanezumab ([redacted] for both dosing regimens). The LSM difference *versus* placebo was [redacted] headache hours (95% CI [redacted]) for quarterly fremanezumab and [redacted] headache hours (95% CI [redacted]) for monthly fremanezumab.

Results from the change in weekly migraine days over the first month of therapy demonstrate that there was a statistically significant difference between placebo and fremanezumab from the first time point of one week ([redacted] and [redacted] for quarterly and monthly fremanezumab, respectively). At this time point there was a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. This efficacy was maintained throughout the first month ([redacted] for both dosing regimens at all time points).

These results demonstrate that fremanezumab is an effective treatment in patients with EM who have failed three or more preventive therapies. The treatment effect is comparable in size to that seen within the overall EM population of the FOCUS trial.

B 2.7.4.1.a) Quality of life outcomes

Fremanezumab (in both dosing regimens) reduced the average MIDAS score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment ([redacted] for both dosing regimens). Placebo treatment provided a mean change of [redacted] (95% CI [redacted]). In comparison, the mean overall change from baseline for quarterly fremanezumab was [redacted] (95% CI [redacted]); and for monthly fremanezumab was [redacted] (95% CI [redacted]). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] (95% CI [redacted]) for quarterly fremanezumab and [redacted] (95% CI [redacted]) for monthly fremanezumab.

Fremanezumab (in both dosing regimens) reduced the average HIT-6 score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment ([redacted] for quarterly and monthly fremanezumab, respectively). Placebo treatment provided a mean change of [redacted] (95% CI [redacted]). In comparison, the mean overall change from baseline for quarterly fremanezumab was [redacted] (95% CI [redacted]); and for monthly fremanezumab was [redacted] (95% CI [redacted]). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] (95% CI [redacted]) for quarterly fremanezumab and [redacted] (95% CI [redacted]) for monthly fremanezumab.

Analysis of the mean change from baseline in the MSQoL scores at four weeks after final dose showed differences from placebo in favour of fremanezumab for all three domains (role function – restrictive, role function – preventive and emotional state, [redacted]), see Table 26 for full results. The LSM differences with placebo for role function – restrictive domain were [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 26 Quality of life results for patients with episodic migraine who have failed three or more classes of preventive therapy in FOCUS clinical trial

	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]
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]
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]
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]

	Placebo (n=[redacted])	Fremanezumab quarterly (n=[redacted])	Fremanezumab monthly (n=[redacted])
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]

B 2.7.4.2 High-frequency episodic migraine

Baseline characteristics of the patients with HFEM who have failed three or more classes of preventive therapy within the FOCUS trial are summarised in Appendix M. Efficacy outcomes were assessed in this group which included [redacted] patients who received placebo, [redacted] who received the quarterly dose of fremanezumab and [redacted] who received the monthly dose of fremanezumab.

The results for HFEM (Table 27) show that fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ([redacted] for both dosing regimens). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. The MMRM analysis supported the above results, with a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. Similar results were also seen for changes in mean headache days of at least moderate severity.

A significantly greater proportion of patients experienced a reduction of at least 50% in the average monthly number of migraine days with fremanezumab compared to placebo treatment ([redacted] for quarterly and monthly fremanezumab, respectively). Overall, [redacted] patients ([redacted]) treated with quarterly fremanezumab and [redacted] patients ([redacted]) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compared to [redacted] patients

([redacted]) in the placebo group. Within these patients with at least a 50% response, fremanezumab was able to provide a mean change in monthly migraine days of [redacted] for quarterly dosing and [redacted] for monthly dosing compared to baseline, with monthly migraine days at 12 weeks after baseline of [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 27 Summary of main efficacy outcomes for patients with high-frequency episodic migraine who have failed three or more classes of preventive therapy 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 50% 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])**
Mean monthly headache hours 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]

Further outcomes within this patient group were also investigated. Fremanezumab (in both dosing regimens) reduced the average monthly number of days with acute headache medication use to a significantly greater degree than was seen with placebo treatment ([redacted] for both dosing regimens). The LSM difference *versus* placebo was [redacted] medication days (95% CI [redacted]) for quarterly fremanezumab and [redacted] medication days (95% CI [redacted]) for monthly fremanezumab.

Mean change from baseline in monthly average number of headache hours of at least moderate severity during the 12-week trial period showed a significant difference from placebo in favour of fremanezumab ([redacted] for both dosing regimens). The LSM difference *versus* placebo was [redacted] headache hours (95% CI [redacted]) for quarterly fremanezumab and [redacted] headache hours (95% CI [redacted]) for monthly fremanezumab.

Results from the change in weekly migraine days over the first month of therapy demonstrate that there was a statistically significant difference between placebo and fremanezumab from the first time point of one week ([redacted] and [redacted] for quarterly and monthly fremanezumab, respectively). At this time point there was a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. This efficacy is maintained throughout the first month ([redacted] for both dosing regimens at all time points).

These results demonstrate that fremanezumab is an effective treatment in patients with HFEM who have failed three or more preventive therapies. The treatment effect is comparable in size to that seen within the overall EM population of the FOCUS trial.

B 2.7.4.2.a) Quality of life outcomes

Fremanezumab (in both dosing regimens) reduced the average MIDAS score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment (for quarterly and monthly fremanezumab, respectively). Placebo treatment provided a mean change from baseline of (95% CI). In comparison, the mean overall change from baseline for quarterly fremanezumab was (95% CI); and for monthly fremanezumab was (95% CI). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of (95% CI) for quarterly fremanezumab and (95% CI) for monthly fremanezumab.

Fremanezumab (in both dosing regimens) reduced the average HIT-6 score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment (for quarterly and monthly fremanezumab, respectively). Placebo treatment provided a mean change of (95% CI). In comparison, the mean overall change from baseline for quarterly fremanezumab was (95% CI); and for monthly fremanezumab was (95% CI). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of (95% CI) for quarterly fremanezumab and (95% CI) for monthly fremanezumab.

Analysis of the mean change from baseline in the MSQoL scores at four weeks after final dose showed differences from placebo in favour of fremanezumab for all three domains (role function – restrictive, role function – preventive and emotional state,); see Table 28 for full results. The LSM differences with placebo for role function – restrictive domain were and for quarterly and monthly fremanezumab, respectively.

Table 28 Quality of life results for patients with high-frequency episodic migraine who have failed three or more classes of preventive therapy in FOCUS clinical trial

	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]
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]
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]
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]
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]

B 2.7.4.3 Chronic migraine

Baseline characteristics of the patients with CM who have failed three or more classes of preventive therapy within the FOCUS trial are summarised in Appendix M. Efficacy outcomes were assessed in this group that included [redacted] patients who received placebo, [redacted] who received the quarterly dose of fremanezumab and [redacted] who received the monthly dose of fremanezumab.

The results for CM (Table 29) show that fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ([redacted] for both dosing regimens). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. The MMRM analysis supported the above results, with a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab.

A significantly greater proportion of patients experienced a reduction of at least 30% in the average monthly number of migraine days with fremanezumab compared to placebo treatment ([redacted] for dosing regimens). Overall, [redacted] patients ([redacted]) treated with quarterly fremanezumab and [redacted] patients ([redacted]) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compares to [redacted] patients ([redacted]) in the placebo group. In these patients with at least a 30% response, fremanezumab was able to provide a mean change in monthly migraine days of [redacted] for quarterly dosing and [redacted] for monthly dosing compared to baseline, with monthly migraine days at 12 weeks after baseline of [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 29 Summary of main efficacy outcomes for patients with chronic migraine who have failed three or more classes of preventive therapy 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]
Mean monthly headache hours 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]

Further outcomes within this patient group were also investigated. Fremanezumab reduced the average monthly number of days with acute headache medication use to a significantly greater degree than was seen with placebo treatment ([redacted]

for both dosing regimens). The LSM difference *versus* placebo was [redacted] medication days (95% CI [redacted]) for quarterly fremanezumab and [redacted] medication days (95% CI [redacted]) for monthly fremanezumab.

Mean change in monthly average number of headache hours of at least moderate severity during the 12-week trial period showed a significant difference from placebo in favour of fremanezumab ([redacted] for quarterly and monthly fremanezumab, respectively). The LSM difference *versus* placebo was [redacted] headache hours (95% CI [redacted]) for quarterly fremanezumab and [redacted] headache hours (95% CI [redacted]) for monthly fremanezumab.

Results from the change in weekly migraine days over the first month of therapy demonstrate that there was a statistically significant difference between placebo and fremanezumab from the first time point of one week ([redacted] for quarterly and monthly fremanezumab, respectively). At this time point there was a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab. This efficacy is maintained throughout the first month ([redacted] for both dosing regimens at all time points, except week 2 for monthly dosing [[redacted]]).

These results demonstrate that fremanezumab is an effective treatment in patients with CM who have failed three or more preventive therapies. The treatment effect is comparable in size to that seen within the overall CM population of the FOCUS trial.

B 2.7.4.3.a) Quality of life outcomes

Fremanezumab (in both dosing regimens) reduced the average MIDAS score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment ([redacted] for quarterly and monthly fremanezumab, respectively). Placebo treatment provided a mean change of [redacted] (95% CI [redacted]). In comparison, the mean overall change from baseline for quarterly fremanezumab was [redacted] (95% CI [redacted]); and for monthly fremanezumab was [redacted] (95% CI [redacted]). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] (95% CI [redacted])

for quarterly fremanezumab and [redacted] (95% CI [redacted]) for monthly fremanezumab.

Fremanezumab (in both dosing regimens) reduced the average HIT-6 score (at four weeks after final dose) to a significantly greater degree than was seen with placebo treatment ([redacted] for quarterly and monthly fremanezumab, respectively). Placebo treatment provided a mean change of [redacted] (95% CI [redacted]). In comparison, the mean overall change from baseline for quarterly fremanezumab was [redacted] (95% CI [redacted]); and for monthly fremanezumab was [redacted] (95% CI [redacted]). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] (95% CI [redacted]) for quarterly fremanezumab and [redacted] (95% CI [redacted]) for monthly fremanezumab.

Analysis of the mean change from baseline in the MSQoL scores at four weeks after final dose showed differences from placebo in favour of fremanezumab for all three domains (role function – restrictive, role function – preventive and emotional state, [redacted], see Table 30 for full results. The LSM differences with placebo for role function – restrictive domain were [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table 30 Quality of life results for patients with chronic migraine who have failed three or more classes of preventive therapy in FOCUS clinical trial

	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]

	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]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
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]
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]
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]

B 2.8 Meta-analysis

No meta-analysis of the fremanezumab results presented in the previous sections have been conducted. This is because the trials presented have investigated the efficacy of fremanezumab in different patient populations. The HALO trials focussed on EM and CM separately, whilst the FOCUS trial investigated patients who had failed on two to four classes of previous migraine preventive therapy in both EM and CM. Therefore, any comparison pooling these results is not appropriate and would not yield any meaningful results.

B 2.9 Indirect and mixed treatment comparisons

A network meta-analysis (NMA) was conducted to compare relevant treatments within the population of interest for this appraisal (patients who have failed three or more prior migraine preventive therapies). Full details on the methodology of this NMA are included within Appendix D. This analysis was done using Bayesian principles, and so results are presented alongside credible interval (CrI) values. The use of a Bayesian approach also means that direct statistical comparison between treatments is not possible and so a significant effect is assumed when the credible intervals do not cross. The results of this analysis are presented below for CM, and no indirect treatment comparison was conducted in EM as no relevant comparators with appropriate efficacy data were available.

B 2.9.1 Chronic migraine

In order to strength the network within the CM patient population, all available clinical data in a population who had failed on three or more previous preventive therapies was utilised. This allowed the inclusion of four clinical trials to inform the network, and therefore allowed the inclusion of fremanezumab, onabotulinumtoxin A and placebo as relevant treatments. Clinical data for erenumab was included in order to strengthen the network, but as this is not a comparator of interest for this appraisal, no results are reported. No appropriate clinical data was found to allow the inclusion of any other treatments within this NMA.

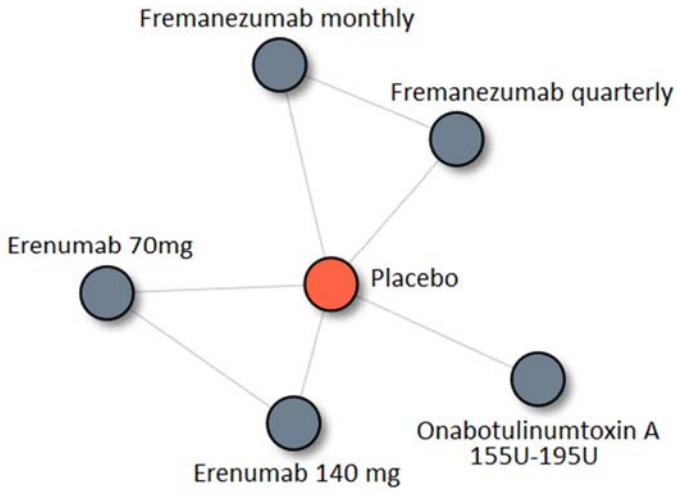
There were no active comparator studies identified and so all comparisons are made through the placebo arms. Table 31 summarises the trials included and the interventions within them, with the network diagram shown in Figure 5. No valid heterogeneity comparisons exist in these data and so a fixed effects model using a Bayesian approach was used. Two outcomes were analysed, the reduction in monthly migraine days and the proportion of patients with at least a 50% reduction in monthly migraine days. These outcomes were chosen as those where the best comparable evidence between treatments exists, and as these inputs were required for the economic model. At least a 30% reduction in monthly migraine days has been identified as a clinically relevant endpoint; however, there were not sufficient data available for this endpoint to be analysed in this NMA.

Table 31 Clinical trials included in network meta-analysis for chronic migraine

	FOCUS (NCT03308968)[61]	Study 295* (NCT02066415)[64]	PREEMPT I and II (NCT00156910, NCT00168428)[45,65,66]
Placebo	Yes	Yes	Yes
Fremanezumab monthly	Yes		
Fremanezumab quarterly	Yes		
Erenumab 70mg		Yes	
Erenumab 140mg		Yes	
Onabotulinumtoxin A 155U-195U			Yes

*Phase II study

Figure 5 Network diagram for network meta-analysis of chronic migraine



B 2.9.1.1 Monthly migraine days

The results for reductions in monthly migraine days are summarised in Figure 6, which shows the pairwise treatment effect *versus* placebo, and in Table 32, which shows the full NMA results. The results showed that whilst both investigated treatments were superior to placebo, fremanezumab (monthly) had a numerically greater treatment effect compared to onabotulinumtoxin A. [redacted]. The results suggest a higher probability of a greater reduction in monthly migraine days with fremanezumab than onabotulinumtoxin A.

Figure 6 NMA results for treatment effect *versus* placebo for monthly migraine days in chronic migraine

CrI: credible interval

Table 32 NMA results for monthly migraine days in chronic migraine

	Placebo	F monthly	F quarterly	O 155U-195U
Placebo				
Fremanezumab monthly				
Fremanezumab quarterly				
Onabotulinumtoxin A 155U-195U				

F: fremanezumab; O: onabotulinumtoxin A

B 2.9.1.2 Patients with at least 50% reduction in monthly average number of migraine days

The results for proportion of patients with at least 50% reduction in monthly migraine days are summarised in Figure 7, which shows the pairwise treatment effect *versus* placebo, and in Table 33, which shows the full NMA results. These results were used as the key efficacy input in the economic model. The results demonstrated that both investigated treatments were superior to placebo. However, fremanezumab had a numerically greater treatment effect compared to onabotulinumtoxin A. [redacted]. Overall, these results suggest a higher probability of response with fremanezumab than onabotulinumtoxin A.

Figure 7 NMA results for treatment effect *versus* placebo for at least a 50% reduction in monthly migraine days in chronic migraine

CrI: credible interval

Table 33 NMA results for at least a 50% reduction in monthly migraine days in chronic migraine

	Placebo	F monthly	F quarterly	O 155U-195U
Placebo				
Fremanezumab monthly				
Fremanezumab quarterly				
Onabotulinumtoxin A 155U-195U				

F: fremanezumab; O: onabotulinumtoxin A

B 2.9.2 Uncertainties in the indirect and mixed treatment comparisons

One of the main uncertainties in this NMA is the fact that no active controlled trials comparing migraine treatments have been conducted and that all comparisons are therefore made through the placebo arms of these trials. This allows no direct comparison between the comparative results produced by the model and any real-life data on the comparative efficacy of treatments. Another source of uncertainty is that none of the clinical trials for migraine preventive therapies have focussed on a patient population with three or more previous failed therapies. Therefore, all the data included within this NMA comes from subgroup analyses. Further assumptions have had to be made to ensure that all relevant data were included in this analysis, and these were:

- The results for onabotulinumtoxin A are reported at 24 weeks and not 12 weeks as was the case for fremanezumab and erenumab; therefore, it has been assumed that the efficacy was equivalent between these time points

- The results for response rates in onabotulinumtoxin A were reported as reduction in monthly headache days; this has been assumed to be equivalent to response in monthly migraine days. This is a conservative assumption, as a migraine day has a more strict definition and so it would be expected that the response rate based on migraine days would actually be lower

- The available published results for erenumab did not give full details in some areas, hence, it was assumed that sample sizes and time points are consistent between all outcomes.

Comparing the results *versus* placebo from the NMA to those of the clinical trials revealed no major disparities and therefore gives confidence in the results of this analysis.

B 2.10 Adverse reactions

The adverse reactions recorded during the clinical trials of fremanezumab will be detailed in the following sections. These results present the full data on adverse events within the full population of the fremanezumab clinical trials. Following this, a separate section details the adverse events recorded in the subgroup of interest for this appraisal (three or more previous failed migraine preventive treatments). There are no other studies identified that provide details on adverse reactions.

B 2.10.1 HALO EM

An overall summary of the adverse events (AEs) recorded in the full population of the HALO EM trial is presented in Table 34, with the associated relative risks and risk differences shown in Table 35. Overall, the results show that the fremanezumab groups had a slightly higher rate of adverse events (p=0.0476 and p=0.0511 for quarterly and monthly fremanezumab, respectively) and treatment related adverse events than the placebo group (p=0.0163 and p=0.0118 for quarterly and monthly fremanezumab, respectively). There were very few serious adverse events, with seven such events reported in the placebo group compared to three in each of the fremanezumab groups (p=0.2219 and p=0.2238 for quarterly and monthly fremanezumab, respectively). Importantly, there was no significant difference between treatment groups in patients discontinuing treatment due to adverse events, with five such instances in each treatment group (p=0.9921 and p=0.9882 for quarterly and monthly fremanezumab, respectively). There was one death recorded within the HALO EM trial, in the quarterly fremanezumab group, which was determined to not be related to the study medication. These results show that fremanezumab was generally a well-tolerated treatment with rates of serious AEs and discontinuation due to AEs that were comparable to placebo.

Table 34 Summary of adverse event numbers in HALO EM trial

	Placebo (n=293) N (%)	Fremanezumab quarterly (n=291) N (%)	Fremanezumab monthly (n=290) N (%)
Number of patients with at least one AE	171 (58.4)	193 (66.3)	192 (66.2)
Number of patients with at least one treatment-related AE	109 (37.2)	137 (47.1)	138 (47.6)
Number of patients with at least one SAE	7 (2.4)	3 (1.0)	3 (1.0)
Number of patients with at least one AE leading to study discontinuation	5 (1.7)	5 (1.7)	5 (1.7)
Number of patients with at least one protocol-defined AE of special interest*	1 (0.3)	1 (0.3)	3 (1.0)
Death	0 (0.0)	1 (0.3)	0 (0.0)

*Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions

Table 35 Relative risk and risk difference of adverse events in HALO EM trial

	Fremanezumab quarterly *versus* placebo		Fremanezumab monthly *versus* placebo	
	Relative risk (95% CI)	Relative difference (95% CI)	Relative risk (95% CI)	Relative difference (95% CI)
Number of patients with at least one AE	1.14 (1.00, 1.29)	0.08 (0.00, 0.16)	1.13 (1.00, 1.29)	0.08 (0.00, 0.16)
Number of patients with at least one treatment-related AE	1.27 (1.04, 1.53)	0.10 (0.02, 0.18)	1.28 (1.06, 1.55)	0.10 (0.02, 0.18)
Number of patients with at least one SAE	0.43 (0.11, 1.65)	-0.01 (-0.03, 0.01)	0.43 (0.11, 1.66)	-0.01 (-0.03, 0.01)
Number of patients with at least one AE leading to study discontinuation	1.01 (0.29, 3.44)	0.00 (-0.02, 0.02)	1.01 (0.30, 3.45)	0.00 (-0.02, 0.02)
Number of patients with at least one protocol-defined AE of special interest*	1.01 (0.06, 16.02)	0.00 (-0.01, 0.01)	3.03 (0.32, 28.97)	0.01 (-0.01, 0.02)

*Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions

Further details on the incidence of adverse events experienced by more than 2% in any treatment group are presented in Table 36, with the associated relative risks and risk differences shown in Appendix F. These data show that the most common adverse events were injection site reactions in all treatment groups. The only individual AE where there was a significant increase to the rate seen in placebo was injection site induration for monthly dosing of fremanezumab (p=0.0066). The other encountered AEs occurred in 5% or less of patients and there were no clear differences between the rates of these conditions between the placebo and active treatment groups.

Table 36 Incidence of adverse events within HALO EM trial

	Placebo (n=293) N (%)	**Fremanezumab quarterly (n=291) N (%)**	**Fremanezumab monthly (n=290) N (%)**
General disorders and administration site conditions*			
Injection site pain	76 (25.9)	86 (29.6)	87 (30.0)
Injection site induration	45 (15.4)	57 (19.6)	71 (24.5)
Injection site erythema	41 (14.0)	55 (18.9)	52 (17.9)
Injection site haemorrhage	6 (2.0)	9 (3.1)	3 (1.0)
Fatigue	4 (1.4)	6 (2.1)	2 (0.7)
Infections and infestations			
Upper respiratory tract infection	15 (5.1)	11 (3.8)	16 (5.5)
Nasopharyngitis	9 (3.1)	11 (3.8)	11 (3.8)
Urinary tract infection	4 (1.4)	10 (3.4)	7 (2.4)
Bronchitis	3 (1.0)	4 (1.4)	6 (2.1)
Sinusitis	8 (2.7)	2 (0.7)	4 (1.4)
Gastrointestinal disorders			
Nausea	5 (1.7)	7 (2.4)	4 (1.4)

* Injection site assessments were proactively performed immediately and one hour after administration of fremanezumab, as opposed to only spontaneous adverse event reporting of injection site reactions. If the patient had a severe injection site reaction at this point, the patient was reassessed at 3 hours after administration and hourly thereafter until the reaction/pain is of moderate or less severity.

Overall, these results demonstrate that fremanezumab is a well-tolerated treatment with a low rate of serious AEs. The main class of AEs encountered in this trial was injection site reactions, which in most cases were transient and not severe; all other

adverse events showed no significant differences in incidence between fremanezumab and placebo groups.

B 2.10.2 HALO CM

An overall summary of the AEs recorded in the full population of the HALO CM trial is presented in Table 37, with the associated relative risks and risk differences shown in Table 38. These figures show that the fremanezumab groups had a slightly higher rate of adverse events (p=0.0589 and p=0.0341 for quarterly and monthly fremanezumab, respectively) and treatment related adverse events than the placebo group (p=0.0524 and p=0.0161 for quarterly and monthly fremanezumab, respectively). However very few of these were serious adverse events, with six such events reported in the placebo group compared to three and five in the quarterly and monthly fremanezumab, respectively (p=0.3274 and p=0.7611 for quarterly and monthly fremanezumab, respectively). In addition, there was no significant difference between treatment groups in patients discontinuing treatment due to adverse events, with eight such instances in the placebo group compared to five and seven in the quarterly and monthly fremanezumab, respectively (p=0.4106 and p=0.7909 for quarterly and monthly fremanezumab, respectively). There was one death recorded within the HALO CM trial, in the quarterly fremanezumab group, which was determined to not be related to the study medication. These results show that fremanezumab was generally a well-tolerated treatment with rates of serious AEs and discontinuation due to AEs that were comparable to placebo.

Table 37 Summary of adverse event numbers in HALO CM trial

	Placebo (n=375) N (%)	**Fremanezumab quarterly (n=376) N (%)**	**Fremanezumab monthly (n=379) N (%)**
Number of patients with at least one AE	240 (64.0)	265 (70.5)	270 (71.2)
Number of patients with at least one treatment-related AE	159 (42.4)	186 (49.5)	194 (51.2)
Number of patients with at least one SAE	6 (1.6)	3 (0.8)	5 (1.3)
Number of patients with at least one AE leading to study discontinuation	8 (2.1)	5 (1.3)	7 (1.8)

	Placebo (n=375) N (%)	Fremanezumab quarterly (n=376) N (%)	Fremanezumab monthly (n=379) N (%)
Number of patients with at least one protocol-defined AE of special interest*	4 (1.1)	7 (1.9)	9 (2.4)
Death	0 (0.0)	1 (0.3)	0 (0.0)

*Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions

Table 38 Relative risk and risk difference of adverse events in HALO CM trial

	Fremanezumab quarterly *versus* placebo		Fremanezumab monthly *versus* placebo	
	Relative risk (95% CI)	Relative difference (95% CI)	Relative risk (95% CI)	Relative difference (95% CI)
Number of patients with at least one AE	1.10 (1.00, 1.22)	0.06 (0.00, 0.13)	1.11 (1.01, 1.23)	0.07 (0.01, 0.14)
Number of patients with at least one treatment-related AE	1.17 (1.00, 1.36)	0.07 (0.00, 0.14)	1.21 (1.04, 1.41)	0.09 (0.02, 0.16)
Number of patients with at least one SAE	0.50 (0.13, 1.98)	-0.01 (-0.02, 0.01)	0.82 (0.25, 2.68)	0.00 (-0.02, 0.01)
Number of patients with at least one AE leading to study discontinuation	0.62 (0.21, 1.89)	-0.01 (-0.03, 0.01)	0.87 (0.32, 2.36)	0.00 (-0.02, 0.02)
Number of patients with at least one protocol-defined AE of special interest*	1.75 (0.52, 5.91)	0.01 (-0.01, 0.03)	2.23 (0.69, 7.17)	0.01 (-0.01, 0.03)

*Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions

Further details on the incidence of all adverse events experienced by more than 2% of any treatment group are presented in Table 39, with the associated relative risks and risk differences shown in Appendix F. There were no significant differences in incidence of any of these AEs between the placebo and fremanezumab groups (both dosing regimens). The most common adverse events were injection site reactions in all treatment groups. The other encountered AEs occurred in 5% or less of patients

and there were no clear differences between the rates of these conditions between the placebo and active treatment groups.

Table 39 Incidence of adverse events within HALO CM trial

	Placebo (n=375) N (%)	Fremanezumab quarterly (n=376) N (%)	Fremanezumab monthly (n=379) N (%)
General disorders and administration site conditions*			
Injection site pain	104 (27.7)	114 (30.3)	99 (26.1)
Injection site induration	68 (18.1)	74 (19.7)	90 (23.7)
Injection site erythema	60 (16.0)	80 (21.3)	75 (19.8)
Injection site haemorrhage	10 (2.7)	7 (1.9)	8 (2.1)
Injection site pruritus	0 (0.0)	6 (1.6)	8 (2.1)
Infections and infestations			
Nasopharyngitis	20 (5.3)	19 (5.1)	15 (4.0)
Upper respiratory tract infection	15 (4.0)	18 (4.8)	16 (4.2)
Sinusitis	10 (2.7)	10 (2.7)	4 (1.1)
Nervous system disorders			
Dizziness	5 (1.3)	9 (2.4)	11 (2.9)
Migraine	8 (2.1)	4 (1.1)	4 (1.1)
Gastrointestinal disorders			
Nausea	11 (2.9)	4 (1.1)	6 (1.6)

* Injection site assessments were proactively performed immediately and one hour after administration of fremanezumab, as opposed to only spontaneous adverse event reporting of injection site reactions. If the patient had a severe injection site reaction at this point, the patient was reassessed at 3 hours after administration and hourly thereafter until the reaction/pain is of moderate or less severity.

B 2.10.3 FOCUS

An overall summary of the AEs recorded in the full population of the FOCUS trial is presented in Table 40, with the associated relative risks and risk differences shown in Table 41. These figures show that the fremanezumab groups had no significant difference in rates of adverse events (p=0.1373 and p=0.4690 for quarterly and monthly fremanezumab, respectively) and treatment related adverse events compared to the placebo group (p=0.8272 and p=0.8773 for quarterly and monthly fremanezumab, respectively). There were few serious adverse events, with four

such events reported in the placebo group compared to two and four in the quarterly and monthly fremanezumab, respectively (p=0.4317 and p=0.9707 for quarterly and monthly fremanezumab, respectively). In addition, there was no significant difference between treatment groups in patients discontinuing treatment due to adverse events, with three such instances in the placebo group compared to one and four in the quarterly and monthly fremanezumab, respectively (p=0.3472 and p=0.7458 for quarterly and monthly fremanezumab, respectively). There were no deaths recorded within the FOCUS trial. These results show that fremanezumab was generally a well-tolerated treatment with rates of serious AEs and discontinuation due to AEs that were comparable to placebo.

Table 40 Summary of adverse event numbers in FOCUS trial

	Placebo (n=277) N (%)	**Fremanezumab quarterly (n=276) N (%)**	**Fremanezumab monthly (n=285) N (%)**
Number of patients with at least one AE	134 (48.3)	151 (54.7)	129 (45.3)
Number of patients with at least one treatment-related AE	55 (19.9)	57 (20.6)	55 (19.3)
Number of patients with at least one SAE	4 (1.4)	2 (0.7)	4 (1.4)
Number of patients with at least one AE leading to study discontinuation	3 (1.1)	1 (0.4)	4 (1.4)
Number of patients with at least one protocol-defined AE of special interest*	[redacted]	[redacted]	[redacted]
Death	0 (0.0)	0 (0.0)	0 (0.0)

*Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions

Table 41 Relative risk and risk difference of adverse events in FOCUS trial

	Fremanezumab quarterly *versus* placebo		Fremanezumab monthly *versus* placebo	
	Relative risk (95% CI)	**Relative difference (95% CI)**	**Relative risk (95% CI)**	**Relative difference (95% CI)**
Number of patients with at least one AE	1.13 (0.96, 1.33)	0.06 (-0.02, 0.15)	0.94 (0.78, 1.12)	-0.03 (-0.11, 0.05)
Number of patients with at least one treatment-related AE	1.04 (0.75, 1.45)	0.01 (-0.06, 0.07)	0.97 (0.70, 1.36)	-0.01 (-0.07, 0.06)
Number of patients with at least one SAE	0.50 (0.09, 2.72)	-0.01 (-0.02, 0.01)	0.97 (0.25, 3.85)	0.00 (-0.02, 0.02)
Number of patients with at least one AE leading to study discontinuation	0.33 (0.04, 3.20)	-0.01 (-0.02, 0.01)	1.30 (0.29, 5.74)	0.00 (-0.02, 0.02)
Number of patients with at least one protocol-defined AE of special interest*	[redacted]	[redacted]	[redacted]	[redacted]

*Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions

Further details on the incidence of all adverse events experienced by more than 2% of any treatment group are presented in Table 42, with the associated relative risks and risk differences shown in Appendix F. There were no significant differences in incidence of any of these AEs between the placebo and fremanezumab groups (both dosing regimens). The most common adverse events were injection site reactions in all treatment groups. The other encountered AEs occurred in 5% or less of patients and there were no clear differences between the rates of these conditions between the placebo and active treatment groups.

Table 42 Incidence of adverse events within FOCUS trial

	Placebo (n=277) N (%)	**Fremanezumab quarterly (n=276) N (%)**	**Fremanezumab monthly (n=285) N (%)**
General disorders and administration site conditions			
Any injection site reaction	[redacted]	[redacted]	[redacted]
Injection site erythema	15 (5.4)	19 (6.9)	16 (5.6)
Injection site induration	12 (4.3)	12 (4.3)	13 (4.6)

	Placebo (n=277) N (%)	Fremanezumab quarterly (n=276) N (%)	Fremanezumab monthly (n=285) N (%)
Injection site pain	8 (2.9)	11 (4.0)	9 (3.2)
Fatigue	3 (1.1)	9 (3.3)	9 (3.2)
Infections and infestations			
Nasopharyngitis	11 (4.0)	13 (4.7)	7 (2.5)
Upper respiratory tract infection	3 (1.1)	4 (1.4)	9 (3.2)
Influenza	2 (0.7)	2 (0.7)	6 (2.1)
Gastroenteritis	7 (2.5)	3 (1.1)	3 (1.1)
Psychiatric disorders			
Insomnia	2 (0.7)	6 (2.2)	7 (2.5)
Nervous system disorders			
Migraine	9 (3.2)	2 (0.7)	3 (1.1)
Gastrointestinal disorders			
Diarrhoea	3 (1.1)	7 (2.5)	2 (0.7)
Constipation	2 (0.7)	7 (2.5)	1 (0.4)

B 2.10.3.1 Patients who have failed three or more classes of preventive migraine treatment

A *post-hoc* analysis was conducted on the FOCUS trial data to allow additional reporting of adverse events within patients who have failed three or more classes of preventive migraine treatment. In total, [redacted] patients receiving placebo, [redacted] receiving quarterly fremanezumab and [redacted] patients receiving monthly fremanezumab failed three or more classes of preventive migraine treatment. This included [redacted] patients who had failed on four classes of migraine preventive therapies, and [redacted] who had failed two or three classes of migraine preventive therapies and valproic acid. The results were similar to those reported above for the overall trial population, with [redacted] of placebo patients reporting at least one adverse event compared to [redacted] for quarterly fremanezumab and [redacted] for monthly fremanezumab. This equated to relative risks *versus* placebo of [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively; and to relative differences *versus* placebo of [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively. These results demonstrate that

there was no significant difference in rates of adverse events between fremanezumab groups and placebo. There were also no meaningful differences between the rates of adverse events for patients with EM and CM within this group. For patients with EM, [redacted] of placebo patients reported at least one adverse event compared to [redacted] for quarterly fremanezumab and [redacted] for monthly fremanezumab. For patients with CM, [redacted] of placebo patients reported at least one adverse event compared to [redacted] for quarterly fremanezumab and [redacted] for monthly fremanezumab.

Further details on the incidence of all adverse events experienced by more than 2% of any treatment group are presented in Table 43, with the associated relative risks and risk differences shown in Appendix F. There were no significant differences in incidence of any of these AEs between the placebo and fremanezumab groups (both dosing regimens). The most common adverse events were injection site reactions in all treatment groups. The other encountered AEs occurred in 5% or less of patients ([redacted]) and there were no clear differences between the rates of these conditions between the placebo and active treatment groups.

Table 43 Incidence of adverse events for patients who have failed three or more classes of preventive migraine treatment within FOCUS trial

	Placebo (n=[redacted]) N (%)	Fremanezumab quarterly (n=[redacted]) N (%)	Fremanezumab monthly (n=[redacted]) N (%)
General disorders and administration site conditions			
Injection site erythema	[redacted]	[redacted]	[redacted]
Injection site induration	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Injection site bruising	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]
Injection site pruritis	[redacted]	[redacted]	[redacted]
Injection site rash	[redacted]	[redacted]	[redacted]
Injection site paraesthesia	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Injection site warmth	[redacted]	[redacted]	[redacted]

	Placebo (n=[redacted]) N (%)	Fremanezumab quarterly (n=[redacted]) N (%)	Fremanezumab monthly (n=[redacted]) N (%)
Infections and infestations			
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Psychiatric disorders			
Insomnia	[redacted]	[redacted]	[redacted]
Nervous system disorders			
Migraine	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders			
Nausea	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Investigations			
Weight increased	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders			
Back pain	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders			
Rash	[redacted]	[redacted]	[redacted]

B 2.10.4 HALO extension

Further evidence regarding the safety of fremanezumab over a longer time period came from the extension of the HALO trials. Safety data were collected within this 12-month extension for both quarterly and monthly fremanezumab. There was no placebo arm within the extension trial and so the rates of adverse events cannot be compared to placebo within this data.

An overall summary of the AEs in the full population of the HALO extension trial is presented in Table 44. Overall, the results show that, compared to the double-blind placebo-controlled HALO trials, over this longer time period a slightly higher

proportion of fremanezumab patients experienced an adverse event or a treatment related adverse event. Most of these adverse events were mild and only a low proportion of patients had a serious adverse event or discontinued treatment due to adverse events; although again these proportions were slightly higher than reported in the main HALO trials. There were no deaths recorded within the HALO extension trials. These results show that over longer term treatment, fremanezumab was generally a well-tolerated treatment, across both monthly and quarterly dosing regimens.

Table 44 Summary of adverse event numbers in HALO trial extension

	Fremanezumab quarterly (n=[redacted]) **N (%)**	**Fremanezumab monthly (n=[redacted])** **N (%)**
Number of patients with at least one AE	[redacted]	[redacted]
Number of patients with at least one treatment-related AE	[redacted]	[redacted]
Number of patients with at least one SAE	[redacted]	[redacted]
Number of patients with at least one AE leading to study discontinuation	[redacted]	[redacted]
Number of patients with at least one protocol-defined AE of special interest*	[redacted]	[redacted]
Death	[redacted]	[redacted]

Further details on the incidence of all adverse events experienced by more than 2% of any treatment group are presented in Table 45. These are a similar list of events to that seen in the main HALO trials. The most common adverse events were injection site reactions, and minor infections. The other encountered AEs occurred in 5% or less of patients and there were no clear differences between the rates of these conditions between treatment groups.

Table 45 Incidence of adverse events within HALO trial extensions

	Fremanezumab quarterly (n=[redacted]) N (%)	Fremanezumab monthly (n=[redacted]) N (%)
General disorders and administration site conditions*		
At least one injection site reaction averse event	[redacted]	[redacted]
Injection site induration	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Injection site haemorrhage	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Infections and infestations		
Upper respiratory tract infection	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Pharyngitis streptococcal	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders		
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]
Gastrointestinal disorders		
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Injury, poisoning and procedural complications		
Procedural pain	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]
Nervous system disorders		
Migraine	[redacted]	[redacted]
Investigations		
Alanine aminotransferase increased	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders		
Cough	[redacted]	[redacted]
Psychiatric disorders		
Insomnia	[redacted]	[redacted]

	Fremanezumab quarterly (n=[redacted]) N (%)	Fremanezumab monthly (n=[redacted]) N (%)
Anxiety	[redacted]	[redacted]
Vascular disorders		
Hypertension	[redacted]	[redacted]

* Injection site assessments were proactively performed immediately and one hour after administration of fremanezumab, as opposed to only spontaneous adverse event reporting of injection site reactions. If the patient had a severe injection site reaction at this point, the patient was reassessed at 3 hours after administration and hourly thereafter until the reaction/pain is of moderate or less severity.

B 2.11 Ongoing studies

The FOCUS trial has entered into an open-label extension, which will provide further information on the longer-term efficacy and safety of fremanezumab in patients who have failed on previous migraine preventive therapies. Results from this trial are expected to be available in late 2019.

B 2.12 Innovation

Preventive treatment of migraine aims to reduce the frequency and impact of attacks whilst also aiming to reduce attack duration and severity.[63] It is recognised that although there are many licensed and unlicensed preventive treatments for migraine, they are often insufficient to manage migraine effectively, with issues of efficacy, tolerance, safety, and adherence, highlighting the need for new treatment options.[67] The reason for this may be due to the fact that current preventive therapies used to manage migraine are repurposed drugs that were not designed to specifically address the underlying biology of the condition and therefore may have a broader mechanism of action. These treatments are effective in achieving the aim of a migraine preventive in a proportion of patients; however, they may be associated with poor tolerability.[68] Data from over 30 published studies have reported poor adherence to and persistence on oral migraine preventive drugs, which can adversely affect treatment outcomes.[69,70,71]

The novel treatment class of anti-CGRP therapies (including fremanezumab) represent a ‘step-change’ in the management of migraine, being the first preventive therapies that are targeted at the underlying biology of this condition. This has come after almost 20 years since the advent of the triptan class of medications, which are licensed only for acute migraine management. Clinical trials have demonstrated fremanezumab to be generally well-tolerated, with an AE profile broadly similar to that of placebo. Traditional preventive therapies largely need to be taken daily; this fact, especially when compounded by issues around tolerability, as discussed above, can reasonably be assumed to affect adherence and persistence to therapy in many patients. Given the relatively low level of serious adverse events and discontinuations due to adverse events in the fremanezumab trials, and the simplicity of monthly and quarterly dosing regimens, it can be postulated that issues with adherence and persistence may occur to a lesser extent with fremanezumab.

Fremanezumab is the first anti-CGRP therapy that can be administered as a quarterly as well as monthly regimen, with monthly/4 weekly administration required for all other currently available drugs in this class. Fremanezumab has the same dose administered as either a monthly or quarterly regimen (225mg per month or 675mg every 3 months [total of 12 x 225mg injections per year]); patients inject their fremanezumab either on the same day every month or every three months, meaning that it is easier for patients to recall when their next dose is due, as opposed to 4-weekly therapies. These two regimens are equivalent in total dose, efficacy, safety and cost. In addition, as fremanezumab can be self-administered by patients, once they are trained on the injection technique, there would be no expected difference in resource requirements between the two regimens. The availability of these two dosing regimens provides flexibility and choice to patients and physicians, with the ability to choose a dosing regimen that best fits the patient’s personal requirements and lifestyle, with the aim of helping to further improve adherence and persistence on this therapy. Furthermore, the flexibility offered means that patients are able to switch between dosing regimens to aid convenience through different life events.

Compared to the administration of onabotulinumtoxin A, the availability of fremanezumab has the potential to reduce the current burden on migraine services,

as well as on the patient. Onabotulinumtoxin A treatment requires a 30-minute hospital appointment every 12 weeks for administration (as stated in the technology appraisal for onabotulinumtoxin A).[45] Administration of this treatment is associated with high clinician burden; patients need to come back into the clinic every 12 weeks for their next treatment cycle. This can have an impact on clinic capacity in terms of waiting list for these clinics. Indeed, clinical experts have reported that these clinics have waiting lists of 2-8 months for newly prescribed patients. In addition to this, onabotulinumtoxin A treatment may place a burden on the patient whom has to take time out of their professional or social life to attend clinics every 12 weeks to receive treatment. Furthermore, onabotulinumtoxin A treatment consists of approximately 31 injections of the medication in the head and neck region, a procedure that may be viewed as relatively invasive.

In contrast, fremanezumab requires only a single monthly injection or 3 injections every quarter, all of which can be self-administered by the patient; thus, fremanezumab offers a convenient alternative to onabotulinumtoxin A treatment, for both the patient and their healthcare providers. Any reduction in use of onabotulinumtoxin A due to the introduction of fremanezumab, therefore, has the potential to reduce the burden on NHS migraine services.

In addition to its direct impact on migraine services, fremanezumab has the potential to have a substantial positive societal impact that would not be captured within the quality-adjusted life year (QALY) calculations. As discussed in Section B 1.3.3.2, several studies have demonstrated that migraine has a tremendous impact on society.[39,41] Most recently it has been estimated that based on a prevalence rate of 23.3% (taken from Global Burden of Disease 2016) and average of 5.7 days lost per person, in the UK it is estimated that 43 million work days are lost every year due to migraine-related absenteeism, at a cost of almost £4.4 billion pounds.[42] The same number of work days lost and attributed cost is associated to migraine-related presenteeism, equating to a total cost of almost £8.8 billion every year in the UK. Even using more conservative prevalence estimates of 15%, it is estimated that migraine-related absenteeism and presenteeism result in 55 million work days lost at

a cost of more than £5.6 billion per year.[42] Whilst these indirect benefits fall outside of the remit of NICE, they can be of great importance to patients and wider society.[36]

B 2.13 Interpretation of clinical effectiveness and safety evidence

Fremanezumab is an effective preventive treatment for migraine

The results from the pivotal HALO EM and HALO CM trials demonstrate that fremanezumab (both quarterly and monthly) is an effective preventive treatment for migraine. In the HALO EM trial, fremanezumab was able to lead to a change from baseline in monthly migraine days of -1.3 (quarterly) and -1.5 (monthly) over 12-weeks of treatment when compared to placebo ($p<0.0001$ for both dosing regimens). In the HALO CM trial, fremanezumab was able to lead to a change from baseline in monthly headache days of at least moderate severity of -1.8 (quarterly) and -2.1 (monthly) over 12-weeks of treatment when compared to placebo ($p<0.0001$ for both dosing regimens). In addition, both studies demonstrated that fremanezumab was able to lead to a reduction in acute headache medication use, number of headache hours, and improve patients' quality of life to a greater degree than placebo. The results from these trials demonstrate that fremanezumab has a significantly greater efficacy than placebo, and the results of this trial formed the basis for the granting of the Marketing Authorisation for this product.

Fremanezumab is an effective treatment for migraine patients that have failed 2-4 prior classes of preventive therapies

The results from the FOCUS trial provide additional evidence that demonstrates the efficacy of fremanezumab in a population of patients with episodic or chronic migraine who have failed previous preventive therapies. These patients represent a population with a high disease burden, demonstrated by both the high number of migraine days experienced by episodic and chronic migraine patients at baseline, and the high levels of disability reported through the MIDAS and HIT-6 scores. Furthermore, the vast majority of the EM and CM participants reported usage of

migraine-specific acute medication at baseline; again highlighting the burden that the condition was having on each individual.

For the FOCUS trial, failure on prior preventive therapies was defined as the failure of two to four classes of migraine preventive therapy. Patients in this trial can be considered to have a high unmet need, due to the number of treatment failures that they have experienced, and subsequent limited treatment options still available to them. This is of particular concern in the management of migraine, as it is known that poor migraine management can increase the risk of chronification and further complications with medication overuse headache (as discussed in Section B 1.3.1).

Fremanezumab was able to significantly reduce migraine days in this highly difficult to treat population of patients. The overall FOCUS results demonstrated the efficacy of fremanezumab in this population, with a change from baseline in monthly migraine days of -3.1 (quarterly) and -3.5 (monthly) over 12-weeks of treatment when compared to placebo ($p<0.0001$ for both dosing regimens). Similar results were obtained in the subgroup analysis of the FOCUS data split by migraine classification. For episodic migraine patients with a baseline of approximately [redacted] migraine days *per* month, this resulted in those patients experiencing an average of less than [redacted] migraine days *per* month. In chronic migraine, where patients started with an average of [redacted] migraine days *per* month, these patients were experiencing a significantly smaller number of migraine days, of approximately [redacted] days, by the end of the 12 week treatment period. Not only did fremanezumab decrease the number of migraine days in this population, but it also reduced levels of disability and acute headache medication use. These results clearly demonstrate how in these very difficult to treat patients, fremanezumab is an effective treatment option.

Fremanezumab is effective in patients who have failed three or more previous preventive therapies

The population of interest for this appraisal is patients who have failed three or more prior preventive migraine treatments. As discussed above, patients whom have failed three or more prior therapies have limited (CM) or no further treatment options (EM). These patients often resort to alternative therapies or overuse acute treatment

to try and achieve some level of symptomatic control. As such, this cohort of patients is at risk of their condition worsening, through lack of effective management or medication overuse. A *post-hoc* analysis of the FOCUS trial data demonstrated that fremanezumab is equally effective in these patients where the unmet need is so high.

For patients with EM who had failed three or more classes of previous therapy, fremanezumab led to an average change from baseline in monthly migraine days of [redacted] (quarterly) and [redacted] (monthly) compared to placebo ([redacted] for both dosing regimens). In addition, fremanezumab led to a significantly greater proportion of patients who experienced a reduction of at least 50% in the average monthly number of migraine days compared to placebo. This endpoint was reached by [redacted] of patients treated with quarterly fremanezumab and [redacted] of those treated with monthly fremanezumab, compared to [redacted] of the placebo group ([redacted] for quarterly and monthly fremanezumab, respectively). Clinical experts agree that for an episodic migraine patient, a reduction of at least 50% of their migraine days is clinically meaningful. For fremanezumab, this meant that almost half of the patients reached this important clinical milestone - approximately [redacted] days at baseline to approximately [redacted] days over the 12 week study. This alone is postulated to have a significant impact on a patient's day-to-day quality of life, where the individual is potentially given back up to almost a whole working week that is migraine free, each month.

Fremanezumab also demonstrated a significant reduction of headache days of at least moderate severity from baseline in this patient population. On average patients suffered from [redacted] headache days of at least moderate severity at baseline, this was reduced to just over [redacted] days after fremanezumab treatment. The study also deduced that the duration of these headaches was significantly reduced along with the consumption of acute headache medication. Overall, this shows that fremanezumab was able to reduce the number of migraines the patients suffered, and also improve the remaining headache days too, in terms of frequency and duration. The impact of this on the patient was demonstrated by the fact that fremanezumab was able to reduce migraine related disability, measured using the

HIT-6 and MIDAS scales, and improve quality of life, demonstrated through the MSQoL results.

For patients with CM who had failed three or more classes of previous therapy, fremanezumab led to an average change from baseline in monthly migraine days of [redacted] (quarterly) and [redacted] (monthly) compared to placebo ([redacted] for both dosing regimens). Clinical experts claim that, in chronic migraine patients, a reduction of at least 30% of migraine days is considered as an acceptable response to treatment that would be meaningful to the patient, as opposed to the higher milestone of at least a 50% reduction that is used in EM. Fremanezumab led to a significantly greater proportion of patients who experienced a reduction of at least 30% in the average monthly number of migraine days compared to placebo. This important clinical milestone was achieved by [redacted] of patients treated with quarterly fremanezumab and [redacted] of those treated with monthly fremanezumab, compared to [redacted] of the placebo group ([redacted] for quarterly and monthly fremanezumab, respectively). In addition to this, as with EM, CM patients experienced fewer and shorter durations of headache days of at least moderate severity, as well as reduced consumption of acute headache medication use and improved disability and quality of life measures.

Fremanezumab is effective in patients with high-frequency episodic migraine whom have failed three or more previous therapies

As discussed in Section B 1.3.1, HFEM patients are considered to be comparable to CM patients in terms of disease burden and disability levels. Indeed, a study published in 2016 demonstrated that HFEM patients, defined as 10-14 headache days, had few clinical differences to CM patients, including poor outcomes related to headache related disability and the impact that migraines have on the patient's life. From this study it was concluded that clinicians should consider HFEM patients to be as disabled as CM patients due to the emotional and functional impact of their migraines.[1] Therefore, EM patients should not be considered as a homogenous population of patients.

A *post-hoc* analysis of FOCUS data has shown that fremanezumab is an effective treatment in patients with HFEM who had failed three or more classes of previous preventive treatment. Fremanezumab treatment resulted in an average change from baseline in monthly migraine days of [redacted] (quarterly) and [redacted] (monthly) compared to placebo ([redacted] for both dosing regimens). In addition, fremanezumab led to a significantly greater proportion of patients who experienced a reduction of at least 50% in the average monthly number of migraine days compared to placebo. This endpoint was reached by [redacted] of patients treated with quarterly fremanezumab and [redacted] of those treated with monthly fremanezumab, compared to [redacted] of the placebo group ([redacted] for quarterly and monthly fremanezumab, respectively). The results also demonstrated that fremanezumab reduced acute headache medication use and improved disability and quality of life measures.

The above results demonstrate the efficacy of fremanezumab (both quarterly and monthly) in the patient group under consideration in this appraisal. This is verified both in reduction in monthly migraine days and the proportion of patients reaching the clinically important milestone of at least a 50% (for EM) or at least a 30% (for CM) reduction in monthly migraine days. Furthermore, the administration of fremanezumab resulted in the reduced consumption of acute headache medications. For the patient, this is a benefit, as not only is it highlighting that the patient does not need to rely on as many acute medications, it also reduces the risk of medication overuse.

Migraine is ranked as the sixth global cause of years of life lost to disability.[10] Three-quarters of patients report to have reduced functional ability,[13] and over 80 percent report that they have reduced ability to carry out their usual activities such as household work and chores.[37] CM and EM patients whom had failed three or more previous preventive therapies reported that their disability levels and quality of life were improved following treatment with fremanezumab. In terms of the disability outcomes assessed, this meant that patients found that their migraines had less of an impact on their ability to function at work, their cognitive function, vitality levels, psychological distress or social functioning after receiving fremanezumab treatment,

which was significantly greater than the improvement observed in patients receiving placebo.

In addition, the MSQoL data demonstrated that fremanezumab was able to improve the impact the patient's migraine had on one's daily work and social activities, how migraine may have prevented the individual from conducting these activities, as well as improving the emotions the patient had toward their migraines.

In summary, it is widely accepted that migraine is not only a prevalent but also a highly disabling condition. Migraine impacts the patients' ability to carry out usual activities not only during an attack but also during the interictal periods. A proportion of patients are unable to manage their migraines effectively, this may be due to a lack of efficacy, poor tolerability, contraindications or low adherence to existing preventive migraine therapies. Given this, patients are at risk of their condition worsening due to poor management and acute medication overuse.

Fremanezumab is a preventive therapy designed to target CGRP, a key player in the underlying pathophysiology of migraine. This is the only available anti-CGRP that offers a monthly and quarterly dosing regimen, allowing flexibility and convenience for the patient and clinician. Fremanezumab has demonstrated efficacy and tolerability in EM, including HFEM, and CM patients whom have failed three or more prior preventive treatments. Treatment with fremanezumab significantly reduced migraine days, the duration and frequency of headache days of at least moderate severity, as well as improving disability levels and quality of life. Importantly, the results for this sub-population are consistent with the overall findings from the FOCUS trial.

Fremanezumab has an acceptable safety profile that is generally comparable to placebo

As discussed in previous sections, traditional oral migraine preventive therapies may or may not be specifically licensed for migraine. Given this, they often have a broad mechanism of action and therefore this may explain why these therapies are often associated with tolerability issues. This in turn has been one of the factors that is thought to underlie the low adherence and persistence seen.

The safety data collected for fremanezumab demonstrate that this treatment has an adverse-event profile that is generally comparable to placebo. The results from the HALO EM trial showed a slightly higher rate of AEs with fremanezumab compared to placebo (p=0.0476 and p=0.0511 for quarterly and monthly fremanezumab, respectively); similar results were reported in the HALO CM trial (p=0.0589 and p=0.0341 for quarterly and monthly fremanezumab, respectively). The FOCUS trial reported no significant difference in rates of AEs between fremanezumab and placebo treated patients (p=0.1373 and p=0.4690 for quarterly and monthly fremanezumab, respectively). The tolerability of fremanezumab is highlighted by the low number of adverse events that are listed within its Summary of Product Characteristics (see Appendix C); the low rate of discontinuations seen in all clinical trials of fremanezumab (under 2% in active treatment groups) with no significant difference *versus* placebo; and the low number of serious AEs seen (under 1.5% in active treatment groups), again with no significant difference *versus* placebo.

The main class of AE commonly reported during clinical trials of fremanezumab was injection site reactions. All injection site reactions resolved within a few hours or days. Furthermore, injection site reactions did not generally necessitate discontinuation of treatment. Injection site reactions are a common event experienced with many injectable therapies. Training and education of patients on correct injection technique, as well as the need to rotate sites can be used to reduce the risk of injection site reactions or complications. However, it should also be remembered that fremanezumab is injected only monthly or quarterly, and thus the negative impact from each dosing cycle should be far less than many other chronic conditions where far more injections would be needed across a similar time-frame.

Likelihood of treatment success favours fremanezumab over onabotulinumtoxin A in patients with CM who have failed three or more previous therapies

The results of the NMA provide evidence of numerically superior results across outcomes for fremanezumab compared to onabotulinumtoxin A and, thereby, a higher probability of treatment success with fremanezumab. For the key modelling input of at least a 50% response, both dosing regimens of fremanezumab had

favourable odds ratios compared to onabotulinumtoxin A, with monthly fremanezumab having an odds ratio of [redacted] (95% CrI [redacted]) and quarterly fremanezumab had an odds ratio of [redacted] (95% CrI [redacted]). As discussed in the previous sections, it is also important to note that fremanezumab may be deemed to be more convenient and less invasive for the patient, as they can self-administer it as a single injection every month, or three every quarter. Whereas, for onabotulinumtoxin A treatment, the patient is required to go into a clinic every 12 weeks and have approximately 31 injections in their head and neck region. In addition, due to onabotulinumtoxin A requiring administration by a highly trained specialist, it is associated with a greater burden on healthcare resources. Furthermore, limited clinic capacity may mean that there are often long waiting lists for these clinics. Overall, it can be concluded that fremanezumab has treatment benefits when compared to onabotulinumtoxin A.

Long-term efficacy

EMA clinical trial guidelines recommend 12-week studies are undertaken when assessing preventive therapies in migraine, however, in reality this may not be a long enough duration to assess the full long-term impact a new preventive medication may have in everyday clinical practice. The extension of the HALO CM and HALO EM trials provide evidence for the efficacy of fremanezumab over a period of up to 15 months of treatment: 3 months of double-blind placebo-controlled phase followed by a 12 months open label phase. The results show that over this time period the efficacy of fremanezumab was maintained in both CM and EM patients for all endpoints, with no evidence of any waning in the treatment effect over the time scale of this trial.

Furthermore, the long term extension of the HALO studies has demonstrated that, in comparison to the end of the double-blind phase of HALO EM and CM, the proportion of patients experiencing at least a 50% reduction in migraine days is maintained over time. Also, only 2% (38/1888) of patients developed anti-drug antibodies after 12 months of fremanezumab treatment; even in these patients anti-drug antibody titres were low and did not affect the safety or efficacy of fremanezumab treatment. Additionally, migraine is not a neurodegenerative disorder;

taken together, this demonstrates the lack of waning in treatment effect observed over 15 months of fremanezumab treatment

The FOCUS trial has now entered into its open-label extension phase which will be able to provide further evidence of the long-term efficacy in patients who have failed on previous migraine preventive therapies.

Fremanezumab monthly and quarterly dosing regimens demonstrate equivalent levels of efficacy and safety

Fremanezumab is available in two dosing regimens: monthly (225mg *per* month) or quarterly (675mg *per* quarter). The total dose a patient receives is the same over a 12 month period. The fremanezumab clinical trials have confirmed equivalence of both efficacy and safety for the monthly and quarterly dosing regimens.

The availability of two dosing regimens aims to provide flexibility and convenience for both the patient and the clinician. Patients are able to choose a regimen that will fit with their professional and personal lifestyle. In addition, fremanezumab offers the patient the flexibility to switch between dosing regimens to aid convenience through different life events. It can be postulated that the level of flexibility offered by fremanezumab may contribute to improved medication adherence.

Strengths and weaknesses in efficacy evidence

The clinical trial programme for fremanezumab was designed to follow relevant European Medicines Agency guidance on trials in migraine.[72] Procedures were put in place to minimise any risks of bias and the trials were well powered, including large patient cohorts to ensure robust analyses. These factors, alongside a clear statistical analysis plan, give confidence in the internal validity of these trials.

The HALO trials included 875 patients with EM and 1130 with CM and provide strong evidence of the efficacy in a general migraine population, which formed the basis of the evidence considered for the granting of a Marketing Authorisation for fremanezumab. FOCUS was conducted as an additional trial to demonstrate the efficacy in a population of patients with previous preventive therapy failures. The size of the population included within the FOCUS trial (838 patients) allowed a

thorough demonstration of efficacy in this important patient group. *Post-hoc* analysis of this study revealed that there were over 400 patients whom had failed three or more prior preventive therapies. This provides a robust level of evidence for the population of interest in this appraisal (three or more previous failed migraine preventive treatments).

The clinical trials of fremanezumab were of a sufficient length to demonstrate efficacy in reducing monthly migraine days, and were in line with EMA guidance for clinical trials in migraine.[72] The double-blind portion of these trials was 12 weeks in length and has been followed (for both FOCUS and HALO trials) by an open-label extension phase to allow longer-term data on the efficacy and safety of fremanezumab to be collected.

A further strength of the FOCUS trial is in its definitions of treatment failure, which is defined as failure on two to four classes of treatments. As discussed in earlier sections, this ensures that the number of treatment failures are determined by class, with different mechanisms of action, rather than individual treatments that may have overlapping mechanisms of action. [redacted]. It should also be highlighted that the FOCUS trial was designed to include both EM and CM patients; together this demonstrates the more robust design of the trial.

One weakness of the FOCUS and HALO trials was that they were not limited specifically to the population of interest for this appraisal (those with three or more previous preventive treatments), and also that this population was not a pre-specified subgroup for analysis. Hence, data from the FOCUS trial was analysed *post-hoc* to investigate the treatment response in this relevant population. Confidence in the results comes from the fact that these results match well to the overall results obtained in this trial. Furthermore, the level of evidence produced through this *post-hoc* was robust due to the relatively high number of patients within this subgroup ([redacted]).

An additional weakness of the CM studies, both HALO and FOCUS, is that the monthly dosing regimen in these patients including an initial loading dose of 675mg. However, as discussed in more detail in section B 1.2, Marketing Authorisation has been granted without the requirement for a loading dose as it was deemed not to be necessary.

In conclusion, the clinical trials of fremanezumab can be considered to be highly relevant to the UK because of both the design of the studies, and the patient population included. The extensive body of evidence clearly demonstrates the clinical value fremanezumab brings to this difficult to treat and highly disabled population of migraine sufferers.

Mortality

There are no data available that suggests that migraine impacts on life expectancy, with a meta-analysis concluding that migraine does not appear to substantially impact mortality.[30] Therefore, based on this, fremanezumab does not meet end of life criteria.

B.3 Cost effectiveness

B 3.1 Published cost-effectiveness studies

Appendix G contains details of the systematic literature review conducted in order to identify relevant cost-effectiveness studies. This identified no studies that investigated the cost-effectiveness of fremanezumab. Two publications were identified which focussed on the cost-effectiveness of preventive migraine treatments in a UK setting, and the results of these are summarised in Appendix G. In addition, the literature review identified cost-effectiveness analyses on onabotulinumtoxin A for the technology appraisal conducted by NICE.

B 3.2 Economic analysis

The economic analysis of onabotulinumtoxin A was used as a guide and a basis for the economic analysis conducted here. However, a *de novo* model was constructed for the analysis of fremanezumab. This was due to the fact that although the general structure and inputs of the previous modelling were well described, exact details were not available. In addition, the model used for the assessment of onabotulinumtoxin A had a number of limitations, one of the main limitations being the grouping of monthly migraine day (MMD) states. The development of a *de novo* model therefore allowed a number of these limitations to be addressed and a more robust model to be produced in relation to fremanezumab. In addition, this model used more recent and more relevant inputs wherever appropriate.

The grouping of MMD states in the economic analysis of onabotulinumtoxin A is an assumption that acts to simplify the modelling, but it risks limiting the ability of the model to distinguish between treatments. This is due to the fact that it reduces the ability of the model to evaluate differences in health effects of different treatments as only the broad groupings are considered. This assumption can also be seen to not represent reality, where patients can present with any number of migraine days (within the range of 0-28) and patients will be distributed across this spectrum. In addition, as MMDs are the primary determinant of health impacts within the modelling of migraine, this loss of information could have an important impact of the

modelled outcomes. Therefore, the model developed by Teva includes the ability to model the full distribution of MMDs. The distribution of these MMDs is informed by the data collected in the clinical trials of fremanezumab.

The development of a *de novo* model also allowed the introduction of a more thorough analysis of responder and non-responder patients. The model developed by Teva analyses the outcomes for responder and non-responder patients separately and uses differential inputs for these different patient populations. This allows an accurate assessment of cost-effectiveness within those patients that show a clinically meaningful response to treatment.

B 3.2.1 Patient population

The patient population included in this economic analysis is adults who have failed three or more prior preventive migraine treatments. The EM and CM populations were also modelled separately due to the differences in comparators between these two groups of patients (onabotulinumtoxin A is licenced only for CM). This population differs to that within the Marketing Authorisation for fremanezumab and reflects the expected positioning of anti-CGRP therapy in UK clinical practice, as explained previously in the submission. This population matches the decision problem that is being addressed by this submission.

In addition to these base case populations, a scenario analysis was run within patients with HFEM. For this submission, HFEM was defined as patients who experienced 8-14 headache days *per* month. The unmet need for treatment is recognised to be particularly high in this group of patients as they currently are not eligible for treatment with onabotulinumtoxin A, however these patients still experience a high level of disease burden and disability, similar to that seen in patients with CM.[1]

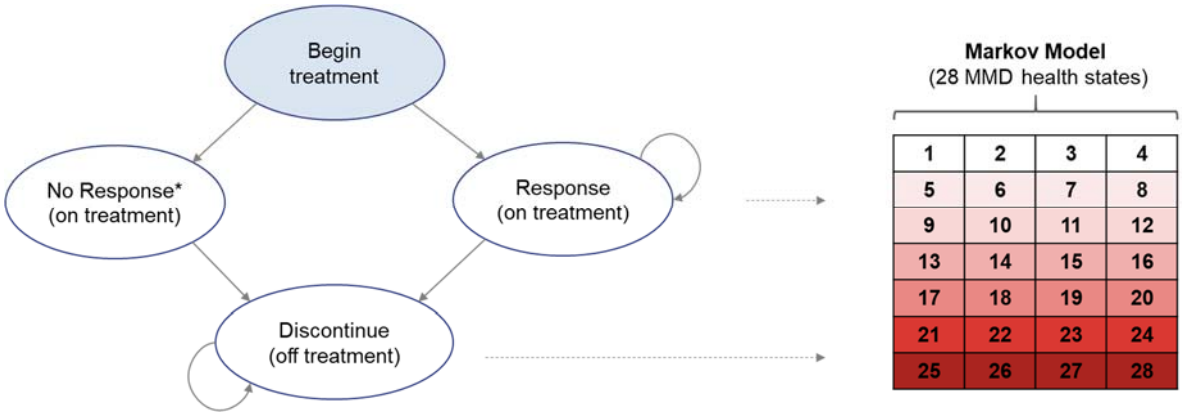
B 3.2.2 Model structure

The economic model developed is best described as a semi-Markov model. Patients begin treatment and are assessed for a response after 12 or 24 weeks (dependant on treatment). Those patients who show a sufficient response (defined as at least a 50% [for EM] or 30% [for CM] reduction in MMDs from baseline) continue on

treatment; whereas the remaining patients (those with no response) discontinue treatment. Within each health state, a Markov model is employed to model the distribution of MMDs. The structure of the model is shown diagrammatically in Figure 8.

This model structure captures treatment based costs and resource use based on the overall health state and then evaluates health based resource use costs and QALYs based on the patient distributions between the different MMD states. It was assumed that as these outcomes were linked to the migraine day health states that this structure would capture the required outcomes. It was assumed that migraine caused no excess mortality above natural background rates seen in the general population.

Figure 8 Structure of the cost-effectiveness model



*No response defined as patients who do not achieve at least a 30% reduction in monthly migraine days (MMDs) for chronic migraine and at least a 50% reduction in MMDs for episodic migraine at 12 weeks

An assessment of response was carried out after 12 weeks for fremanezumab and 24 weeks for onabotulinumtoxin A, as this matched the time scales of the relevant clinical trials. The clinical efficacy data for both therapies showed a robust ability to determine response at this time period, with a significant treatment effect seen during these trials. After this period, patients continued on treatment if they showed a clinically significant response. Those who did not show a response were assumed to discontinue treatment (and receive only acute migraine medications, *i.e.* best supportive care [BSC]) and reverted to the MMDs seen in the BSC group (based on the clinical trial placebo arms) at week 12 (or week 24 for onabotulinumtoxin A). Responders remained on treatment until discontinuation (based on the rates of

discontinuation from the long-term data on fremanezumab); these patients then reverted to their baseline MMDs.

A positive stopping rule was included to reflect the fact that patients with well controlled migraine are likely to have their necessity to continue treatment assessed at regular intervals. The recently published EHF guidelines recommend that the need to continue treatment with an anti-CGRP therapy should be assessed after 6-12 months.[53] In this model it is assumed that, 52 weeks after the initial efficacy assessment (*i.e.* starting at week 64), and after every subsequent 52-week period, an assessment for treatment continuation is made. The assessment consists of a 12-week treatment break of for an evaluation of response; with 20% of patients who started this treatment break not recommencing therapy. These patients were modelled to retain their treatment benefit throughout the remainder of the model time horizon (except when treatment waning is applied as the patients follow the same response as treated patients). Treatment waning was included as an option in this model and consisted of a linear reduction in treatment effect over 10 years, such that, at the end of this time, mean MMDs for treated patients align with BSC. The waning effect applies to treated patients as well as those who stop treatment under the positive stopping rule.

This model had a fixed cycle length of 28 days (4 weeks), as this matched the assessment periods within the fremanezumab clinical trials. This allowed for data from each monthly assessment of the clinical trial to be used to inform the modelling of the distribution of MMDs. A summary comparing the features of the economic model used in this submission to those used in the appraisal of onabotulinumtoxin A are included in Table 46.[45] The economic modelling has not been compared to the ongoing appraisal of erenumab,[73] as the committee's final preferences for economic modelling are not known. Some modelling aspects identified from the published ACD have been considered in this appraisal (where appropriate), and reference is made within the following sections where appropriate.

Table 46 Features of the economic analysis

	Previous appraisals	Current appraisal	
Factor	**Onabotulinum-toxin A[45]**	**Chosen values**	**Justification**
Model structure	Markov model	Semi-Markov model	The structure of the current model allows for an accurate modelling of MMDs than was possible within the model used for onabotulinumtoxin A, which was limited by the use of banding for MMDs. The current model allows modelling of patients across the entire migraine day spectrum, and allows all information on migraine days to be captured which would otherwise be lost with the application of banding in MMDs. Our model also allows the evaluation of response to fully include an analysis of patients who respond and those who do not respond to treatment
Time horizon	2 years	10 years	A two-year time horizon was not considered to be appropriate and a longer time horizon was considered more appropriate. Based on the assumed treatment discontinuation rates (based on the available long-term clinical trial evidence) only a very small number of patients remain on treatment beyond 10 years. Therefore, a 10 year time horizon is considered appropriate to capture all meaningful differences in costs and QALYs between treatments. A longer time horizon than 10 years was also not considered appropriate due to natural variations in migraine over time; it has not been possible to include these natural history changes within the model as insufficient data are available to base the modelling on. In addition, life events such as the menopause can have a significant impact on migraine frequency.[74] This makes modelling migraine over longer time horizons very challenging and would be likely to lead to considerable uncertainties in the modelling
Source of utilities	Patient-level MSQoL data from clinical trials	Patient-level MSQoL data from FOCUS trial mapped to EQ-5D-3L	The NICE reference case states that, where possible, EQ-5D data from patients reflective of the UK population of interest should be used. Where this is not possible it is stated that mapping from other quality of life measures should be undertaken. The best available data with the level of detail required (utilities for each MMD group) comes from the FOCUS clinical trial data. This trial collected EQ-5D-5L

			data; however, in migraine, the EQ-5D does not accurately assess the quality of life in patients. This is due to the fact that these data are collected during clinic visits and measures the quality of life that day. Should a patient be experiencing a migraine attack, it is unlikely that they would visit the clinic and, thus, the full impact of migraine on quality of life is missed through this measure. Instead, the MSQoL is a more appropriate quality of life measure for migraine as it includes a four-week recall period and thereby assesses the patient's overall quality of life including the impact of migraine attacks. The MSQoL data has been mapped to EQ-5D-3L using the published algorithm of Gillard *et al*.[75] This approach matches that used in the ongoing erenumab appraisal[73]
Source of costs	BNF, PSSRU, NHS reference costs	BNF, PSSRU, NHS reference costs	Established sources for UK costs
Resource use	International Burden of Migraine study	Vo *et al*.[76] publication of National Health and Wellness Survey	These are similar surveys that were conducted with similar aims. The more recent data have been chosen for use in this appraisal
Health effects measure	QALYs	QALYs	NICE reference case
Discount rate for costs and QALYs	3.5% *per* year	3.5% *per* year	NICE reference case
Perspective	NHS	NHS/PSS	NICE reference case
Treatment waning effect	Not considered	Considered as a scenario	The efficacy data for fremanezumab currently only extends to 15 months and no waning in treatment effect was seen over this timescale. There is no available evidence that suggests the potential for a waning effect or a mechanism for such an effect to occur with anti-CGRP therapies. Based on the available evidence, the most plausible assumption is that the treatment effect from fremanezumab persists throughout the time horizon of the analysis. However, it is also possible that a waning effect may occur. Therefore, a treatment waning effect has been included as an option in this model and used in a scenario analysis

BNF: British National Formulary; MSQoL: migraine-specific quality-of-life questionnaire; NHS: National Health Service; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year

B 3.2.3 Intervention technology and comparators

B 3.2.3.1 Intervention

The intervention of interest in this economic analysis is fremanezumab. Fremanezumab is supplied as a 225mg/1.5mL single dose injection in a prefilled syringe with two dosing options – 225mg monthly administered as one subcutaneous injection, or 675mg every three months (quarterly), administered as three subcutaneous injections. Therefore, fremanezumab can be seen to have a single dose administered as two different regimens (225mg *per* month or 675mg every 3 months [total of 12 x 225mg injections *per* year]). The availability of these two dosing regimens aims to provide flexibility and choice to patients and physicians, with the ability to choose a dosing regimen that best fits the patient's personal requirements and lifestyle. It can be postulated that this can help to further improve adherence and persistence on this therapy. Furthermore, the flexibility offered means that patients are able to switch between dosing regimens to aid convenience through different life events. These two regimens are equivalent in total dose and cost. The efficacy data presented within this submission (Section B.2) demonstrated equivalence in efficacy between these regimens, with no significant differences in treatment effect seen. Importantly, there were also no differences observed in the safety profile between the two dosing regimens. Therefore, Teva has conducted a single cost-effectiveness analysis using the treatment costs (which are the same for both regimens) and combined efficacy data. Although it has been assumed that fremanezumab will be self-administered by patients, a scenario analysis has been conducted to investigate the impact of a proportion of patients requiring fremanezumab to be administered by a healthcare professional and the differences that the monthly and quarterly regimens would have in this situation.

As is the case throughout this submission, fremanezumab has been presented to reflect part of its full Marketing Authorisation. This submission addresses patients who have failed on three or more previous preventive treatments, as this is the population where it is expected that fremanezumab will be used during routine clinical practice.

Patients treated with fremanezumab are assumed to continue treatment with acute headache medications throughout the model. This reflects clinical practice, and the clinical trial data, where patients using fremanezumab will continue to use acute headache medications, as required.

B 3.2.3.2 Comparators

Due to the restriction of onabotulinumtoxin A to CM patients, the patient populations of EM and CM have different comparators. In EM, the relevant comparator after three prior preventive therapies is BSC (acute medication usage only); NICE guidelines recommend no further treatments.[43] In real-life, clinical practice, it is possible that these patients may be prescribed a fourth oral preventive treatment; however, clinical opinion gathered by Teva suggests that this was due only to the lack of other treatment options being available and there was little expectation of efficacy in these cases. In addition, no suitable clinical data exist that demonstrate efficacy of oral preventive treatments within patients who have failed multiple previous therapies. Therefore, it was not possible or considered appropriate to include an oral comparator for EM.

In CM, the relevant comparators are onabotulinumtoxin A and BSC (acute medication usage only). Onabotulinumtoxin A has been recommended by NICE for usage in CM for patients who have failed three or more previous preventive treatments,[45] and it is therefore considered in line with these recommendations in this appraisal. Clinical opinion gathered by Teva was that a fourth oral treatment was not a relevant comparator in CM due to the availability of onabotulinumtoxin A for these patients. In addition, as outlined above, no suitable clinical data exist that demonstrate efficacy of oral preventive treatments within patients who have failed multiple previous therapies. Therefore, it is not considered to be appropriate or possible to include an oral comparator for CM.

B 3.3 Clinical parameters and variables

Clinical parameters for this model were based on the results of the FOCUS clinical trial (within the subgroup of interest – patients with three or more previous failed migraine preventive treatments, see Section B 2.7.4) and the results of the network meta-analysis (see Section B 2.9). The model analyses EM and CM as two separate populations (see Section B 3.2.1), these populations are then further split into those patients responding and those patients not responding to treatment at 12 weeks (24 weeks for onabotulinumtoxin A), which are all modelled using separate clinical inputs. In the base case of the model, the required response was defined based on clinical opinion and in line with the committee's preference in the ongoing erenumab appraisal,[73] as:

- For EM, at least a 50% decrease in MMDs from baseline to 12 weeks (24 weeks for onabotulinumtoxin A)
- For CM, at least a 30% decrease in MMDs from baseline to 12 weeks (24 weeks for onabotulinumtoxin A).

B 3.3.1 Patient baseline characteristics and monthly migraine days

Patient characteristics, such as starting age and gender, were taken from the FOCUS clinical trial separately for the CM and EM populations and are used to drive the background mortality calculations within the model (Table 47).

Table 47 Patient baseline characteristics

	Chronic migraine	Episodic migraine
Mean age, years	[redacted]	[redacted]
Proportion female	[redacted]	[redacted]

Baseline MMDs and their respective distributions (Table 48) were taken from the patient-level FOCUS clinical trial data for the CM (responders and non-responders) and EM (responders and non-responders) populations.

Table 48 Baseline monthly migraine days and migraine day distributions

	Chronic migraine		Episodic migraine	
	Responders	**Non-responders**	**Responders**	**Non-responders**
Initial migraine days *per* 28 days	[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]
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]

B 3.3.2 Modelling changes in monthly migraine days

The treatment effect on migraine days was incorporated into the model in two main ways. Firstly, the reduction in mean migraine days, which was applied as an input, and, secondly, the distribution of patients amongst the migraine day health states. This distribution was required to model the dispersion of patients around this mean value.

A number of statistical modelling techniques were investigated for their ability to describe the observed patient distributions from the FOCUS clinical trial (the data for the subgroup of interest, three or more previous failed migraine preventive treatments, was used for these analyses). Longitudinal models were fitted using the gamlss function in the GAMLSS (Generalized Additive Model for Location, Scale and Shape) package. The gamlss function allows for separate models for distribution parameters. Based on the goodness of fit for the modelled distributions, beta binomial distributions were selected and subsequently used to estimate the dispersion of patients across migraine day states through the trial treatment period (12 weeks). Figure 9 provides an illustrative representation of how the migraine day distributions are mapped over time and how they can alter substantially with changes in the mean MMD value. Beta binomial distributions were produced separately for responder and non-responder patients; for CM and EM patients; and for treated (fremanezumab) and placebo patients (used for BSC). As there were not sufficient data available for onabotulinumtoxin A to produce equivalent distributions, the dispersion data for fremanezumab was used.

Figure 9 Mean monthly migraine day distributions

MMDs: monthly migraine days

The FOCUS clinical trial provided data on the change in MMDs from baseline to the end of the assessment period in responder and non-responder patients. These values are detailed in Table 49 alongside the absolute mean values for MMDs that this outputs at the relevant time point (12 weeks for fremanezumab and 24 weeks for onabotulinumtoxin A). The mean migraine day inputs were used within the model to shift the calculated beta binomial distributions to ensure that the desired mean MMD value was achieved. Again, sufficiently detailed results for onabotulinumtoxin A were not available to allow the calculation of results in responder and non-responder patient groups, therefore the mean MMD reductions observed in fremanezumab were applied. There was therefore no difference in efficacy (regarding MMD reduction) assumed between active treatments in this model.

Table 49 Mean reduction in monthly migraine days and resultant efficacy outputs

	Chronic migraine		Episodic migraine	
	Responders	**Non-responders**	**Responders**	**Non-responders**
Mean reduction in monthly migraine days *versus* placebo				
Fremanezumab (at 12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
Onabotulinumtoxin A (at 24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
Modelled absolute monthly migraine days values at efficacy assessment				
Fremanezumab (at 12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
Onabotulinumtoxin A (at 24	[redacted]	[redacted]	[redacted]	[redacted]

weeks)				

B 3.3.3 Response assessment

Treatment response at 12 or 24 weeks was calculated based on the network meta-analysis data to provide comparative response rates between the intervention and comparators of interest. The response criteria used were at least a 50% reduction in MMDs for EM and at least a 30% reduction in MMDs for CM. The model calculates weighted average outputs based on the percentage of patients who respond to treatment, producing results that incorporate the correct proportion of responder and non-responder patients. Patients who do not respond sufficiently to treatment discontinue treatment and do not incur drug acquisition or drug administration costs.

The proportion of patients with at least 30% reduction in MMDs is a relevant outcome in CM, and is required as an input for the cost-effectiveness modelling. However, no data for this outcome for onabotulinumtoxin A within published literature were discovered. An estimate for this figure has therefore been produced, based on the relative treatment effect seen between onabotulinumtoxin A and fremanezumab found in the NMA covering at least a 50% reduction in MMDs. This effect size was then used to calculate an estimate for the proportion of patients with at least 30% reduction in MMDs for onabotulinumtoxin A based on the figures for fremanezumab. Responder rates at 12 or 24 weeks used in the model are provided in Table 50.

Table 50 Responder rates at 12 or 24 weeks

	Chronic migraine	Episodic migraine
Fremanezumab (12 weeks)	[redacted]	[redacted]
Onabotulinumtoxin A (24 weeks)	[redacted]	[redacted]
Placebo (12 weeks)	[redacted]	[redacted]

B 3.3.4 Long-term efficacy

There are limited available data to show the long-term efficacy of fremanezumab treatment. Data from the HALO extension trial (Section B 2.6.3) showed that efficacy is maintained at similar levels for up to 64 weeks of treatment. There is, therefore, no evidence available to suggest that any reduction in treatment efficacy

will occur during long-term treatment. The model therefore assumes that the modelled migraine days at week 12 are maintained for the rest of the time horizon. It is felt that this is the most plausible assumption, as all available evidence shows no sign of a waning in treatment effect for fremanezumab. Furthermore, the available evidence shows that only 2% (38/1888) of patients developed anti-drug antibodies after 12 months of fremanezumab treatment; even in these patients anti-drug antibody titres were low and did not affect the safety or efficacy of fremanezumab treatment. Therefore, anti-drug antibodies would not be expected to reduce the efficacy of fremanezumab over time. In addition, it should be noted that migraine is not a neurodegenerative condition and therefore treatment efficacy can be assumed to not be affected by this. However, despite the beliefs of Teva that a treatment waning effect is not a justified assumption, such an effect has been included as an option in the model (based on the ongoing erenumab appraisal where this has been considered by the committee).[73] This treatment waning effect reduces the treatment effect over time by adjusting the difference in MMDs compared to placebo to zero over a defined time horizon (the model default is set to 10 years).

B 3.3.5 Discontinuation

Discontinuation rates from the long-term HALO data were used for intervention and comparators (see Section B 2.6.3). Discontinuation rates were adjusted to match the 4-week cycles of the model, which produced a discontinuation rate of [redacted] *per* cycle for fremanezumab and onabotulinumtoxin A. It was assumed that the discontinuation rate for onabotulinumtoxin A matched that of fremanezumab in the absence of alternative data; this input was calculated to match the onabotulinumtoxin A 12-week treatment cycle.

B 3.3.6 Mortality

There was no migraine-specific mortality included in this model. There are no data available that suggests migraine impacts on life expectancy; with a meta-analysis concluding that migraine does not appear to substantially impact mortality.[30] Mortality for all causes was implemented through data on general mortality based on the Office for National Statistics National Life Tables.[77] These tables were used,

combined with the age and sex of the patient population, to calculate a *per* cycle mortality rate.

B 3.4 Measurement and valuation of health effects

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

Health-related quality of life data was collected in both the HALO and FOCUS clinical trials. However, the data from the FOCUS trial is considered here, as it is the most relevant with respect to the population of interest for this appraisal (patients who have failed three or more previous migraine preventive treatments).

The FOCUS clinical trial collected EQ-5D-5L data; however in migraine, the EQ-5D does not accurately assess the quality of life in these patients. This is due to the fact that these data were collected during clinic visits within the clinical trial and measures the quality of life only on that day. Should a patient be experiencing a migraine attack, it is unlikely that they would visit the clinic and, thus, the full impact of migraine on quality of life is missed through the EQ-5D measure. Instead, the MSQoL is a more appropriate disease-specific quality of life measure for migraine as it includes a four-week recall period and thereby assesses the patient's overall quality of life, including the impact of migraine attacks. Therefore, utility values mapped from the MSQoL were considered to be the most representative for the overall quality of life for people with migraine and, hence, this approach was used in the base case of this economic model. The mapping of MSQoL to EQ-5D has also been used within previous appraisals of migraine, for both onabotulinumtoxin A and the ongoing appraisal of erenumab.[45,73]

The MSQoL questionnaire was completed by all patients in the FOCUS clinical trial at baseline (week 0), at the end of the first month of treatment (week 4) and at the end of the double-blind treatment period (week 12). The questionnaire was completed during scheduled clinic visits.

B 3.4.2 Mapping

The MSQoL data from the FOCUS clinical trial was mapped to the EQ-5D-3L scale to provide utility values in line with the NICE reference case and for use within the

current economic analysis. This mapping was conducted using the published algorithm of Gillard *et al*.,[75] which was also used in the ongoing erenumab appraisal for a similar purpose.[73]

This publication included mapping algorithms separately for both EM and CM, with two variations on each of these algorithms. The first of these variations utilised only MSQoL subgroup scores, whereas the second included MSQoL subgroup scores as well as a number of additional patient characteristics.[75] However, within the FOCUS trial results there was not enough data collected to reliably match all of the required characteristics of this more detailed algorithm. Therefore, the first algorithm variations were utilised in this analysis to map the MSQoL scores to EQ-5D. These algorithms were used as described in the publication and are reproduced below:[75]

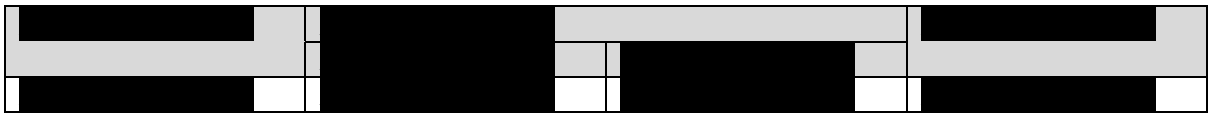
$$EQ\text{-}5D_{EM} = 0.2858 + 0.0029MSQoL_{RP} + 0.0001MSQoL_{RR} + 0.0027MSQoL_{EF}$$

$$EQ\text{-}5D_{CM} = -0.0492 + 0.0065MSQoL_{RP} + 0.0013MSQoL_{RR} + 0.0011MSQoL_{EF}$$

EM: episodic migraine; CM: chronic migraine; MSQoL: migraine specific quality of life questionnaire; RP: role preventive; RR: role restrictive; EF: emotional function

The analysis was conducted on patient-level data using the full FOCUS trial population to provide the most robust analysis possible. The transformed data were then analysed split between "off treatment" and "on treatment"; with "off treatment" consisting of an analysis of baseline data for all patients and "on treatment" using the data for patients receiving fremanezumab at both available time points (week 4 and week 12). These data were fitted to a beta regression model using the gamlss function in the GAMLSS (Generalized Additive Model for Location, Scale and Shape) package in R. Model selection was determined by the Bayesian information criterion (BIC). The parameters of the selected model are presented in Table 51. The mean of the EQ-5D scores was calculated based on these parameters in the logit scale before being transformed back to original scale required for input into the model.

Table 51 Parameters for utilities beta regression model



Company evidence submission for fremanezumab for preventing chronic and episodic migraine [ID1368]

B 3.4.3 Health-related quality of life studies

The details of the systematic search conducted in order to identify relevant health-related quality of life data are included in Appendix H. These searches identified a total of 16 relevant publications that contained data on the quality of life in patients with migraine. However, none of these studies reported values in the format required by this model (*i.e.* utility values for all MMD states) and therefore the required quality of life data was extracted from the FOCUS clinical trial data. Similar data produced for previous NICE submissions (onabotulinumtoxin A and erenumab) have never been publically published.[45,73]

B 3.4.4 Adverse reactions

Based on the clinical trial data, it can be seen that the adverse events associated with fremanezumab are infrequent, usually not severe and occurred at rates that were comparable to those seen with placebo (Section B 2.10). The rates of serious adverse events were also low, and were comparable to the rates seen with placebo. Therefore, the impact of adverse events on utilities has not been considered within this model. As the improved tolerability for fremanezumab over onabotulinumtoxin A is one of the distinguishing features between these treatments, this decision is conservative with respect to the cost-effectiveness comparison to onabotulinumtoxin A.

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

The derivation of the utility values used within the cost-effectiveness analysis was described in Section B 3.4.2. These values were selected as the most appropriate and representative for the migraine population under consideration in this appraisal. The utility values used within the model are detailed within Table 52.

Table 52 Utility values for each monthly migraine day state

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

The “off treatment” value was used for the analysis of BSC and for patients who had discontinued treatment, whilst the “on treatment” value was used for patients on any preventive treatment within the model (onabotulinumtoxin A and fremanezumab). The utility values were used within the model alongside the modelled distribution of patients between these states to calculate the overall average utility value within each population at each time point. As the number of MMDs is a key determinant of quality of life in patients with migraine, these utility inputs were used in combination with the modelled distribution of patients to assess the overall quality of life during treatment. The quality of life within each migraine day health state was assumed to be constant and not to vary over time. Changes in utilities over time were calculated in the model based on changes in the distribution of patients between migraine day states.

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

Details of the search strategies employed and the relevant evidence sources used for costs and healthcare resource data can be found in Appendix I.

B 3.5.1 Intervention and comparators' costs and resource use

Drug acquisition and administration costs for fremanezumab and onabotulinumtoxin A can be found in Table 53. For fremanezumab, the drug acquisition costs of £450.00 *per* injection has been converted to a *per* cycle (4-week) cost of £415.38. Therapy initiation was assumed to consist of a one-hour training session with a Band 5 hospital based nurse,[78] which had a cost of £37.00 and this was applied during the first cycle of treatment. Treatment monitoring was assumed to require a 15 minute appointment with a consultant every 6 months (unit cost of £27.00),[78] and this was adjusted to a *per* cycle cost of £4.50.

The list price for onabotulinumtoxin A was used for the drug acquisition costs. Unlike fremanezumab, onabotulinumtoxin A is administered by a healthcare professional; therefore, it was assumed that patients would require an outpatient appointment for this purpose, as *per* the onabotulinumtoxin A NICE submission.[45] In the model, a cost of £85.50 has been used, accounting for a 30 minute neurologist visit,[79] as this was the best data available. The committee in the onabotulinumtoxin A appraisal noted that these costs may be low and underestimate the time required for onabotulinumtoxin A admission.[45]

Table 53 Costs associated with intervention and comparator

	Fremanezumab	Onabotulinumtoxin A	Reference and justification
Technology cost	£415.38 *per* cycle	£276.40 *per* 12 weeks	List price for fremanezumab Cost of one 200 unit vial of onabotulinumtoxin A.[80] Assumed that all patients use one 200 unit vial *per* treatment (as *per* NICE appraisal)[45]
Therapy initiation cost	£37.00 (one off cost in first cycle)	£0.00	One hour training session with Band 5 hospital based nurse for fremanezumab, PSSRU[78]

	Fremanezumab	Onabotulinumtoxin A	Reference and justification
Administration cost	£0.00	£85.50 *per* 12 weeks	Fremanezumab is self-administered and so has no costs Onabotulinumtoxin A assumed to require 30 minute neurologist visit,[79] (as *per* NICE appraisal)[45]
Monitoring cost	£4.50 *per* cycle	£0.00	Fremanezumab assumed to require 15 minute appointment with medical consultant every 6 months, PSSRU[78] Assumed for onabotulinumtoxin A that monitoring would occur during administration visits
Adverse events costs	£0.00	£0.00	Assumed that all minor adverse events have no medical costs

B 3.5.2 Health-state unit costs and resource use

Healthcare resource use data was sourced from a study by Vo *et al*.[76] on the burden of migraine across Europe; responses from France, Germany, Italy, Spain and the UK were included in the study. There are some limitations to the study in the use of these data in the model; primarily that resource use is based on the number of headache days *per* month and not migraine days. However, this is likely to produce a conservative assumption of costs based on MMDs and therefore may underestimate the true cost burden. This assumption is also likely to reduce the cost benefits (in terms of resource use) for more efficacious treatments, as the benefits from treatment are likely to be underestimated. Furthermore, the resource use is not available to the granular level required by the model and is reported in bandings (0, 1-3, 4-7, 8-14 and ≥15 monthly headache days). However, these were the best available data identified and were used in the model for the MMD health states; details are included in Table 54. These are the same resource use data that were utilised in the ongoing appraisal of erenumab.[73] Resource use costs were taken from NHS reference costs, and data from the PSSRU was used when relevant costs were not available in the NHS reference costs. Details of these figures and their

sources are included in Table 55. The resource uses were multiplied by unit costs to calculate the total weighted cost for each health state (Table 54).

Table 54 Resource use by monthly migraine days[76]

Monthly migraine days	General practitioner visits	Emergency department visits	Hospitalisations	Nurse practitioner visits	Neurologist visits	Oral triptan usage	Weighted cost value *per* health state
0	0.202	0.030	0.023	0.063	0.003	0.000	£28.55
1	0.288	0.067	0.042	0.102	0.015	0.295	£51.35
2	0.288	0.067	0.042	0.102	0.015	0.789	£52.04
3	0.288	0.067	0.042	0.102	0.015	1.283	£52.74
4	0.413	0.058	0.040	0.175	0.013	1.777	£58.42
5	0.413	0.058	0.040	0.175	0.013	2.271	£59.11
6	0.413	0.058	0.040	0.175	0.013	2.765	£59.81
7	0.413	0.058	0.040	0.175	0.013	3.259	£60.51
8	0.553	0.092	0.040	0.048	0.038	3.753	£69.85
9	0.553	0.092	0.052	0.048	0.038	4.247	£77.98
10	0.553	0.092	0.052	0.048	0.038	4.741	£78.67
11	0.553	0.092	0.052	0.048	0.038	5.235	£79.37
12	0.553	0.092	0.052	0.048	0.038	5.729	£80.07
13	0.553	0.092	0.052	0.048	0.038	6.223	£80.76
14	0.553	0.092	0.052	0.048	0.038	6.717	£81.46
15	0.585	0.117	0.052	0.127	0.073	7.211	£94.95
16	0.585	0.117	0.052	0.127	0.073	7.705	£95.64
17	0.585	0.117	0.052	0.127	0.073	8.199	£96.34
18	0.585	0.117	0.052	0.127	0.073	8.693	£97.04
19	0.585	0.117	0.052	0.127	0.073	9.187	£97.73
20	0.585	0.117	0.052	0.127	0.073	9.681	£98.43
21	0.585	0.117	0.052	0.127	0.073	10.175	£99.13
22	0.585	0.117	0.052	0.127	0.073	10.669	£99.82

Monthly migraine days	General practitioner visits	Emergency department visits	Hospitalisations	Nurse practitioner visits	Neurologist visits	Oral triptan usage	Weighted cost value *per* health state
23	0.585	0.117	0.052	0.127	0.073	11.163	£100.52
24	0.585	0.117	0.052	0.127	0.073	11.657	£101.22
25	0.585	0.117	0.052	0.127	0.073	12.151	£101.91
26	0.585	0.117	0.052	0.127	0.073	12.645	£102.61
27	0.585	0.117	0.052	0.127	0.073	13.139	£103.31
28	0.585	0.117	0.052	0.127	0.073	13.633	£104.00

Table 55 Resource use unit costs

Resource	Unit costs	Source	Description
General practitioner visit	£37.00	PSSRU[78]	Cost *per* surgery consultation lasting 9.22 minutes, excluding travel
Nurse visit	£36.00	PSSRU[78]	Assumed be the cost of an hour of nurse time at a general practitioner practice
Neurologist visit	£171.00	NHS reference costs[79]	Consultant led neurology visit (service code 400) unit cost
Emergency department visit	£112.63	NHS reference costs[79]	HRG code VB09Z, as *per* onabotulinumtoxin A submission[45]
Hospitalisation	£636.67	NHS reference costs[79]	Weighted average of HRG codes AA31C, AA31D and AA31E
Triptan use	£1.41	Prescription cost analysis	Weighted cost of 1 triptan tablet

B 3.5.3 Adverse reaction unit costs and resource use

Adverse reactions associated with the intervention and comparator are infrequent, usually not severe, and occurred at rates that were comparable to those seen with placebo (see Section B 2.10). It was assumed that no resource use, and therefore no costs, would be associated with these.

B 3.5.4 Miscellaneous unit costs and resource use

There are no other miscellaneous costs included in the base case. However the large societal costs of migraine are included as an analysis option in the model. As migraine most commonly affects people of working age, it was assumed that migraine would have a substantial burden in the form of work days missed. Data for this were taken from a US publication as the most relevant data identified.[81] Based on ONS data showing a median hourly UK wage of £12.73 in 2018,[82] and assuming a 7.5 hour working day, it was assumed there was a cost of £100.00 associated with every work day missed.

B 3.6 Summary of base case analysis inputs and assumptions

B 3.6.1 Summary of base case analysis inputs

A summary of the base case is presented in Table 46.

Table 56 Base case economic model inputs

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty: values used in sensitivity analyses	Reference to section in submission
Time horizon	10 years	OWSA ±20%	Sections B 3.2.2 and B 3.6.2
Comparators	BSC Onabotulinumtoxin A (for CM only)	N/A	Section B 3.2.3.2
Discount rate	3.5%	OWSA ±20%	Section B 3.2.2
Model cycle length	4 weeks	N/A	Section B 3.6.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty: values used in sensitivity analyses	Reference to section in submission
Clinical inputs			
Baseline characteristics	See Section B 3.3.1, using FOCUS clinical trial data	OWSA ±20% (age, % female)	Section B 3.3.1
MMD distribution	See Section B 3.3.2, using FOCUS clinical trial data	N/A	Section B 3.3.2
MMD reduction	See Section B 3.3.2, using FOCUS clinical trial data	PSA normal distribution	Sections B 2.7.4 and B 3.3.2
Response rate	See Section B 3.3.3, using NMA data	N/A	Sections B 2.9 and B 3.3.3
Discontinuation rate	[redacted] *per* cycle	OWSA ±20% PSA normal distribution	Sections B 2.6.3 and B 3.3.5
Utility and cost inputs			
Utilities	Mapped from FOCUS data, see Section B 3.4.5	OWSA ±20% (treatment effect) PSA normal (baseline and treatment effect)	Section B 3.4.5
Drug acquisition cost	Fremanezumab £415.38 *per* cycle Onabotulinumtoxin A £276.40 *per* injection (every 12 weeks)	OWSA ±20%	Section B 3.5.1
Drug initiation and administration cost	Initiation: Fremanezumab £37.00 Onabotulinumtoxin A £0.00 Administration: Fremanezumab £0.00 Onabotulinumtoxin A £85.50	OWSA ±20%	Section B 3.5.1
Resource use	Vo *et al*.[76]	N/A	Section B 3.5.2
Resource costs	NHS reference costs[79] and PSSRU[78]	PSA γ distribution	Section B 3.5.2
Modelling assumptions			
Negative stopping rule	Patients who do not respond to treatment (at least a 50% reduction in MMDs for EM or at least a 30% reduction for CM) stop after 12 weeks assessment	N/A	Section B 3.6.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty: values used in sensitivity analyses	Reference to section in submission
	(24 weeks for onabotulinumtoxin A)		
Positive stopping rule	52 weeks after initial assessment, all patients have a 12-week treatment break to assess response after which 20% discontinue treatment, this rule is then applied every 52 weeks thereafter	N/A	Section B 3.6.2
MMDs after therapy discontinuation	After negative stopping rule – return to baseline MMDs After *per* cycle discontinuation – return to placebo (BSC) MMDs After positive stopping rule – retain treatment MMDs	N/A	Section B 3.6.2
Waning	No waning in treatment effect occurs	N/A	Sections B 3.2.2 and B 3.6.2
Mortality	No migraine specific mortality	N/A	Sections B 3.3.6 and B 3.6.2

BSC: best supportive care; CM: chronic migraine; EM: episodic migraine; MMDs: monthly migraine days; N/A: not applicable; NHS: National Health Service; OWSA: one way sensitivity analysis; PSSRU: Personal Social Services Research Unit; PSA: probabilistic sensitivity analysis

B 3.6.2 Assumptions

The model was based on a number of assumptions, which are detailed alongside their justifications within Table 57.

Table 57 Key modelling assumptions

Assumption	Justification
No natural history variation in migraine is included within the model	This assumption has been made to simplify the modelling and as there is no clear evidence on which to base any modelling. Data are available to suggest that patients can transition from both EM to CM and *vice versa*,[15,16] but no data of sufficient detail are available to accurately model natural migraine variation over time. This is an area of considerable complexity as life events such as the menopause can have a significant impact on migraine

Assumption	Justification
	frequency,[74] but again exact effects are unclear. Therefore, based on the inconclusive evidence and to simplify the modelling to a manageable level no natural history variation in migraine has been included
Base case time horizon is 10 years	A 10 year time horizon was considered appropriate to capture all differences in costs and QALYs between treatments. This is as it is not expected for patients to remain on treatment indefinitely. In clinical practice it is likely that patients showing a sufficient response will have treatment halted (see positive stopping rule), and if necessary treatment would be restarted at a later time. In addition, based on the assumed treatment discontinuation rates (based on the available long-term clinical trial evidence) only a very small number of patients may remain on treatment after 10 years. Therefore, a 10 year time horizon is sufficient to capture all meaningful differences in costs and QALYs between treatments. A longer time horizon than 10 years was also not considered appropriate due to natural variations in migraine over time; it has not been possible to include these natural history changes within the model as insufficient data are available to base the modelling on. In addition, life events such as the menopause can have a significant impact on migraine frequency.[74] This makes modelling migraine over longer time horizons very challenging and would have led to considerable uncertainties in the modelling
Cycle length is 4 weeks	This cycle length was chosen to match the 4-week assessment routine from the FOCUS clinical trial
Fremanezumab is included as a combined dosing regimen	The monthly and quarterly regimens of fremanezumab are equal in total dose, cost and show no differences in efficacy or safety (see Sections B 3.2.3.1 and B 2.10). The aim of making two dosing regimens available is to allow flexibility for the patient and clinician; allowing a choice of regimen that fits with the patient's personal preference with the aim of aiding increased treatment adherence. Therefore it was considered appropriate to consider these as a combined regimen to simplify the analysis
The MMD distributions derived from the fremanezumab FOCUS trial data are assumed to be generalizable to other active treatments	This assumption was made as sufficiently detailed data for onabotulinumtoxin A were not available to produce such distributions for onabotulinumtoxin A
Efficacy data for placebo is used to provide an efficacy of BSC	This assumption was made as this is the most plausible data to be used for the efficacy of BSC. This is a conservative assumption as BSC is assumed to include acute treatment of migraine attacks only and so no improvement in condition would be expected. However, it is plausible that some patients may improve given BSC and

Assumption	Justification
	the placebo data is the only data available on which to base efficacy in BSC
Data on MMD reductions for responders and non-responders receiving onabotulinumtoxin A are assumed to be equivalent to fremanezumab	As sufficiently detailed data for onabotulinumtoxin A are not available to produce response data for responders and non-responders, it was assumed that all active treatments (*i.e.* onabotulinumtoxin A and fremanezumab) produced equal efficacy in terms of MMD reduction. This is a conservative assumption as the NMA results suggested that fremanezumab has a greater treatment effect (although no significant differences between treatments were seen)
Responder rate in onabotulinumtoxin A based on data for at least a 50% reduction in MMDs	The at least 30% response rate for onabotulinumtoxin A was not available within the available published literature. Therefore, an estimate was produced based on the relative treatment effect seen between onabotulinumtoxin A and fremanezumab found in the NMA for at least a 50% response rate. This effect size was used to estimate the proportion of patients with at least a 30% response rate for onabotulinumtoxin A based on the figures for fremanezumab. The impact of uncertainty in this value are explored within the scenario analyses conducted within the model
Resource use costs are accumulated based on MMDs *per* 28 days	Monthly migraine days have been demonstrated to be related to resource use,[76] and this approach has been utilised within previous economic analyses of migraine conducted for NICE[45,73]
Health-state utilities are accumulated based on MMDs *per* 28 days and on treatment/off treatment status	Monthly migraine days show a strong correlation to utility values and this approach has been utilised within previous economic analyses of migraine conducted for NICE.[45,73] It has also been demonstrated that patients on treatment can be seen to have an improvement in quality of life compared to those not receiving treatment, this is also consistent with previous economic analyses of migraine conducted for NICE[45,73]
A negative stopping rule was applied in the model where patients who do not respond to treatment (at least a 50% reduction in MMDs for EM or at least a 30% reduction for CM) stop after a 12-week assessment (24 weeks for onabotulinumtoxin A)	It was assumed that an evaluation of treatment efficacy would occur within clinical practice and such an assumption is consistent with previous NICE appraisals.[45,73] At least a 50% response in EM and at least a 30% response in CM are clinically relevant reduction in MMDs and hence have been chosen as the response criteria, this is consistent with the response rates preferred by the committee in the ongoing erenumab appraisal.[73] An assessment of onabotulinumtoxin A after 24 weeks is consistent with previous NICE appraisals[45,73]
A positive stopping rule was applied in the model where 52 weeks after initial assessment, all patients have a 12 week treatment break to assess response after which 20%	It was assumed that patients would be unlikely to remain on treatment indefinitely in clinical practice. It is established practice in migraine to discontinue treatment in patients who show a sufficient response to treatment.[43] Recently published guidelines from EHF recommend a similar approach for anti-CGRPs.[53] The proportion of patients who would stop under such a rule is not clear. A value of 20%

Assumption	Justification
discontinue treatment, this rule is then applied every 52 weeks thereafter	has been assumed based on expert opinion, but the impact of varying this value is explored within the scenario analyses conducted
MMDs after treatment discontinuation are assumed to be the following: Return to baseline MMDs (after negative stopping rule) Return to placebo (BSC) MMDs (after *per* cycle discontinuation) Retain treatment MMDs (after positive stopping rule)	As a negative stop occurs in non-responding patients, it was assumed that these patients revert to their baseline MMD values as they have experienced an insufficient treatment benefit. This is a conservative assumption as it is likely that they may maintain some treatment benefit for some period For patients who discontinue on a *per* cycle basis, it is assumed that these patients transition to best supportive care and they therefore follow the response of these patients. This is again a conservative assumption as it is likely that they may maintain some treatment benefit for some period For patients who discontinue due to the positive stopping rule, it is assumed that they maintain the treatment benefit throughout the model horizon. The long-term data available for fremanezumab support the maintained efficacy of this treatment; however, limited data are available for patients once they have discontinued treatment. Therefore, although it has been assumed that the treatment effect is maintained, this benefit is reduced over time when the treatment waning effect is applied in the model
Waning in treatment effect does not occur over the 10-year horizon of the model	There is no available data to suggest that a waning effect occurs with fremanezumab, with the HALO extension data showing that efficacy was maintained for at least 15 months of treatment. Migraine is not a degenerative disease, fremanezumab exhibits low levels of anti-drug antibodies (2% of patients developed such antibodies after 12 months of fremanezumab treatment, and there is no evidence to suggest that these antibodies impact the safety or efficacy of fremanezumab), which together make a waning in treatment effect less plausible. There is also no evidence to inform an appropriate timescale over which a waning effect may occur or the size that this effect may have. On the available evidence, the most plausible assumption is that there is no waning in the treatment effect. However, as recognised during the ongoing erenumab appraisal, there is a possibility that a waning effect does occur.[73] The impact of including a waning effect are therefore explored within the scenario analyses
No migraine specific mortality was assumed in this model	There are no data available that suggests that migraine impacts on life expectancy, with a meta-analysis concluding migraine does not appear to substantially impact mortality[30]
Placebo effect maintained within the model	There is no strong evidence available to show over what time period any placebo effect is maintained within patients with migraine. Therefore, it has been conservatively assumed that this effect is maintained indefinitely throughout the time horizon of the model. This assumption was also required to accurately capture the relevant treatment effect

Assumption	Justification
	of active treatments, as these are modelled as differences in mean MMDs to placebo
Adverse events were not included within the model	Based on clinical trial data, adverse events associated with fremanezumab were infrequent, usually not severe and occurred at rates that were comparable to those seen with placebo (Section B 2.10). The rates of serious adverse events were also low, and were comparable to the rates seen with placebo. As the improved tolerability for fremanezumab over onabotulinumtoxin A is one of the distinguishing features between these treatments, this decision is conservative with respect to the cost-effectiveness comparison to onabotulinumtoxin A

BSC: best supportive care; EHF: European Headache Federation; MMD: monthly migraine day; NMA: network meta-analysis; QALY: quality-adjusted life year

B 3.7 Base case results

B 3.7.1 Base case incremental cost-effectiveness analysis results

Clinical outcomes from the model as well as disaggregated results for the base case are presented in Appendix J.

B 3.7.1.1 Episodic migraine

The results of the base case analysis in EM are presented in Table 58. The results of this analysis show that fremanezumab had greater costs than BSC, but also resulted in greater QALYs. When the incremental cost-effectiveness ratio (ICER) is considered, it can be seen that fremanezumab can be considered to be a cost-effective treatment in this patient population (£13,954 *per* QALY).

Table 58 Base case results in episodic migraine

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£13,954**

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

B 3.7.1.2 Chronic migraine

The results of the base case analysis in CM are presented in Table 59. The results of this analysis show that fremanezumab had greater costs than both BSC and onabotulinumtoxin A, but also resulted in higher QALYs compared to both treatments. When the ICERs are considered, it can be seen that fremanezumab can be considered to be a cost-effective treatment in this patient population in comparison to both BSC (£11,825 *per* QALY) and onabotulinumtoxin A (£16,227 *per* QALY).

Table 59 Base case results in chronic migraine

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER *versus* BSC (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
OBA	[redacted]	[redacted]	[redacted]	[redacted]	**£6,777**	**£6,777**
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£11,825**	**£16,227**

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

B 3.8 Sensitivity analyses

B 3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was incorporated into the model to allow the simultaneous variation of multiple input values, enabling assessments of interactions that occur between inputs. The PSA involved running the model a large number of times (1000 replications), with different sets of inputs, to make it possible to estimate credible limits of the ICER. The values of the inputs were determined by random variation within statistical distributions. These distributions were defined according to the type of parameters in order to reflect the distribution that they generally follow. Details of the inputs included within the PSA and the distributions used to model each input are included in Table 56 (Section B 3.6.1).

B 3.8.1.1 Episodic migraine

The summary results of the PSA are presented in Table 60, with full results for the analysis of fremanezumab *versus* BSC presented in Figure 10, and the cost-effectiveness acceptability curve is presented in Figure 11. The PSA results show a good agreement with the deterministic analysis and provide confidence in the ICER results produced by this model. Analysis at a willingness-to-pay threshold of £30,000 gave a probability of [redacted]% that fremanezumab would be a cost-effective treatment, and a probability of [redacted]% at a threshold £20,000.

Table 60 Probabilistic results for episodic migraine

Technologies	Mean costs (£) [SE]	Mean QALYs [SE]	Incremental costs (£) [SE]	Incremental QALYs [SE]	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£13,843**

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

Figure 10 Probabilistic cost and effectiveness results for episodic migraine *versus* best supportive care

[redacted]

PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay

Figure 11 Cost-effectiveness acceptability curve for episodic migraine *versus* best supportive care

PSA: probabilistic sensitivity analysis; ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay

B 3.8.1.2 Chronic migraine

The summary results of the PSA are presented in Table 61, with full results for the analysis of fremanezumab *versus* BSC presented in Figure 12 and the results *versus* onabotulinumtoxin A in Figure 13. Cost-effectiveness acceptability curves are presented *versus* BSC in Figure 14 and *versus* onabotulinumtoxin A in Figure 15. The PSA results show a good agreement with the deterministic analysis and provide confidence in the ICER results produced by this model. Analysis at a willingness-to-pay threshold of £30,000 gave a probability of [redacted]% that fremanezumab would be

a cost-effective treatment compared to BSC and a probability of [redacted]% compared to onabotulinumtoxin A, and probabilities of [redacted]% and [redacted]%, respectively, at a threshold £20,000.

Table 61 Probabilistic results for chronic migraine

Technologies	Mean costs (£) [SE]	Mean QALYs [SE]	Incremental costs (£) [SE]	Incremental QALYs [SE]	ICER versus BSC (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
OBA	[redacted]	[redacted]	[redacted]	[redacted]	**£6,932**	**£6,932**
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£12,102**	**£16,654**

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

Figure 12 Probabilistic cost and effectiveness results for chronic migraine *versus* best supportive care

[redacted]

PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay

Figure 13 Probabilistic cost and effectiveness results for chronic migraine *versus* onabotulinumtoxin A

PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay

Figure 14 Cost-effectiveness acceptability curve for chronic migraine *versus* best supportive care

PSA: probabilistic sensitivity analysis; ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay

Figure 15 Cost-effectiveness acceptability curve for chronic migraine *versus* onabotulinumtoxin A

PSA: probabilistic sensitivity analysis; ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay

B 3.8.2 Deterministic sensitivity analysis

A deterministic one-way sensitivity analysis was conducted. In this analysis, one parameter was varied at a time whilst the others were held constant. The procedure was based on an estimated variation of ±20% in a number of key variables within the model. Details on the variables included in this sensitivity analysis are included in Table 56 (Section B 3.6.1). This analysis helps to show key inputs for the model that

cause the greatest variation in outputted results. Results of this analysis are expressed as net monetary benefit based on a willingness-to-pay threshold of £30,000 *per* QALY.

B 3.8.2.1 Episodic migraine

A tornado plot of the results of the deterministic sensitivity analysis for the comparison to BSC is presented in Figure 16. The results reveal that the model can be considered stable to changes in key inputs, and that the inputs that have the greatest impact were fremanezumab cost, the time horizon and utility treatment effect.

Figure 16 Tornado plot of deterministic sensitivity analysis for episodic migraine *versus* best supportive care

#: number; Tx: treatment

B 3.8.2.2 Chronic migraine

A tornado plot of the results of the deterministic sensitivity analysis for the comparison to BSC is presented in Figure 17 and compared to onabotulinumtoxin A in Figure 18. The results reveal that the model can be considered stable to changes in key inputs, and that the inputs that have the greatest impact were fremanezumab cost, onabotulinumtoxin A cost, the time horizon and utility treatment effect.

Figure 17 Tornado plot of deterministic sensitivity analysis for chronic migraine *versus* best supportive care

#: number; Tx: treatment

Figure 18 Tornado plot of deterministic sensitivity analysis for chronic migraine *versus* onabotulinumtoxin A

#: number; Tx: treatment

B 3.8.3 Scenario analysis

A number of scenario analyses have been conducted to investigate the impact of assumptions made within the base case for this model. A description of these analyses is presented in Table 62, where an explanation of the changes from the base case are also included.

Table 62 Description of scenario analyses conducted

Scenario number	Description	Explanation
1	Time horizon of 5 years	Time horizon reduced to 5 years
2	Lifetime time horizon	Time horizon increased to lifetime
3	Waning of treatment effect occurs over 10 years	A waning in the treatment effect was applied, which reduced MMDs for treated patients back to that of BSC over 10 years
4	Lifetime horizon with waning of treatment effect over 10 years	Over a lifetime horizon, it is more likely that a waning effect may be observed and so the impact of combining these scenarios was considered
5	Treatment administration cost for fremanezumab set to £1.85 *per* cycle (monthly administration)	Fremanezumab can be self-administered by patients and it is expected that the vast majority of patients will self-administer. However, some patients may be unable to self-administer and will therefore incur an administration cost. For this analysis, it

Scenario number	Description	Explanation
6	Treatment administration cost for fremanezumab set to £0.62 *per* cycle (quarterly administration)	has been assumed that 10% of patients will need treatment to be administered (a high and conservative estimate due to the average age and comorbidity status of patients with migraine meaning that it is unlikely that they would struggle with self-injection). This has been costed as a 30 minute appointment with a Band 5 hospital based nurse (£18.50 PSSRU[78]). This has been adjusted *pro rata* for monthly and quarterly dosing
7	Positive stopping rule affects 10% of currently treated patients	The assumption regarding the proportion of patients affected by the positive stopping rule has some uncertainty. Therefore, an alternative scenario where this rule affects 10% of patients, and where it is not applied have been investigated
8	No positive stopping rule applied	
9	Treatment response rate for onabotulinumtoxin A increased by 15% to [redacted]%	As there is some uncertainty in the comparison between fremanezumab and onabotulinumtoxin A, an increased and decreased treatment effect for onabotulinumtoxin A has been investigated
10	Treatment response rate for onabotulinumtoxin A decreased by 15% to [redacted]%	
11	50% reduction in MMDs used as response threshold in CM	At least a 50% reduction in MMDs has also been used as a response definition in CM, and so this threshold has been investigated
12	Impact of lost work days considered	Migraine has a significant impact on the lives of patients and the impact on work is one of these areas. Therefore, a wider analysis on the societal impact of migraine has been investigated
13	Quarterly fremanezumab dosing	Efficacy data for quarterly and monthly fremanezumab considered separately
14	Monthly fremanezumab dosing	

BSC: best supportive care; CM: chronic migraine; MMDs: monthly migraine days

B 3.8.3.1 Episodic migraine

The results of these scenario analyses are presented in Table 63. These show that in all the scenarios considered that fremanezumab remains a cost-effective treatment. Reducing the time horizon of the model to five years and removing the positive stopping rule had the greatest effect on increasing the ICER; whereas a consideration of the societal impact of migraine through the impact on work had the greatest impact on lowering the ICER.

Table 63 Summary of scenario analyses results in episodic migraine

Scenario	ICER *versus* BSC
Base case	£13,954
1 – 5 year horizon	£22,598
2 – Lifetime horizon	£4,767
3 – Waning of treatment effect over 10 years	£14,202
4 – Lifetime horizon and waning over 10 years	£4,835
5 – Treatment administration costs included for fremanezumab (monthly: £1.85 *per* cycle)	£14,054
6 – Treatment administration costs included for fremanezumab (quarterly: £0.62 *per* cycle)	£13,987
7 – Positive stopping rule affects 10% of currently treated patients	£16,620
8 – No positive stopping rule	£20,214
9 – Proportion of patients responding to onabotulinumtoxin A increased to [redacted]%	N/A
10 – Proportion of patients responding to onabotulinumtoxin A increased to [redacted]%	N/A
11– 50% reduction in MMDs used as response threshold in CM	N/A
12 – Impact of lost work days	Dominates
13 – Quarterly fremanezumab dosing	£13,976
14 – Monthly fremanezumab dosing	£13,909

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

B 3.8.3.2 Chronic migraine

The results of these scenario analyses are presented in Table 64. These show that in all the scenarios considered that fremanezumab remains a cost-effective treatment. Reducing the time horizon of the model to five years and removing the positive stopping rule had the greatest effect on increasing the ICER; whereas a consideration of the societal impact of migraine through the impact on work had the greatest impact on lowering the ICER.

Table 64 Summary of scenario analyses results in chronic migraine

Scenario	ICER *versus* BSC	ICER *versus* onabotulinumtoxin A
Base case	£11,825	£16,825
1 – 5 year horizon	£19,328	£27,517
2 – Lifetime horizon	£4,085	£5,555
3 – Waning of treatment effect over 10 years	£12,017	£16,382
4 – Lifetime horizon and waning over 10 years	£4,131	£5,589
5 – Treatment administration costs included for fremanezumab (monthly: £1.85 *per* cycle)	£11,907	£16,380
6 – Treatment administration costs included for fremanezumab (quarterly: £0.62 *per* cycle)	£11,853	£16,278
7 – Positive stopping rule affects 10% of currently treated patients	£14,017	£19,634
8 – No positive stopping rule	£16,951	£24,756
9 – Proportion of patients responding to onabotulinumtoxin A increased to [redacted]%	£11,825	£22,411
10 – Proportion of patients responding to onabotulinumtoxin A increased to [redacted]%	£11,825	£12,742
11– 50% reduction in MMDs used as response threshold in CM	£10,724	£17,155
12 – Impact of lost work days	Dominates	Dominates
13 – Quarterly fremanezumab dosing	£12,243	£17,325
14 – Monthly fremanezumab dosing	£11,462	£15,326

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; MMDs: monthly migraine days

B 3.8.4 Summary of sensitivity analyses results

Overall, the sensitivity results demonstrate the robustness of this economic model and the results produced by it. These analyses demonstrated that fremanezumab is a cost-effective treatment under a large variety of scenarios and when key parameters within the model are varied.

B 3.8.4.1 Episodic migraine

The PSA demonstrated a good agreement with the base case deterministic results and gave a probability of [redacted]% that fremanezumab would be a cost-effective treatment at a willingness-to-pay threshold of £30,000 (and a probability of [redacted]% at a threshold £20,000).

The deterministic sensitivity analysis showed that the model is stable to changes in most analysed inputs. This analysis revealed that the inputs which had the greatest impact were fremanezumab cost, the time horizon and utility treatment effect.

Analysis of a number of scenarios varying key assumptions in the model base case showed that fremanezumab was cost-effective under all modelled scenarios. Reducing the time horizon to five years, removing the positive stopping rule and including the societal impact of migraine had the greatest impact on ICER values.

B 3.8.4.2 Chronic migraine

The PSA demonstrated a good agreement with the base case deterministic results and gave a probability of [redacted]% (*versus* BSC) and [redacted]% (*versus* onabotulinumtoxin A) that fremanezumab would be a cost-effective treatment at a willingness-to-pay threshold of £30,000 (and probabilities of [redacted]% and [redacted]%, respectively, at a threshold £20,000).

The deterministic sensitivity analysis showed that the model is stable to changes in most analysed inputs. This analysis revealed that the inputs which had the greatest impact were fremanezumab cost, onabotulinumtoxin A cost, the time horizon and utility treatment effect.

Analysis of a number of scenarios varying key assumptions in the model base case showed that fremanezumab was cost-effective under all modelled scenarios. Reducing the time horizon to five years, removing the positive stopping rule and including the societal impact of migraine had the greatest impact on ICER values.

B 3.9 Subgroup analysis

High-frequency episodic migraine has been presented throughout this submission as a subgroup of particular interest for this appraisal. This is due to the fact that HFEM has a substantial impact on patients, similar to that seen in patients with CM.[1] There is also a current lack of treatment options for these patients after failure of three preventive therapies, with onabotulinumtoxin A limited to CM.

Due to the importance of this group an additional economic analysis focussed on HFEM has been conducted. This utilised efficacy data from the FOCUS clinical trial in patients with 8-14 monthly headache days. This patient group was assumed to have overall characteristics (average age and percentage female) that matched the overall EM population. Within the patients with HFEM, responders had baseline mean MMDs of [redacted] compared to [redacted] for non-responders. The fremanezumab treatment effect compared to placebo was [redacted] MMDs in responders and [redacted] MMDs in non-responders. At least a 50% reduction in MMDs was seen in [redacted]% of fremanezumab patients and [redacted]% of placebo (BSC) patients.

The results of the analysis in this subgroup are presented in Table 65, and demonstrate that fremanezumab is a cost-effective treatment within this patient subgroup. The ICER value is lower in patients with HFEM than was seen within the whole EM population.

Table 65 Base case results in high-frequency episodic migraine

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£12,275**

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

B 3.10 Validation

B 3.10.1 Validation of cost-effectiveness analysis

The model structure and all key inputs were reviewed and agreed by UK clinical experts during an advisory board meeting.[54] Subsequent to the advisory board,

Teva UK sought clinical opinions from consultant neurologists who specialise in headache and are considered as thought leaders in the field of migraine. This allowed Teva UK to validate key assumptions made within the submission, in particular where there is a lack of published data. Three experts were engaged from the South of England and the North of England using a structured format, including a pro forma followed by a telephone discussion; for transparency the pro forma is included within Appendix N of this submission. The model has also been reviewed by an expert in health economics to ensure that the model structure and calculations were working as intended. Finally, clinical trial data were used to provide an internal validation of the model calculations.

B 3.11 Interpretation and conclusions of economic evidence

Fremanezumab is a cost-effective treatment

The economic evidence presented here clearly demonstrates that fremanezumab is a cost-effective treatment for the prevention of migraine (after three prior preventive treatments). The results show that fremanezumab is cost-effective in both CM and EM populations. In EM, fremanezumab had an ICER *versus* BSC of £13,954; while in CM fremanezumab had an ICER *versus* BSC of £11,825 and *versus* onabotulinumtoxin A of £16,227.

An additional analysis was conducted in a specific subgroup of interest, patients with HFEM. Fremanezumab was demonstrated to be a highly cost-effective treatment in this patient subgroup, with an ICER *versus* BSC of £12,275.

Generalisability of analysis

This economic analysis conducted focussed on the population of interest for this appraisal (those who had failed on three or more previous migraine preventive therapies) and can therefore be considered generalisable to UK clinical practice. The population of interest was selected as this is where it is expected that anti-CGRP therapy would be utilised in UK clinical practice based on expert clinical opinion.

Sensitivity analyses produced consistent results

The PSA conducted produced results that were consistent with the deterministic analysis and showed a high degree of confidence in the results. The PSA produced probabilities of [redacted]% (*versus* BSC in EM), [redacted]% (*versus* BSC in CM) and [redacted]% (*versus* onabotulinumtoxin A in CM) that fremanezumab would be a cost-effective treatment at a willingness-to-pay threshold of £30,000. All the sensitivity analyses and scenario analyses conducted demonstrated the cost-effectiveness of fremanezumab in both EM and CM.

Factors not considered in economic analysis

The economic analysis considered all factors that were feasible to include within the model. However, the impact in one important area is not fully captured by the model. The administration of onabotulinumtoxin A currently leads to a significant burden on headache clinics as every administration of onabotulinumtoxin A is required to be administered by an expert physician. This has therefore led to a significant burden on these clinics; clinical experts consulted by Teva have indicated that there are long waiting times for onabotulinumtoxin A administration in many headache clinics due to capacity issues.

Fremanezumab has the potential to significantly relieve pressure on headache clinics as this treatment can be self-administered at home by patients. It is expected that, in line with current practice, fremanezumab will be prescribed from specialist clinics. However, once a patient is established on treatment and able to self-administer, this will reduce the burden on clinics compared to the requirements for all

onabotulinumtoxin A administrations to be conducted in hospital. The model includes the direct costs that are incurred through the administration of onabotulinumtoxin A, but the burden and the potential relief of this burden on headache clinics was not captured within the model. It can therefore be expected that the introduction of fremanezumab would be more economically beneficial than is assumed by the analysis conducted here.

Another area where the full impact of migraine has not been captured is the burden from a societal perspective. A societal perspective falls outside of the NICE base case; however, the societal perspective is particularly important when considering migraine as this disease is most common in people of working age.[25] The societal impact of this disease from lost productivity is substantial.[42] A societal perspective was included as an option in this model and used in a scenario analysis. This demonstrated that fremanezumab is more cost-effective when a societal perspective is included within the economic analysis.

Strengths and limitations of the economic evaluation

The strengths of this analysis include that it was focussed on the relevant UK patient population, used data from high quality RCTs, had a detailed model structure with 28 MMD states, and used key clinically meaningful efficacy measures as inputs. The key clinical data within the model, which includes the baseline characteristics, the patient distributions between MMD states and the utilities data, were all derived from the FOCUS clinical trial. This gives a consistency in all of these key model inputs that may have varied if data from multiple clinical trials had been required. This clinical trial was focussed on patients who had failed previous lines of therapies and included patients with both CM and EM. This closely matches the population of interest and included a significant number of patients who exactly match this population (three or more previous failed migraine preventive therapies).

The use of a detailed structure employing 28 MMD states allowed an accurate analysis of the economic impact of treatment. This also allowed small and subtle

variations in the distribution of migraine days to fully impact the results of the analysis. This is important as it allows the model to closely resemble reality, as the full impact of treatment on the population is considered.

The reduction in MMDs and the proportion of patients who respond to treatment are key clinically relevant measures in migraine. These data were used as the efficacy inputs in the model and therefore gives confidence that the most clinically relevant changes have been modelled in this analysis. In addition, this model incorporated separate analyses of responders and non-responders to allow the most relevant data to be included. It is expected that in clinical practice, and in line with established practice for current migraine preventive treatments, that an assessment of efficacy will be conducted after a relevant time period (assumed to be 12 weeks for fremanezumab and 24 weeks for onabotulinumtoxin A) and at this point non-responding patients will be discontinued from treatment.

A limitation of this model results from the lack of granularity within the published data for onabotulinumtoxin A. This has led to some limitations within the NMA conducted to compare the efficacy of fremanezumab and onabotulinumtoxin A (no direct studies are available), which are outlined in Section B 2.9. Fremanezumab demonstrates consistently numerically superior results to onabotulinumtoxin A, but due to the limitations in the NMA there is some uncertainty to the exact size of this difference. To counteract this limitation, scenarios where the response rate for onabotulinumtoxin A was varied by ±15% were conducted.

It has not been possible to include any natural history variation in migraine or a fourth oral preventive treatment due to a lack of data. There is little available published detailed evidence on the natural history of migraine that could be used to include these effects within the model. It is also worth noting that should such data have been available, it would have been very challenging to build the complex model that would be required to model these effects. Whilst additional oral therapies may be used within clinical practice in this patient population, this is mainly due to a lack of any other options (as validated by clinical opinion). There is also no available evidence showing efficacy of oral migraine preventive therapies in the patients of interest for this appraisal (patients who have failed on three or more previous

migraine preventive therapies). Fourth-line oral treatments were therefore not considered to be relevant comparators.

B.4 **Appendices**

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Inclusion and exclusion criteria

Appendix M: Additional baseline characteristics

Appendix N: Pro forma used for structured clinical expert engagement

B.5 References

1 Torres-Ferrús M, Quintana M, Fernandez-Morales J *et al*. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. *Cephalalgia* 2017; 37: 104–113.

2 Tso AR, Goadsby PJ. Anti-CGRP Monoclonal Antibodies: the Next Era of Migraine Prevention? *Curr Treat Options Neurol* 2017; 19: 27.

3 Benemei S, Nicoletti P, Capone JG *et al*. CGRP receptors in the control of pain and inflammation. *Curr Opin Pharmacol* 2009; 9: 9–14.

4 Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol* 1990 ;28: 183–187.

5 Juhasz G, Zsombok T, Jakab B *et al*. Sumatriptan causes parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache during nitroglycerin induced migraine attack. *Cephalalgia* 2005; 25: 179–183.

6 AJOVY Summary of Product Characteristics. Teva UK Limited.

7 Aimovig. Summary of Product Characteristics. Novartis Pharmaceuticals UK Limited.

8 [redacted]

9 GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1545–1602.

10 Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015 ; 386: 743–800.

11 Institute for Health Metrics and Evaluation. Available at: http://vizhub.healthdata.org/gbd-compare [Accessed: April 2019].

12 Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalagia* 2018; 38: 1–211.

13 Lipton RB, Bigal ME, Diamond M *et al*. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; 68: 343–349.

14 BASH 2010. Guidelines for all healthcare professionals in the diagnosis and management of migraine. Available at: https://www.bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf [Accessed April 2019].

15 Bigal ME, Serrano D, Buse D *et al*. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008; 48: 1157–1168.

16 Manack A, Buse DC, Serrano D *et al*. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. *Neurology* 2011; 76: 711–718.

[17] Office for National Statistics. Population estimates analysis tool. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesanalysistool [Accessed April 2019].

[18] Buse DC, Manack AN, Fanning KM *et al*. Chronic migraine prevalence, disability, and sociodemographic factors: Results from the American Migraine Prevalence and Prevention Study. *Headache* 2012; 52: 1456–1470.

[19] Serrano D, Lipton RB, Scher AI *et al*. Fluctuations in episodic and chronic migraine status over the course of 1 year: Implications for diagnosis, treatment and clinical trial design. *J Headache Pain* 2017; 18: 101.

[20] Martin VT. Migraine and the menopausal transition. *Neurol Sci* 2014;35 Suppl 1:65–69.

[21] Lipton RB, Fanning KM, Serrano D *et al*. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology* 2015; 84: 688–695.

[22] May A, Schulte LH. Chronic migraine: Risk factors, mechanisms and treatment. *Nat Rev Neurol* 2016; 12: 455–464.

[23] Manzoni GC, Stovner LJ. Epidemiology of headache. *Handb Clin Neurol* 2010; 97: 3–22.

[24] Cheng H, Treglown L, Green A *et al*. Childhood onset of migraine, gender, parental social class, and trait neuroticism as predictors of the prevalence of migraine in adulthood. *J Psychosom Res* 2016; 88 54–58.

[25] Steiner TJ, Scher AI, Stewart WF *et al*. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia* 2003; 23: 519–527.

[26] Becker C, Brobert GP, Almqvist PM *et al*. Migraine incidence, comorbidity and health resource utilization in the UK. *Cephalalgia* 2008; 28: 57–64.

[27] Straube A & Andreou A. Primary headaches during lifespan. *J Headache Pain* 2019; 20: 35.

[28] Bloudek LM, Stokes M, Buse DC *et al*. Cost of healthcare for patients with migraine in five European countries: Results from the International Burden of Migraine Study (IBMS). *J Headache Pain* 2012; 13: 361–378.

[29] Sanderson JC, Devine EB, Lipton RB *et al*. Headache-related health resource utilisation in chronic and episodic migraine across six countries. *J Neurol Neurosurg Psychiatry* 2013; 84: 1309–1317.

[30] Schürks M, Rist PM, Shapiro RE *et al*. Migraine and mortality: A systematic review and meta-analysis. *Cephalalgia* 2011; 31: 1301–1314.

[31] Åsberg AN, Stovner LJ, Zwart JA *et al*. Migraine as a predictor of mortality: The HUNT study. *Cephalalgia* 2015; 36: 351–357.

[32] Borsook D & Dodick DW. Neurology Clinical Practice. 2015 – Taking the headache out of migraine. *Neurol Clin Pract* 2015; 5: 317–325.

[33] Stafford MR, Hareendran A, Ng-Mak DS *et al*. EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of migraineurs. *Health Qual Life Outcomes* 2012; 10: 65.

[34] Stovner LJ, Andree C. Impact of headache in Europe: A review for the Eurolight project. *J Headache Pain* 2008; 9: 139–146.

[35] Lipton RB, Liberman JN, Kolodner KB *et al*. Migraine headache disability and health-related quality-of-life: A population-based case-control study from England. *Cephalalgia* 2003; 23: 441–450.

[36] Steiner TJ, Stovner L, Katsarava Z *et al*. The impact of headache in Europe: principal results of the Eurolight project. *J Headache Pain* 2014; 15: 1–11.

[37] D'Amico D & Tepper SJ. Prophylaxis of migraine: general principles and patient acceptance. *Neuropsychiatr Dis Treat* 2008; 4: 1155–1167.

[38] Silberstein SD, Lee L, Gandhi K *et al*. Health care resource utilization and migraine disability along the migraine continuum among patients treated for migraine. *Headache* 2018; 58: 1579–1592.

[39] Varon S, Burk CT, Buse DC *et al*. Impact of chronic (CM) and episodic migraine (EM) on work presenteeism in 9 countries. *Value Health* 2009; 12: A367–A368.

[40] Ng-Mak DS, Ho TW, Stanford B *et al*. Results of a 2-year retrospective cohort study of newly prescribed triptan users in European nationwide practice databases. *Cephalalgia* 2012; 32: 875–887.

[41] Linde M, Gustavsson A, Stovner LJ *et al*. The cost of headache disorders in Europe: The Eurolight project. *Eur J Neurol* 2012; 19: 703–711.

[42] The Work Foundation 2018. Available at: http://www.theworkfoundation.com/wp-content/uploads/2018/04/Society%E2%80%99s-headache-the-socioeconomic-impact-of-migraine.-Work-Foundation.pdf [Accessed April 2019].

[43] NICE 2015. Headaches in over 12s: diagnosis and management (CG150). Available at: https://www.nice.org.uk/guidance/cg150 [Accessed April 2019].

[44] NICE 2013. Headaches in over 12s (QS42). Available at: https://www.nice.org.uk/guidance/qs42 [Accessed April 2019].

[45] NICE 2012. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (TA260). Available at: https://www.nice.org.uk/guidance/ta260 [Accessed April 2019].

[46] NICE 2014. Transcranial magnetic stimulation for treating and preventing migraine. Available at: https://www.nice.org.uk/guidance/ipg477 [Accessed April 2019].

[47] NICE 2010. Percutaneous closure of patent foramen ovale for recurrent migraine (IPG370). Available at: https://www.nice.org.uk/guidance/ipg370 [Accessed April 2019].

[48] NICE 2013. Occipital nerve stimulation for intractable chronic migraine (IPG452). Available at: https://www.nice.org.uk/guidance/ipg452 [Accessed April 2019].

[49] NICE 2016. Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine (IPG559). Available at: https://www.nice.org.uk/guidance/ipg559 [Accessed April 2019].

[50] NICE 2016. Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552). Available at: https://www.nice.org.uk/guidance/ipg552 [Accessed April 2019].

[51] NICE 2015. Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache (IPG527). Available at: https://www.nice.org.uk/guidance/ipg527 [Accessed April 2019].

[52] SIGN 2018. Pharmacological management of migraine. Available at: https://www.sign.ac.uk/assets/sign155.pdf [Accessed April 2019].

[53] Sacco S, Bendtsen L, Ashina M *et al*. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *J Headache Pain* 2019; 20: 6.

[54] [redacted]

[55] Gerber WD, Diener HC, Scholz E *et al*. Responders and non-responders to metoprolol, propranolol and nifedipine treatment in migraine prophylaxis: a dose-range study based on time-series analysis. *Cephalalgia* 1991; 11: 37–45.

[56] Silberstein SD, Neto W, Schmitt J *et al*. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004; 61: 490–495.

[57] Silberstein SD, Dodick DW, Aurora SK *et al*. Per cent of patients with chronic migraine who responded per onabotulinumtoxin A treatment cycle: PREEMPT. *J Neurol Neurosurg Psychiatry* 2015; 86: 996–1001.

[58] Couch JR, Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache* 2011; 51: 33–51.

[59] Dodick DW, Silberstein SD, Bigal ME *et al*. Effect of fremanezumab compared with placebo for prevention of episodic migraine: A randomized clinical trial. *JAMA* 2018; 319: 1999–2008.

[60] Silberstein SD, Dodick DW, Bigal ME *et al*. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med* 2017; 377: 2113–2122.

[61] Teva. FOCUS clinical study report. Data on file. 2019.

[62] Tassorelli C, Diener HC, Dodick DW, *et al*. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. *Cephalalgia* 2018; 38: 815–832.

[63] Silberstein SD. Emerging target-based paradigms to prevent and treat migraine. *Clin Pharmacol Ther* 2013; 93: 78-85.

[64] Ashina M, Tepper S, Brandes JL *et al*. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2018; 38: 1611–1621.

[65] Dodick DW, Turkel CC, DeGryse RE *et al*. Onabotulinumtoxin A for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 2010; 50: 921–936.

[66] Aurora SK, Winner P, Freeman MC *et al*. Onabotulinumtoxin A for treatment of chronic migraine: Pooled analyses of the 56-week PREEMPT clinical program. *Headache* 2011; 51: 1358–1373.

[67] Mitsikostas DD, Rapoport AM. New players in the preventive treatment of migraine. *BMC Med* 2015; 13: 279.

[68] Silberstein SD. Preventive Migraine Treatment. *Continuum (Minneap Minn)* 2015; 21: 973–989.

[69] Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. *J Manag Care Pharm* 2014; 20: 22–33.

[70] Hepp Z, Dodick DW, Varon SF *et al*. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia* 2015; 35: 478–488.

[71] Hepp Z, Dodick DW, Varon SF *et al*. Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis. *Cephalalgia* 2017; 37: 470–485.

[72] EMA. Clinical investigation of medicinal products for treatment of migraine. Available at: https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-migraine [Accessed April 2019].

[73] NICE 2019. Erenumab for preventing migraine [ID1188]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10302 [Accessed April 2019].

[74] Makita K, Inagaki M, Kitamura S *et al*. Changes in migraine before and after menopause in Japanese climacteric women. *Cephalalgia* 2017; 37: 1088–1092.

[75] Gillard PJ, Devine B, Varon SF *et al*. Mapping from disease-specific measures to health-state utility values in individuals with migraine. *Value Health* 2012; 15: 485–494.

[76] Vo P, Fang J, Bilitou A *et al*. Patients' perspective on the burden of migraine in Europe: A cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain* 2018; 19: 82.

[77] Office for National Statistics, National life tables: England and Wales. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables [Accessed April 2019].

[78] PSSRU. Unit costs of health & social care 2018. Available at https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/ [Accessed April 2019].

[79] NHS trust and NHS foundation trusts. National schedule of reference costs 2017/18.

[80] NICE. British National Formulary. Available from: https://bnf.nice.org.uk/ [Accessed April 2019].

[81] Lipton RB, Brennan A, Palmer S *et al*. Estimating the clinical effectiveness and value-based price range of erenumab for the prevention of migraine in patients with prior treatment failures: A US societal perspective. *J Med Econ* 2018; 21: 666–675.

[82] Office for National Statistics, Annual survey of hours and earnings. Available at: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2018/relateddata [Accessed April 2019].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fremanezumab for preventing chronic and episodic migraine [ID1368]

Clarification questions

May 2019

File name	Version	Contains confidential information	Date
Teva clarification response Part B	FINAL	No	12 June 2019

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Literature searches, systematic review methods

A1. Appendix D. Please supply the Embase literature search strategies (only Medline and Cochrane present in the appendices).

Medline and Embase were searched together using the Embase.com interface; therefore, Table 1 in Appendix D includes the search terms and results for both Medline and Embase search. As there were a number of changes made to Appendix D as a result of answering these questions, we have sent a revised version alongside this document.

A2. Appendix D. Please state which platform was used for the literature searches (e.g. Ovid, Embase.com). In addition, please specify this for each database searched.

Embase.com was used to search the Medline and Embase databases and the Wiley Online Library was used to search the Cochrane Library.

A3. Appendix D. Please confirm whether or not Medline-in-Process was searched. If so, please provide the platform and the search strategy used.

Medline in-process records were searched automatically as part of the aforementioned searches on Embase.com.

A4. Appendix D. Please detail the methods used for both data extraction and critical appraisal of the final included studies for the review of clinical effectiveness, including efficacy and safety.

The literature review involved:

1. SEARCHING – searches were conducted using Medline and Embase and The Cochrane library to retrieve records; citations, titles and abstracts were then exported into a master Excel file

2. TITLE AND ABSTRACT SCREENING – titles and abstracts were screened against the pre-determined inclusion/exclusion criteria (Table 4) to derive the list of records eligible for full-text screening

3. FULL-TEXT SCREENING – full-text records were screened against pre-determined inclusion/exclusion criteria (Table 4) to determine potential for data extraction and inclusion in the review

4. DATA EXTRACTION – data were extracted from records into standardised data extraction tables in Excel

5. QUALITY ASSESSMENT - For RCTs identified in the clinical effectiveness searches, quality assessments will be performed, using the checklist from NICE's single technology appraisal template.

The relevant data from all identified studies were extracted into standardised data extraction tables in Excel and the studies selected according to the inclusion and exclusion criteria and the PICOS (population, intervention, comparators, outcomes, and study types) framework. These tables were focussed on the outcomes of interest as defined by the appraisal scope.

The critical appraisal of the included studies was conducted using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) and using the Jadad score (Jadad AR *et al*. *Control Clin Trials* 1996; 17: 1–12), which have been presented in Appendix D for all six studies included in the network meta-analysis (HALO EM, HALO CM and FOCUS: Table 7

and Table 8 for JADAD and Cochrane risk-of-bias, respectively; Study 295 and PREEMPT trials: Table 11 and Table 12 for JADAD and Cochrane risk-of-bias, respectively).

A5. Appendix D page 23. Please clarify whether there were 441 final includes for the systematic review or whether further study identification methods were then used to reduce the numbers further. Please detail which methods were used.

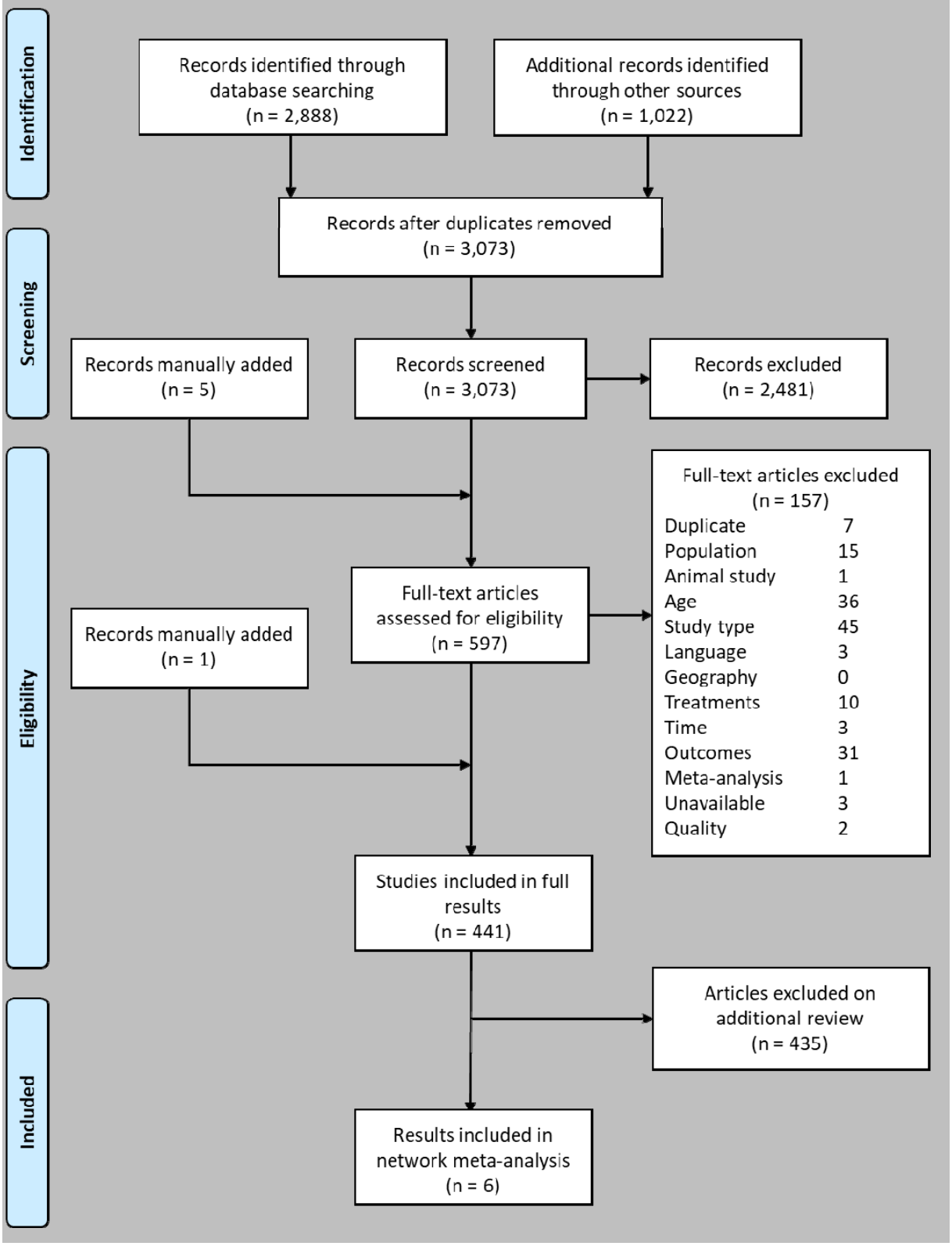
As stated in Appendix D, the searches conducted by Teva had a wider remit than the NICE appraisal. The 441 references identified by this systematic review were then subjected to an additional round of review to identify the studies that were relevant to the scope of this appraisal. Full text records for all 441 references were screened in this additional round against the NICE scope and studies outside this scope were excluded. For studies not including fremanezumab (which were used to inform the network meta-analysis (NMA), only studies focussed on the subpopulation of interest were considered (adult patients with three or more previous migraine preventive treatment failures). This round of review was conducted by two independent reviewers, and where disagreement occurred between the two reviewers, a third reviewer was used.

This search identified only the HALO EM and HALO CM trials as providing relevant evidence on fremanezumab; with three further studies informing the NMA (Study 295, PREEMPT I and PREEMPT II – reported within six references: Tepper S *et al*. *Lancet Neurol* 2017; 16: 425–434; Ashina M *et al*. *Cephalalgia* 2018; 38: 1611–162; Aurora SK *et al*. *Cephalalgia* 2010; 30: 793–803; Diener HC *et al*. *Cephalalgia* 2010; 30: 804–814; Dodick DW *et al*. *Headache* 2010; 50: 921–936; Aurora SK *et al*. *Headache* 2011; 51: 1358–1373). An updated PRISMA clarifying this additional review round and the final included studies can be found in the answer to question A6.

A6. Appendix D, Figure 1, page 24. The number of full text excludes does not tally, could you please provide updated figures.

Please find the updated and corrected PRISMA below.

Figure 1 PRISMA flow diagram of clinical effectiveness search



A7. Appendix D, Figure 1, page 24. Please detail how the 1,022 “additional records identified through other sources” were identified, including which methods/sources were used to find them.

The “additional records identified through other sources” were the results from the grey literature search conducted, as detailed in Table 3 of Appendix D.

A8. Appendix G. Please detail what methods were used for screening, data extraction and critical appraisal for the systematic review of cost-effectiveness.

The systematic review involved:

1. SEARCHING – searches were conducted using Medline and Embase and The Cochrane library to retrieve records; citations, titles and abstracts that were then exported into to a master Excel file

2. TITLE AND ABSTRACT SCREENING – titles and abstracts were screened against the pre-determined inclusion/exclusion criteria (Table 4) to derive the list of records eligible for full-text screening

3. FULL-TEXT SCREENING – full-text records were screened against pre-determined inclusion/exclusion criteria (Table 4) to determine potential for data extraction and inclusion in the review

4. DATA EXTRACTION – data were extracted from records into standardised data extraction tables in Excel

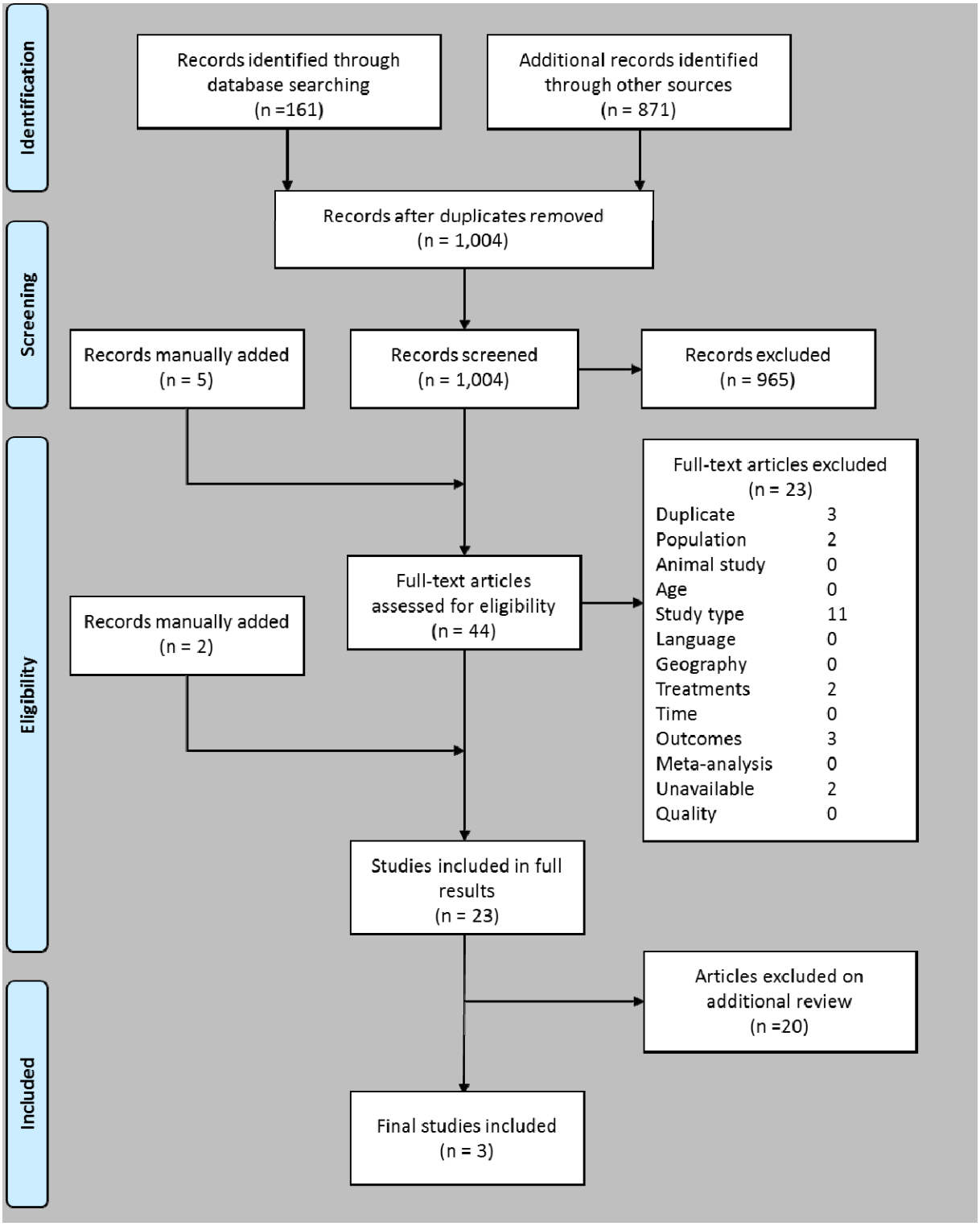
5. QUALITY ASSESSMENT - For RCTs identified in the clinical effectives searches, quality assessments will be performed, using the checklist from NICE’s single technology appraisal template.

The relevant data from all identified studies were extracted into standardised data extraction tables in Excel and the studies selected according to the inclusion and exclusion criteria and the PICOS (population, intervention, comparators, outcomes, and study types) framework.

The critical appraisal of the included studies was conducted using the methods of Philips *et al*. (*Health Technol Assess* 2004; 8: 36) and these results can be found in Table 2 of Appendix G.

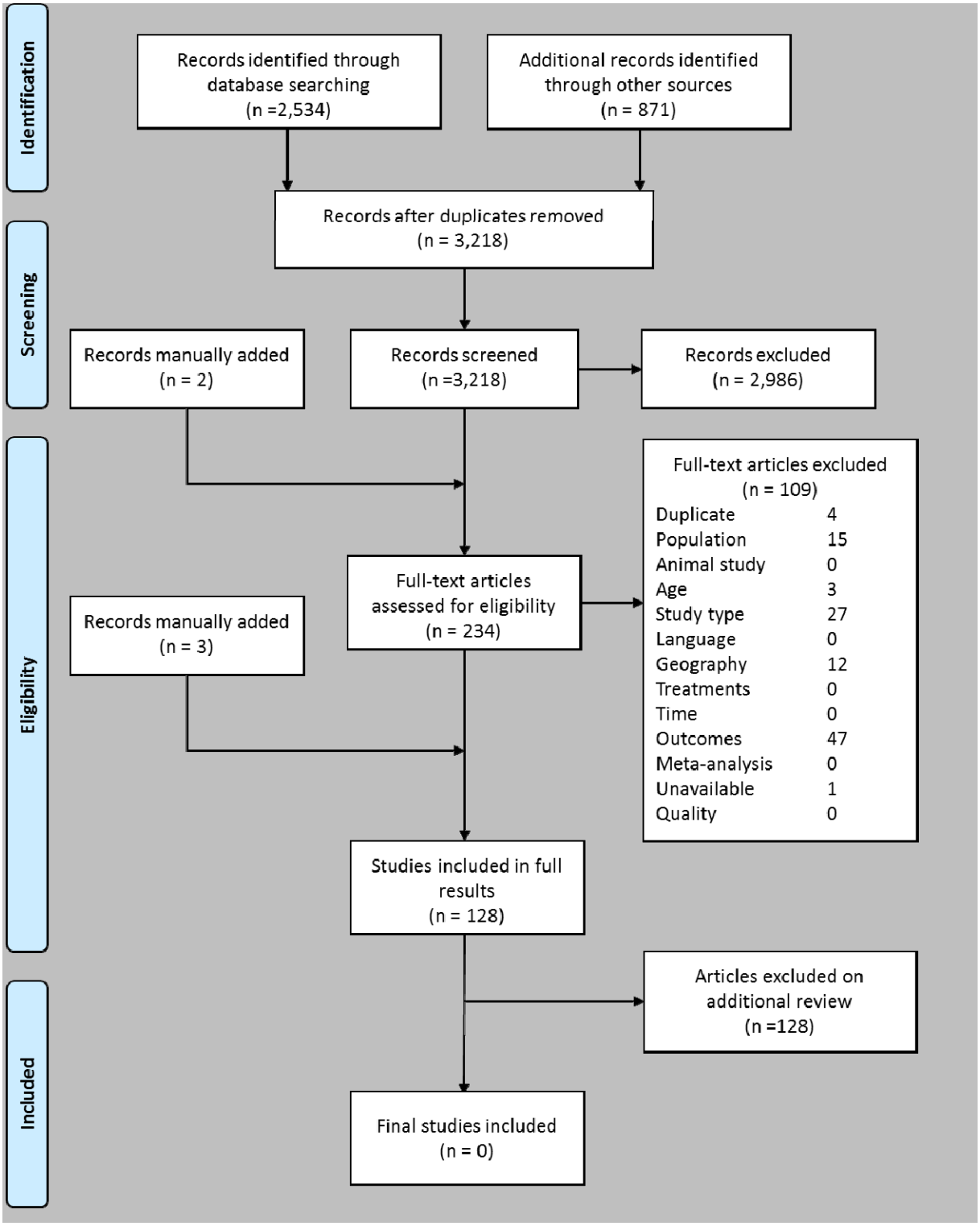
A9. Appendix G, Figure 1, page 4. Please clarify the final figure in the PRISMA flow diagram as the diagram states 23 final includes whereas the text on page 3 states 3 final includes.

The 23 records identified in the PRISMA diagram were subjected to a further round of review to identify studies relevant to the scope of this appraisal. Full text records for all references were screened in this additional round against the NICE scope and studies outside this scope were excluded. This round of review was conducted by two independent reviewers, and where disagreement occurred between the two reviewers, a third reviewer was used. After this additional round of review, only three relevant studies were identified. An updated PRISMA that includes this additional round of review is included below to provide clarity on these searches.


Identification
Screening
Eligibility
Included
Records identified through database searching (n =161)
Additional records identified through other sources (n = 871)
Records after duplicates removed (n = 1,004)
Records manually added (n = 5)
Records screened (n = 1,004)
Records excluded (n = 965)
Full-text articles excluded (n = 23)
Duplicate 3
Population 2
Animal study 0
Age 0
Study type 11
Language 0
Geography 0
Treatments 2
Time 0
Outcomes 3
Meta-analysis 0
Unavailable 2
Quality 0
Full-text articles assessed for eligibility (n = 44)
Records manually added (n = 2)
Studies included in full results (n = 23)
Articles excluded on additional review (n =20)
Final studies included (n = 3)

A10. Appendix H, Figure 1, page 3. The Figure appears to be missing. The numbers given in the text on page 3 do not tally with the numbers in the PRISMA flow diagram on page 5, is this referring to a different Figure? Please explain this discrepancy.

Unfortunately, an incorrect version of the PRISMA diagram was included within the file supplied to NICE. The figures within the text were correct and the updated and corrected PRISMA diagram is supplied below.


Identification
Screening
Eligibility
Included
Records identified through database searching (n =2,534)
Additional records identified through other sources (n = 871)
Records after duplicates removed (n = 3,218)
Records manually added (n = 2)
Records screened (n =3,218)
Records excluded (n = 2,986)
Full-text articles excluded (n = 109)
Duplicate 4
Population 15
Animal study 0
Age 3
Study type 27
Language 0
Geography 12
Treatments 0
Time 0
Outcomes 47
Meta-analysis 0
Unavailable 1
Quality 0
Records manually added (n = 3)
Full-text articles assessed for eligibility (n = 234)
Studies included in full results (n = 128)
Articles excluded on additional review (n =128)
Final studies included (n = 0)

A11. Appendix H, unlabelled Figure, page 5. Please clarify the final figure in the PRISMA flow diagram. The diagram states 119 final includes whereas the text on page 5 states no final includes.

It appears that the file for Appendix H has become corrupted, as there was only a single figure within this file. A corrected, uncorrupted version of Appendix H has been submitted to rectify this.

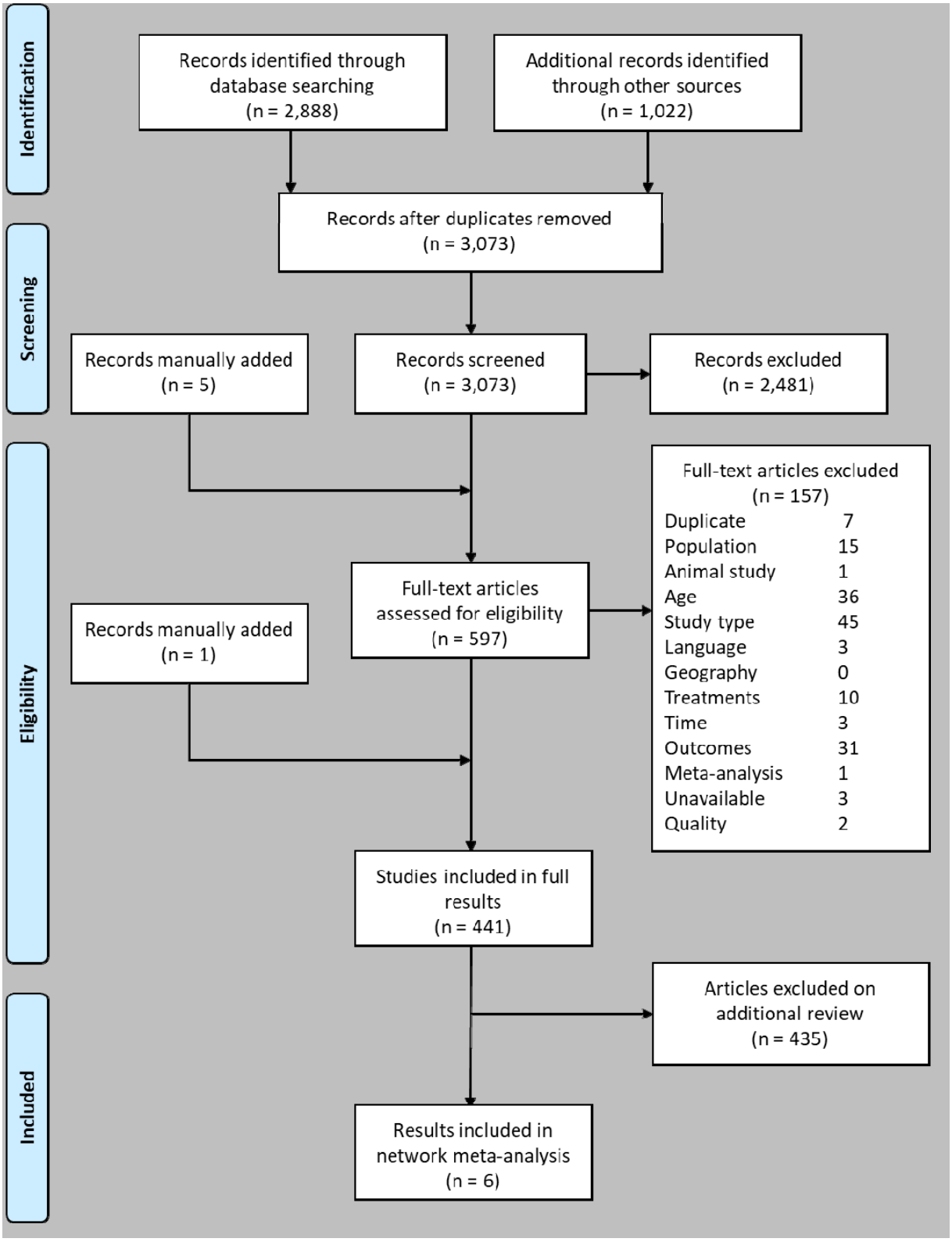
Regarding the final number of studies included, the 119 references identified by the systematic review were subjected to an additional round of review to identify the studies that were relevant to the scope of this appraisal, as these searches conducted by Teva originally had a wider remit than the NICE appraisal. Full text records for all 119 references were screened in this additional round against the NICE scope and studies outside this scope or where insufficient detail was reported were excluded. This round of review was conducted by two independent reviewers, and where disagreement occurred between the two reviewers, a third reviewer was used. After this additional round of review, no relevant studies were identified. An updated PRISMA that includes this additional round of review is included in the response to question A10.

A12. Appendix G, Figure 1, page 4. Please detail how the 871 “additional records identified through other sources” were identified, including the methods/sources used to find them.

The “additional records identified through other sources” were the results from the grey literature search conducted, as detailed in Table 3 of Appendix D, please note only the results from 02 February were included within this search.

A13. Appendix I. Please clarify which search strategy in Appendix D was used for this search – A, B, C or D? Please supply a PRISMA flow diagram.

Search C was used for Appendix I; the relevant PRISMA is presented below.



A14. Appendix H, unlabelled Figure, page 5. Please explain how the 647 “additional records identified through other sources” were identified, including the methods/sources used to find them.

The "additional records identified through other sources" were the results from the grey literature search conducted, as detailed in Table 3 of Appendix D, please note only the results from 02 February were included within this search (871 records in corrected PRISMA).

Trials and indirect comparison

A15. Please detail what proportion of patients in the HALO trials had previously received preventative therapies prior to the trial. In addition, please provide proportions for those who had received both 1 and 2 prior preventative therapies.

In the HALO trials, patients were only able to receive up to one class of prior preventive treatment before the trial, as the failure of two or more prior preventive treatment clusters (as described in question A18) was an exclusion criterion. Prior treatment with topiramate and onabotulinumtoxin A and preventive treatment use at baseline can be found in Table A15.1 for EM and Table A15.2 for CM.

In the FOCUS trial, data were captured on all preventive treatment failures (by drug class) and subgroup analysis was undertaken on those patients failing ≥3 prior preventive migraine treatments – the population that matches the positioning of fremanezumab in clinical practice within the NHS. Therefore, the FOCUS trial represents the most appropriate data source for use in this submission.

Table A15.1 HALO EM prior preventive treatments

HALO EM Baseline characteristic	Placebo (n=294)	Fremanezumab quarterly (n=291)	Fremanezumab monthly (n=290)
Previous topiramate use for migraine, n (%)			
Yes	53 (18)	51 (18)	64 (22)
No	241 (82)	240 (82)	226 (78)
Previous onabotulinumtoxin A use for migraine, n (%)			
Yes	9 (3)	15 (5)	16 (6)
No	285 (97)	276 (95)	274 (94)
Preventive medication use at baseline, n (%)	62 (21)	58 (20)	62 (21)

Table A15.2 HALO CM prior preventive treatments

HALO CM Baseline characteristic	Placebo (n=375)	Fremanezumab quarterly (n=376)	Fremanezumab monthly (n=379)
Previous topiramate use for migraine, n (%)			
Yes	117 (31)	106 (28)	117 (31)
No	258 (69)	270 (72)	262 (69)
Previous onabotulinumtoxin A use for migraine, n (%)			
Yes	49 (13)	66 (18)	50 (13)
No	326 (87)	310 (82)	329 (87)
Preventive medication use at baseline, n (%)	77 (21)	77 (20)	85 (22)

A16. Please state how many patients were classified as having 'medicine overuse headache' as opposed to migraine (Inclusion criteria: Table 4, Appendix D, page 23).

As mentioned at the beginning of Appendix D, the initial searches had a wider remit than this appraisal; however, an additional round of review was conducted to ensure the final included studies met the NICE scope. These inclusion criteria were therefore defined for this broader purpose, but the final included studies (as *per* the updated PRISMA in question A6) had no patients that were defined as having medicine overuse headache as opposed to migraine. In both HALO trials and the FOCUS trial, all patients required a confirmed migraine diagnosis, according to ICHD-3 beta criteria for migraine with or without aura, to be included in the trials.

A17. Please state how many patients, randomised to fremanezumab in the HALO trials, were transferred to the placebo arm following non-response or adverse events (page 41).

In the HALO clinical trials, no patients randomised to fremanezumab were transferred to placebo following non-response or adverse event. Please note that missing data from patients in the active groups who discontinued the study due to lack of efficacy or adverse events were imputed as if they were placebo treated patients, which may have led to some confusion. There were 8 and 5 patients in monthly and quarterly dose groups, respectively, who discontinued due to lack of efficacy or adverse events in the HALO CM study. In the HALO EM study, 4 patients in the monthly dose group and 5 patients in the quarterly dose group discontinued the study due to lack of efficacy or adverse events.

A18. Priority question: Please confirm that topiramate was not one of the drugs included in the inclusion and exclusion criteria for HALO EM/CM or FOCUS, with respect to whether patients 'failed' prior lines of treatment.

In the HALO EM and HALO CM trials, topiramate was not included within the list of exclusion criteria relating to 'failed' prior lines of treatment. The specific exclusion criterion was as follows:

"Patients who have previously failed (lack of efficacy) two or more of the clusters of the following medications for treatment of EM or CM after adequate therapeutic trial defined as use for at least three months at accepted migraine therapeutic doses:

- cluster A: divalproex sodium and sodium valproate
- cluster B: flunarizine and pizotifen
- cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine
- cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol."

In FOCUS, topiramate was included as one of the medications used to define the number of prior 'failed' treatment classes. The full list of medication classes used in this study is as follows:

- beta-blockers: propranolol, metoprolol, atenolol, and bisopropol
- anticonvulsants: topiramate
- tricyclics: amitriptyline
- calcium channel blocker: flunarizine
- angiotensin II receptor antagonist: candesartan
- onabotulinumtoxin A
- valproic acid

A19.Please detail how compliance was evaluated in the HALO trials.

Study drug was administered at the study centres by qualified study personnel as subcutaneous injections approximately every 28 days for a total of 3 doses, The 4-week (28-day) period was determined relative to the planned dosing day provided the patient returned to the study centre within the tolerance window (±3 days). If the patient returned to the study centre more than 3 days late, then the 4-week period was determined from the actual dosing day rather than the planned dosing day.The

total number of subcutaneous injections and their locations were recorded at each dosing visit (visits 2, 3, and 4).

Study drug and kit accountability checks were performed at each monitoring visit, and a record of study drug accountability (*i.e.* study drug and other materials received, used, retained, returned, or destroyed) was prepared and signed by the principal investigator or designee, with an account given for any discrepancies.

Patients had to complete daily electronic headache diary entries with questions about the previous day, beginning on day -27 (the day after the screening visit) through to the end of treatment/early withdrawal visit. The electronic headache diary device allowed entry of headache information for up to 48 hours after a given day. During the run-in period, diary compliance was evaluated by using the first 28 days in the period to see if patients had at least 24 days with completed diary entries to be eligible for the study (~85% diary compliance). The diary compliance rate was calculated by days with diary divided by days in each specific period for each patient.

A20. Priority question: Please present estimates, using an ITT analysis strategy, for all outcomes presented in the submission

The ITT results for the primary endpoints from the HALO trials and the FOCUS trial are presented below, alongside the main analysis set results from these trials. As can be seen, the overall patient numbers in each arm are similar between the analysis sets and the corresponding results are also similar.

Primary endpoint clinical effectiveness results of the HALO trials

Table 14 Summary of main efficacy outcomes in HALO EM trial

	Placebo		**Fremanezumab quarterly**		**Fremanezumab monthly**	
	FAS (n=290)	**ITT (n=[redacted])**	**FAS (n=288)**	**ITT (n=[redacted])**	**FAS (n=287)**	**ITT (n=[redacted])**
Mean monthly migraine days						
Baseline (SD)	9.1 (2.7)	[redacted]	9.3 (2.7)	[redacted]	8.9 (2.6)	[redacted]
LSM change (95% CI)	-2.2 (-2.68 to -1.71)	[redacted]	-3.4 (-3.94 to -2.96)	[redacted]	-3.7 (-4.15 to -3.18)	[redacted]
Difference *vs* placebo			-1.3 (-1.79 to -0.72)	[redacted]	-1.5 (-2.01 to -0.93)	[redacted]

	Placebo		Fremanezumab quarterly		Fremanezumab monthly	
	FAS (n=290)	**ITT (n=[redacted])**	**FAS (n=288)**	**ITT (n=[redacted])**	**FAS (n=287)**	**ITT (n=[redacted])**
(95% CI)						
P-value *vs* placebo			<0.0001	[redacted]	<0.0001	[redacted]
Patients with at least 50% reduction in monthly average migraine days						
Number achieving endpoint (%)	81 (27.9)	[redacted]	128 (44.4)	[redacted]	137 (47.7)	[redacted]
P-value *vs* placebo			<0.0001	[redacted]	<0.0001	[redacted]
Mean monthly days of use of any acute headache medication						
Baseline (SD)	7.7 (3.6)	[redacted]	7.8 (3.7)	[redacted]	7.7 (3.4)	[redacted]
LSM change (95% CI)	-1.6 (-2.04 to -1.20)	[redacted]	-2.9 (-3.34 to -2.48)	[redacted]	-3.0 (-3.41 to -2.56)	[redacted]
Difference *vs* placebo (95% CI)			-1.3 (-1.76 to -0.82)	[redacted]	-1.4 (-1.84 to -0.89)	[redacted]
P-value *vs* placebo			<0.0001	[redacted]	<0.0001	[redacted]
Migraine Disability Assessment score						
Baseline (SD)	37.3 (27.6)	[redacted]	41.7 (33.0)	[redacted]	38.0 (33.2)	[redacted]
LSM change (95% CI)	-17.5 (-20.62 to -14.47)	[redacted]	-23.0 (-26.10 to -19.82)	[redacted]	-24.6 (-27.68 to -21.45)	[redacted]
Difference *vs* placebo (95% CI)			-5.4 (-8.90 to -1.93)	[redacted]	-7.0 (-10.51 to -3.53)	[redacted]
P-value *vs* placebo			<0.0001	[redacted]	<0.0001	[redacted]

Table 16 Summary of main efficacy outcomes in HALO CM trial

	Placebo		Fremanezumab quarterly		Fremanezumab monthly	
	FAS (n=371)	**ITT (n=[redacted])**	**FAS (n=375)**	**ITT (n=[redacted])**	**FAS (n=375)**	**ITT (n=[redacted])**
Mean monthly headache days of at least moderate severity						
Baseline (SD)	13.3 (5.8)	[redacted]	13.2 (5.5)	[redacted]	12.8 (5.8)	[redacted]
LSM change	-2.5 (-3.06	[redacted]	-4.3 (-4.87	[redacted]	-4.6 (-5.16	[redacted]

	Placebo		Fremanezumab quarterly		Fremanezumab monthly	
	FAS (n=371)	**ITT (n=[redacted])**	**FAS (n=375)**	**ITT (n=[redacted])**	**FAS (n=375)**	**ITT (n=[redacted])**
(95% CI)	to -1.85)	[redacted]	to -3.66)	[redacted]	to -3.97)	[redacted]
Difference *vs* placebo (95% CI)			-1.8 (-2.46 to -1.15)	[redacted]	-2.1 (-2.76 to -1.45)	[redacted]
P-value *vs* placebo			<0.0001	[redacted]	<0.0001	[redacted]
Mean monthly migraine days						
Baseline (SD)	16.4 (5.2)	[redacted]	16.2 (4.9)	[redacted]	16.0 (5.2)	[redacted]
LSM change (95% CI)	-3.2 (-3.86 to -2.47)	[redacted]	-4.9 (-5.59 to -4.20)	[redacted]	-5.0 (-5.70 to -4.33)	[redacted]
Difference *vs* placebo (95% CI)			-1.7 (-2.48 to -0.97)	[redacted]	-1.8 (-2.61 to -1.09)	[redacted]
P-value *vs* placebo			<0.0001	[redacted]	<0.0001	[redacted]
Patients with at least 50% reduction in monthly average migraine days						
Number achieving endpoint (%)	74 (19.9)	[redacted]	115 (30.7)	[redacted]	125 (33.3)	[redacted]
P-value *vs* placebo			0.0008	[redacted]	<0.0001	[redacted]
Mean monthly days of use of any acute headache medication						
Baseline (SD)	13.0 (6.9)	[redacted]	13.1 (6.8)	[redacted]	13.1 (7.2)	[redacted]
LSM change (95% CI)	-1.9 (-2.48 to -1.28)	[redacted]	-3.7 (-4.25 to -3.06)	[redacted]	-4.2 (-4.79 to -3.61)	[redacted]
Difference *vs* placebo (95% CI)			-1.8 (-2.43 to -1.12)	[redacted]	-2.3 (-2.97 to -1.67)	[redacted]
P-value *vs* placebo			<0.0001	[redacted]	<0.0001	[redacted]
Headache Impact Test score						
Baseline (SD)	64.1 (4.8)	[redacted]	64.3 (4.7)	[redacted]	64.6 (4.4)	[redacted]
LSM change (95% CI)	-4.5 (-5.38 to -3.60)	[redacted]	-6.4 (-7.31 to -5.52)	[redacted]	-6.8 (-7.71 to -5.97)	[redacted]
Difference *vs* placebo (95% CI)			-1.9 (-2.90 to -0.96)	[redacted]	-2.4 (-3.32 to -1.38)	[redacted]

	Placebo		Fremanezumab quarterly		Fremanezumab monthly	
	FAS (n=371)	**ITT (n=[redacted])**	**FAS (n=375)**	**ITT (n=[redacted])**	**FAS (n=375)**	**ITT (n=[redacted])**
P-value *vs* placebo			<0.0001	[redacted]	<0.0001	[redacted]

Primary endpoint clinical effectiveness results of the FOCUS trial

Table 17 Summary of main efficacy outcomes in FOCUS clinical trial

	Placebo		Fremanezumab quarterly		Fremanezumab monthly	
	mITT (n=[redacted])	**ITT (n=[redacted])**	**mITT (n=[redacted])**	**ITT (n=[redacted])**	**mITT (n=[redacted])**	**ITT (n=[redacted])**
Mean monthly migraine days						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)			[redacted]	[redacted]	[redacted]	[redacted]
P-value *vs* placebo			[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least 50% reduction in monthly average migraine days						
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)			[redacted]	[redacted]	[redacted]	[redacted]
P-value *vs* placebo			[redacted]	[redacted]	[redacted]	[redacted]
Mean monthly days of use of any acute headache medication						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)			[redacted]	[redacted]	[redacted]	[redacted]
P-value *vs*			[redacted]	[redacted]	[redacted]	[redacted]

	Placebo		Fremanezumab quarterly		Fremanezumab monthly	
	mITT (n=[redacted])	**ITT (n=[redacted])**	**mITT (n=[redacted])**	**ITT (n=[redacted])**	**mITT (n=[redacted])**	**ITT (n=[redacted])**
placebo						
Migraine Disability Assessment score						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)			[redacted]	[redacted]	[redacted]	[redacted]
P-value *vs* placebo			[redacted]	[redacted]	[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]	

*FOCUS ITT data not currently available

A21. Please clarify the full range of health-related quality of life outcomes published for the included trials.

Health-related quality of life data was collected in both the HALO and FOCUS clinical trials. However, the data from the FOCUS trial was considered most appropriate in the submission and cost-effectiveness model, as it is the most relevant with respect to the population of interest for this appraisal (patients who have failed three or more previous migraine preventive treatments). The FOCUS trial collected health-related quality of life data using the MIDAS, HIT-6 and MSQoL measures. The FOCUS trial was the only study that reported values in the format required for the model (*i.e.* utility values for all MMD states); therefore, the FOCUS data were used in the model. No health-related quality of life data from FOCUS have been published, but all available data from FOCUS have been included in the submission (FOCUS overall

migraine population B2.6.2.5; the following data are in patients that have failed three or more classes of preventive migraine treatment: EM B2.7.4.1.a; HFEM B2.7.4.2.a; CM B2.7.4.3.a).

In the HALO trials, health-related quality of life was assessed using MIDAS and MSQoL in HALO EM and HIT-6 and MSQoL in HALO CM. All assessed health-related quality of life outcomes from the HALO trials are presented in the submission (B2.6.1.1.e for HALO EM and B2.6.1.2.f for HALO CM).

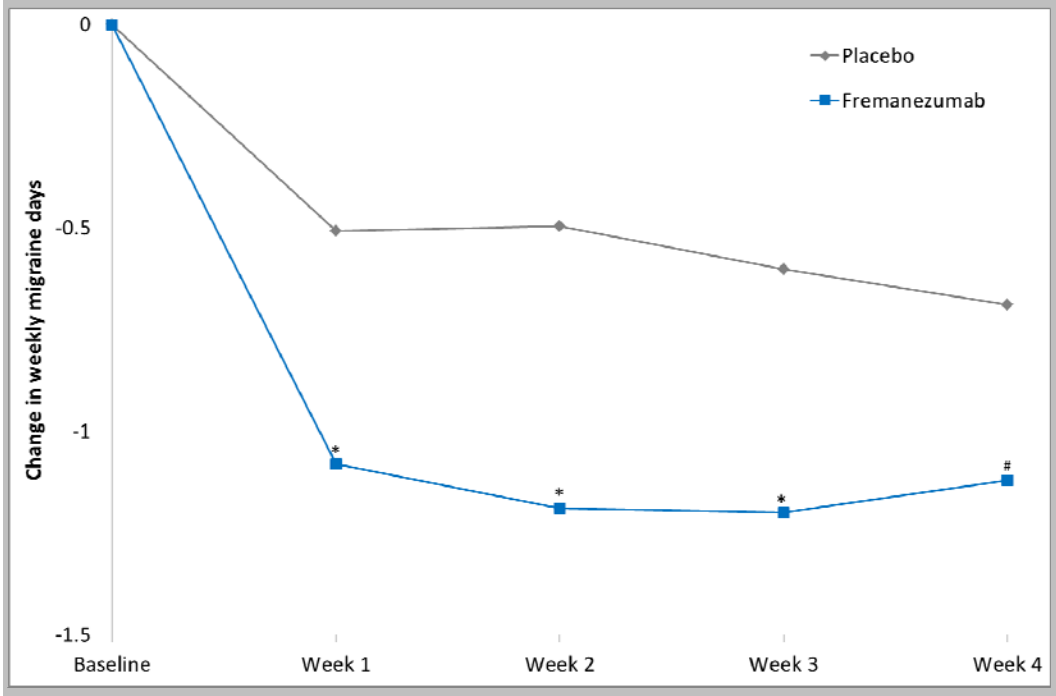
A22. Please clarify if the p-values provided for Figure 3 (page 60) in the company submission are correct as they do not appear to match the text in the submission.

The p-values reported in both the text and the figure were incorrect in the original submission, the revised text should read:

Overall, this led to a reduction in p-values for fremanezumab, with a p-value of 0.0031 at week 4. These results demonstrate the rapid onset of action with fremanezumab.

The revised Figure and Figure footnote are presented below:

Figure 3 Change in weekly migraine days over time (MMRM analysis)



*p<0.0001; #p=0.0031 *vs* placebo

A23. In Figures 2 and 3 of Appendix D, patient flows for HALO EM/CM are presented. Please detail what the key reasons underpinning the group of patients excluded under 'other' were.

The key reason underpinning the group of patients excluded before randomisation under 'other' was 'withdrawal of consent' (approximately 80% for each trial); the additional 'other' reasons reported (before randomisation) were for various miscellaneous exclusions, such as enrolment had stopped, randomisation not completed in time, poor compliance, study window missed, electronic diary failure, transport issues, medical reasons, *etc.*, where no particular reason occurred a substantial number of times.

A24. Please clarify if the relative risks presented for adverse events in the company submission are odds ratios, risk ratios, or another risk estimator.

Risk ratios were presented for adverse events labelled as relative risk.

A25. Please provide data points (means and standard deviation) for the timepoints represented in Figure 2 (page 53), Figure 3 (page 60), and Figure 4 (page 65) of the company submission.

Figure 2 (page 53)

Visit	Category	Statistic	Placebo	Quarterly fremanezumab	Monthly fremanezumab
Week 1	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 2	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 3	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]

Visit	Category	Statistic	Placebo	Quarterly fremanezumab	Monthly fremanezumab
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 4	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]

Figure 3 (page 60)

Visit	Category	Statistic	Placebo	Fremanezumab
Week 1	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]
		95% CI		[redacted]
		p-Value		[redacted]
Week 2	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]
		95% CI		[redacted]
		p-Value		[redacted]
Week 3	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]
		95% CI		[redacted]
		p-Value		[redacted]
Week 4	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]
		95% CI		[redacted]
		p-Value		[redacted]

Figure 4 (page 65)

Visit	Category	Statistic	Placebo	Quarterly fremanezumab	Monthly fremanezumab
Week 1	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 2	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 3	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 4	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]

Figure 4 Change in weekly migraine days over time (MMRM analysis)

[redacted]

[redacted] *vs* placebo

A26. Priority question: Please confirm if outcome data is available for the other subgroups highlighted in the NICE scope (frequency of episodic migraine; number of previous treatments) for the HALO trials.

In the HALO trials, patients with two or more preventive treatment cluster failures, as *per* the defined clusters in question A18, were excluded from the study. Therefore, data are available only in patients with zero or one prior preventive treatment class failure. Limited data on prior preventive treatment failures were collected in HALO; therefore, the FOCUS data was deemed the most appropriate data source to use in this submission (as detailed data were available for patients failing ≥3 prior preventive migraine treatments in this trial, as *per* the clinical positioning).

In the HALO trials, select subgroup analysis has been performed, but not published, using data in patients who had previous topiramate or onabotulinumtoxin A use or preventive migraine medication use in the past and discontinued due to lack of efficacy or poor tolerability. Subgroup analysis on the change from baseline in monthly average number of headache days of at least moderate severity using the HALO data are presented below in Table A26.1 and Table A26.2.

As mentioned previously, FOCUS was used as the primary trial for all clinical and cost effectiveness data, as it specifically looked at prior preventive migraine medication class failures as an outcome in the trial.

Table A26.1: HALO EM: Change from baseline in monthly average number of headache days of at least moderate severity (ANCOVA)

Category	Statistic	Placebo (N=[redacted])	Quarterly fremanezumab (N=[redacted])	Monthly fremanezumab (N=[redacted])
Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]
Difference (*vs.* Placebo)	Least squares means (SE)		[redacted]	[redacted]
	95% CI		[redacted]	[redacted]
	p-value		[redacted]	[redacted]

Table A26.2: HALO CM: Change from baseline in monthly average number of headache days of at least moderate severity (ANCOVA)

Category	Statistic	Placebo (N=[redacted])	Quarterly fremanezumab (N=[redacted])	Monthly fremanezumab (N=[redacted])
Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]
Difference (*vs.* Placebo)	Least squares means (SE)		[redacted]	[redacted]
	95% CI		[redacted]	[redacted]
	p-value		[redacted]	[redacted]

In the main submission, data are presented on the main efficacy outcomes for patients with EM (defined as having 6 to 14 headache days per month, with at least 4 days fulfilling ICHD-3 beta criteria for migraine with or without aura) from the HALO EM trial. Separate analysis has been undertaken using data in those patients

defined as having HFEM with 10-14 headache days *per* month from the HALO EM trial. In our main submission, the population of interest when looking at HFEM was those patients with 8-14 headache days *per* month, as there is no clear and agreed definition for HFEM. It is known that patients with HFEM have a high unmet need due to experiencing a similar disease burden to that of chronic migraine and onabotulinumtoxin A being unavailable to them.[1] For HALO, data are currently available only for those patients with 10-14 headache days *per* month, so these data have been presented here (Table A26.3). No other breakdowns looking at frequency of EM were undertaken.

Table A26.3: Outcomes in patients with high-frequency episodic migraine (10-14 headache days) in HALO EM clinical trial

	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Change in mean monthly migraine days			
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Patients with at least 50% reduction in monthly average migraine days			
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Change in mean monthly headache days			
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Change in Migraine Disability Assessment score (MIDAS)			
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]

[1] Torres-Ferrús M, Quintana M, Fernandez-Morales J *et al*. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. *Cephalalgia* 2017; 37: 104–113.

A27. Priority question: Please provide the study-level effect estimates used to generate the network meta-analyses presented.

Study-level effect estimates used to generate the network meta-analyses are presented below.

Chronic Migraine

Monthly Migraine Days (Weeks 9-12)

[redacted]

30% Responder Rate (Weeks 9-12)

[redacted]

50% Responder Rate (Weeks 9-12)

[redacted]

75% Responder Rate (Weeks 9-12)

[redacted]

A28. Priority question: Please detail, on what basis, the transitivity in the network meta-analyses presented was judged to be adequate.

For the network meta-analyses (NMAs), the "transitivity assumption" indicates that all of the trials in the network are similar with respect to any characteristics that are potential treatment effect modifiers. Given that patients are not randomly assigned to each treatment in the network (the randomisation is within trials), to justify this assumption it was checked that all the trials in the NMAs were conducted in a similar way, particularly with regard to assessments of treatment efficacy, and recruited participants were allocated to similar groups (*e.g.* specific treatment failure (TF) populations).

Additionally, for the fremanezumab and erenumab trials in chronic migraine, it was checked that the baseline characteristics were on average similar across trials (see Table A28.1 below).

Table A28.1 Baseline characteristic comparison between fremanezumab and erenumab in the ≥3 treatment failure population for chronic migraine						
	Fremanezumab			**Erenumab**		
	FOCUS (NCT03308968)			**Ashina, 2018 (NCT02066415)**		
	Fremanezumab quarterly N=[redacted]	Fremanezumab monthly N=[redacted]	Placebo N=[redacted]	Erenumab 140 mg N=190	Erenumab 70 mg N=191	Placebo N=286
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	44.1 (11.3)	42.8 (11.5)	42.4 (11.5)
Female, n (%)	[redacted]	[redacted]	[redacted]	59 (90.8)	62 (89.9)	72 (73.5)
Mean disease duration, years (SD)	[redacted]	[redacted]	[redacted]	24.6 (11.9)	24.5 (13.3)	24.8 (13.2)
Mean monthly migraine days (SD)	[redacted]	[redacted]	[redacted]	19.0 (4.7)	18.9 (4.4)	18.6 (4.3)
Use of migraine-specific medication, n (%)	[redacted]	[redacted]	[redacted]	60 (92.3)	62 (89.9)	90 (91.8)
Mean monthly acute migraine-specific medication days (SD)	[redacted]	[redacted]	[redacted]	12.5 (6.1)	11.0 (7.6)	12.0 (7.1)
Medication overuse, n (%)	[redacted]	[redacted]	[redacted]	27 (41.5)	30 (43.5)	42 (42.9)

Notes:

[1] Sample sizes, mean age, percent female, mean disease duration, migraine-specific medication use, mean monthly acute migraine-specific medication days, and medication overuse for FOCUS are based on the safety analysis population. Mean MMDs are based on the mITT population.

[2] Data are mean (SD) or n (%).

For the LIBERTY trial in episodic migraine, baseline characteristics were not reported in the key publications for the subgroup of patients with at least three prior preventive treatment failures. However, the baseline characteristics for the 2-4 treatment failure population were similar to that of FOCUS (see Table 28.2 below), except for “monthly acute migraine-specific medication days”, which is larger in the FOCUS population (although this difference may be partly due to differences in definitions in this variable in FOCUS [days of use of any acute headache medication] and LIBERTY [days of use of acute migraine-specific medication]). In the absence of data for the ≥3 preventive treatment failures subgroup, it was deemed reasonable

to assume that the baseline characteristics in FOCUS and the 2-4 preventive treatment failures subgroup in LIBERTY are also similar, which would in turn justify the transitivity assumption.

Table A28.2 Baseline characteristic comparison between fremanezumab in the ≥3 treatment failure population and erenumab in the 2-4 treatment failure population for episodic migraine

	Fremanezumab			**Erenumab**	
	FOCUS, NCT03308968			**LIBERTY (NCT03096834)**	
	Fremanezumab quarterly N=[redacted]	Fremanezumab monthly N=[redacted]	Placebo N=[redacted]	Erenumab 140 mg N=121	Placebo N=125
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	44.6 (10.5)	44.2 (10.6)
Female, n (%)	[redacted]	[redacted]	[redacted]	97 (80)	103 (82)
Race, White, n (%)	[redacted]	[redacted]	[redacted]	112 (93)	115 (92)
Ethnicity, Hispanic or Latino, n (%)	[redacted]	[redacted]	[redacted]	9 (7)	5 (4)
Ethnicity, Not Hispanic or Latino, n (%)	[redacted]	[redacted]	[redacted]	104 (86)	109 (87)
Mean weight, kg	[redacted]	[redacted]	[redacted]	72.8 (14.4)	72.1 (16.2)
Mean body-mass index, kg/m^2 (SD)	[redacted]	[redacted]	[redacted]	25.0 (4.2)	24.9 (5.1)
Mean monthly migraine days (SD)	[redacted]	[redacted]	[redacted]	9.2 (2.6)	9.3 (2.7)
Mean monthly headache days[1] (SD)	[redacted]	[redacted]	[redacted]	10.1 (2.8)	10.1 (2.7)
4-7 monthly migraine days, n (%)	[redacted]	[redacted]	[redacted]	36 (30)	38 (30)
8-14 monthly migraine days, n (%)	[redacted]	[redacted]	[redacted]	85 (70)	87 (70)
Migraine-specific, n (%)	[redacted]	[redacted]	[redacted]	102 (84)	109 (87)

Notes:

[1] While not specified, it is assumed Reuter, 2018 refers to monthly headache days of *any* severity.

[2] Sample sizes, and all other variables for FOCUS are based on the safety analysis population, other than the mean MMDs and mean monthly headache days which are based on the mITT population.

[3] Data are mean (SD) or n (%).

For the onabotulinumtoxin A trials included in the NMA, baseline characteristics were not reported for the subgroup of patients with at least 3 preventive treatment failures in the PREEMPT trial. However, the baseline characteristics for the full PREEMPT trial population

were similar to that of the FOCUS trial (see Table 28.3 below). In the absence of data for the ≥3 preventive treatment failures subgroup, it is reasonable to assume that the baseline characteristics in FOCUS and the ≥3 preventive treatment failures subgroup in PREEMPT were also similar, which would in turn justify the transitivity assumption.

Table A28.3 Baseline characteristic comparison between fremanezumab in the ≥3 treatment failure population and onabotulinumtoxin A in the overall population for chronic migraine

	Fremanezumab			**Onabotulinumtoxin A**	
	FOCUS (NCT03308968)			**PREEMPT 1&2 (NCT00156910 & NCT00168428)**	
	Fremanezumab quarterly N=[redacted]	Fremanezumab monthly N=[redacted]	Placebo N=[redacted]	Onabotulinumtoxin A N = 688	Placebo N = 696
Mean age, years	[redacted]	[redacted]	[redacted]	41.1 (10.4)	41.5 (10.7)
Female, n (%)	[redacted]	[redacted]	[redacted]	(87.6)	(85.2)
Caucasian, n (%)	[redacted]	[redacted]	[redacted]	(89.7)	(90.5)
Mean frequency of headache days (SD)	[redacted]	[redacted]	[redacted]	19.9 (3.7)	19.8 (3.7)
Mean frequency of migraine days (SD)	[redacted]	[redacted]	[redacted]	19.1 (4.0)	18.9 (4.1)
Mean frequency of moderate/severe headache days (SD)	[redacted]	[redacted]	[redacted]	18.1 (4.1)	18.0 (4.3)
% Patients with severe (≥60) HIT-6 score, n (%)	[redacted]	[redacted]	[redacted]	(93.5)	(92.7)
Mean frequency of migraine episodes (SD)	[redacted]	[redacted]	[redacted]	11.4 (5.0)	12.2 (5.4)
% Patients overusing acute headache medication, n (%)	[redacted]	[redacted]	[redacted]	(64.8)	(66.1)
Mean frequency of acute headache medication days (SD)	[redacted]	[redacted]	[redacted]	14.6 (6.4)	14.9 (6.4)
Mean HIT-6 score (SD)	[redacted]	[redacted]	[redacted]	65.5 (4.1)	65.4 (4.3)
Role restrictive	[redacted]	[redacted]	[redacted]	38.5 (16.6)	38.7 (17.3)

Role preventive	[redacted]	[redacted]	[redacted]	56.0 (21.2)	56.1 (21.7)
Emotional functioning	[redacted]	[redacted]	[redacted]	42.1 (24.1)	42.4 (25.0)

Notes:

[1] Sample sizes, mean age, per cent female, per cent Caucasian, and mean disease duration for FOCUS are based on the safety analysis population. Mean MMDs, mean frequency of acute headache medication days, mean frequency of headache days, mean frequency of moderate/severe headache days, mean HIT-6 score and mean MSQ scores are based on the mITT population.

[2] Data are mean (SD) or n (%).

A29. Priority question: Please detail how data from the PREEMPT trials were pooled for the network meta-analysis.

Results for onabotulinumtoxin A were obtained directly from the NICE HTA submission for erenumab (2019)[2] which report estimates from the pooled PREEMPT trials. Based on our assessment of Aurora, 2011 (the publication that reports pooled results of the PREEMPT trials),[3] the results are pooled by sample size.

A30. Priority question: In the network meta-analysis of monthly mean migraine days, please explain the basis for averaging the variance from weekly estimates to generate a pooled estimate. In addition, please explain for which trials this was necessary.

The abovementioned variance calculation only applied to the MMD analyses conducted during weeks 1-12. However, MMD at weeks 1-12 was not an outcome in the ≥3 prior treatment failure group; therefore, these variance calculations were not used to determine any of the presented results in this submission and should not have been described in the NMA methods in the submission.

A31. Priority question: Please explain how standard errors were calculated for the percentage change from baseline. In addition, were the results for this NMA presented?

For the NMA, in the population with ≥3 prior treatment failures that was presented in the submission, no percentage change from baseline outcomes were included. Since this was the case, standard errors were not calculated and this line should not have been included in the NMA methods in the submission.

[2] Erenumab for preventing migraine [ID1188]. National Institute for Health and Care Excellence Single Technology Appraisal. 2019.

[3] Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, VanDenburgh AM, Nolan ME, Turkel CC. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache: The Journal of Head and Face Pain. 2011 Oct;51(9):1358-73.

A32. Priority question: Please present the relevant diagrams to evidence the Brooks-Gelman-Rubin tests of convergence.

To assess convergence, trace plots and Brooks-Gelman-Rubin tests were used. Specifically, the scale reduction factor for each treatment effect was computed. A factor of 1 indicates the between chain variance and within chain variance are equal, whereas larger values indicate there is still a difference between the chains. As a rule of thumb, values of 1.1 or less suggests adequate convergence. For the NMA conducted, convergence was achieved based on these tests and criteria.

Chronic Migraine

Monthly Migraine Days (Weeks 9-12)

Trace and Density Plots

Gelman-Rubin Plot for Scale Reduction Factor

Gelman-Rubin Table for Scale Reduction Factor

30% Responder Rate (Weeks 9-12)

Trace and Density Plots

Gelman-Rubin Plot for Scale Reduction Factor

Gelman-Rubin Table for Scale Reduction Factor

[redacted]

50% Responder Rate (Weeks 9-12)

Trace and Density Plots

[redacted]

Gelman-Rubin Plot for Scale Reduction Factor

Gelman-Rubin Table for Scale Reduction Factor

75% Responder Rate (Weeks 9-12)

Trace and Density Plots

Gelman-Rubin Plot for Scale Reduction Factor

Gelman-Rubin Table for Scale Reduction Factor

[redacted]

A33. The main text states on page 94 that 'no valid heterogeneity comparisons exist in these data' leading to a choice of a fixed effects model, yet Appendix D states that random effects models were considered. Based on the trials used in the network, would a random effects model have been possible and if so, what are the findings corresponding to a random effects model?

Given that no pair of regimens were compared by more than one study (*i.e.* only one trial per network link), assessment of heterogeneity was not feasible in this NMA. Also, since the evidence networks for all the analyses consisted of only one trial *per* link, the random effects models, though technically possible to run, would render non-informative credible intervals and ultimately unreliable results. Therefore, whilst we did consider the possibility of a random effects model, we used only a fixed effects model.

A34. Priority question: Please detail what the prior distributions used were in the network meta-analysis models?

Non-informative priors were selected for the parameters of interest to avoid artificially biasing results, and to ensure maximal objectivity of the results. The selection of priors was done in accordance to NICE technical support guidelines.[4]

Categorical outcomes (responder rates):

Defining *rik* as the number of events (responders), out of the total number of patients in each arm, *nik*, for arm *k* of trial *i*, the data is assumed to follow a binomial likelihood *i.e.*

r[i,k] ~ dbin(p[i,k],n[i,k])

where *pik* represents the probability of an event in arm *k* of trial

[4] Dias, Sofia, et al. "NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials." (2011).

A transformation function (logit link function) was used to map the probabilities into a continuous measure on the infinity scale, as below:

logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]

Continuous outcomes (monthly migraine days):

For continuous outcomes, the data is assumed to be approximately normally distributed, and the likelihood can be written as:

y[i,k] ~ dnorm(theta[i,k],prec[i,k])

where the parameter of interest is the mean *theta[i,k]*

The identity link is used to transform the model into the natural scale as outlined below:

theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]

In accordance to NICE technical support guideline, for both categorical and continuous models, vague prior normal distributions were assumed for trial baselines and treatment effects, as follows:

mu[i] ~ dnorm(0,.0001) (vague priors for trial baselines, where *mu[i]* is the baseline of trial *i*)

d[t]~dnorm(0,.0001) (vague priors of treatment effects, where *d[t]* is treatment effect associated with arm *t*)

Codes for the models used in the NMA are outlined below.

Bayesian continuous outcome, fixed effects [normal distribution]	
model{	
for(i in 1:ns) {	# indexes studies
mu[i] ~ dnorm(0,.0001)	# vague priors for all trial baselines
for (k in 1:na[i]) {	# indexes arms
varr[i,k] <- pow(se[i,k],2)	# calculate variances
prec[i,k] <- 1/varr[i,k]	# sets precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k])	# normal likelihood
theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]	# model for linear predictor
# deviance contribution	
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]	

}	# close arm loop
resdev[i] <- sum(dev[i,1:na[i]])	# summed deviance contribution
}	# close study loop
totresdev <- sum(resdev[])	# total residual deviance
d[1]<-0	# effect is 0 for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }	# vague priors for treatment effects
}	# close treatment loop
Bayesian categorical outcome, fixed effects [binomial distribution]	
model{	
for(i in 1:ns) {	# indexes studies
mu[i] ~ dnorm(0,.0001)	# vague priors for all trial baselines
for (k in 1:na[i]) {	# indexes arms
r[i,k] ~ dbin(p[i,k],n[i,k])	# binomial likelihood
logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]	# model for linear predictor
rhat[i,k] <- p[i,k] * n[i,k]	# expected value of the numerators
# deviance contribution	
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))	
}	# close arm loop
resdev[i] <- sum(dev[i,1:na[i]])	# summed deviance contribution
}	# close study loop
totresdev <- sum(resdev[])	# total residual deviance
d[1]<-0	# effect is 0 for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }	# vague priors for treatment effects
}	# close treatment loop

A35. The company submission states on page 94 that ‘no indirect treatment comparison was conducted in EM as no relevant comparators with appropriate efficacy data were available’. Please explain the basis for this judgment.

There is no established fourth-line oral medication for EM, with no specific recommendations for this in the available NICE guidance or in any clinical practice guidelines published by societies in the area. Through the literature review conducted, no data for treatment of EM patients who had failed three or more previous treatments was identified for inclusion within an indirect treatment comparison. In addition, expert advice obtained by Teva demonstrated that there is

an unmet need in these patients. At present, patients will get treated if there is a clinical need, but experts are waiting for anti-CRGPs to use in these patients, as there is currently a lack of preventive treatment options available at this stage. Based on these reasons it was not considered appropriate or possible to conduct a meaningful indirect treatment comparison in EM.

A36. Priority question: Please clarify how trials were assessed to be similar, in respect of positioning, for the NMA.

Because patients are not randomly assigned to each treatment in the network (the randomisation is within trials), it was checked that all the trials in the NMA were conducted in a similar way, particularly with respect to efficacy assessments, and recruited participants that belong to similar groups (*e.g.* specific treatment failure populations). Other similarities include: double-blind, placebo-controlled trials, inclusion/exclusion criteria, patients with confirmed migraine, from Western countries, *etc*. In addition, it was checked that the baseline characteristics were, on average, similar across the trials included in the NMA. For data on baseline characteristics in the trials used in the NMA, please refer to the response outlined for A28. For information on the comparator trials, please see Appendix D.1.4

A37. Please confirm that the data provided from FOCUS, outcomes from which are marked as AIC, relate to the final data cut for this trial.

Yes, we can confirm that this is the final cut of the data for the double-blind portion of the trial. The trial has now entered its open-label extension phase and this is still ongoing.

A38. Please clarify if there is a difference in the definition of the full analysis set (FAS) used in HALO EM and HALO CM, as is reported in Table 12 (page.38) and pages 41 and 43, as the sets were described as matching on page 47.

The FAS for the HALO CM trial was erroneously described in the original submission. The FAS included all randomised patients who received at least one dose of study drug and had at least *10 days post-baseline efficacy assessments* for the primary endpoint. This is as reported in the published paper on the HALO CM trial. The FAS was therefore defined in the same way within both HALO trials.

A39. Please provide sensitivity analyses for the FOCUS HFEM subgroup data (p.76/77) based on a cut-off of 10-14 headache days per month.

Efficacy outcomes for those with HFEM defined as 10-14 headache days *per* month were assessed in [redacted] patients who received placebo, [redacted] who received the quarterly dose of fremanezumab and [redacted] who received the monthly dose of fremanezumab.

The results for HFEM 10-14 (Table A39.1) show that fremanezumab (in both dosing regimens) reduced the average monthly number of migraine days to a significantly greater degree than was seen with placebo treatment over the period from baseline to week 12 ([redacted] for both dosing regimens). Results of the ANCOVA analysis showed a LSM difference *versus* placebo of [redacted] migraine days (95% CI ([redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI ([redacted]) for monthly fremanezumab. The MMRM analysis supported the above results, with a LSM difference *versus* placebo of [redacted] migraine days (95% CI [redacted]) for quarterly fremanezumab and [redacted] migraine days (95% CI [redacted]) for monthly fremanezumab.

A significantly greater proportion of patients experienced a reduction of at least 50% in the average monthly number of migraine days with fremanezumab compared to placebo treatment ([redacted] for dosing regimens). Overall, [redacted] patients ([redacted]) treated with quarterly fremanezumab and [redacted] patients ([redacted]) treated with monthly fremanezumab reached this threshold of migraine days reduction, which compares to [redacted] patients ([redacted]) in the placebo group. In these patients with at least a 50% response, fremanezumab was able to provide a mean change in monthly migraine days of [redacted] for quarterly dosing and [redacted] for monthly dosing compared to baseline; monthly migraine days at 12 weeks after baseline were [redacted] and [redacted] for quarterly and monthly fremanezumab, respectively.

Table A39.1 Summary of main efficacy outcomes for patients with high-frequency episodic migraine (10-14 headache days) 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]

	Placebo (n=[redacted])	Fremanezumab quarterly (n=[redacted])	Fremanezumab monthly (n=[redacted])
Difference *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Patients with at least 50% 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]

A40. Priority question: Please provide a summary (proportions) of drug classes/clusters failed for the relevant FOCUS trial population of patients who have failed three or more classes of preventive treatment?

Please find below a summary of the drug classes failed for patients with EM (Table A40.1) and CM (Table A40.2), who failed three or more classes of preventive migraine treatment, in the FOCUS trial.

Table A40.1 EM patients who had failed ≥3 classes of preventive medications for migraine in the past 10 years

	Placebo (n=[redacted])	Fremanezumab quarterly (n=[redacted])	Fremanezumab monthly (n=[redacted])
Beta-blockers, n (%)	[redacted]	[redacted]	[redacted]
Anticonvulsants, n (%)	[redacted]	[redacted]	[redacted]
Tricyclics, n (%)	[redacted]	[redacted]	[redacted]
Flunarizine, n (%)	[redacted]	[redacted]	[redacted]
Candesartan, n (%)	[redacted]	[redacted]	[redacted]
Onabotulinumtoxin A, n (%)	[redacted]	[redacted]	[redacted]
Valproic acid, n (%)	[redacted]	[redacted]	[redacted]

Table A40.2 CM patients who had failed ≥3 classes of preventive medications for migraine in the past 10 years

	Placebo (n=[redacted])	Fremanezumab quarterly (n=[redacted])	Fremanezumab monthly (n=[redacted])
Beta-blockers, n (%)	[redacted]	[redacted]	[redacted]
Anticonvulsants, n (%)	[redacted]	[redacted]	[redacted]
Tricyclics, n (%)	[redacted]	[redacted]	[redacted]
Flunarizine, n (%)	[redacted]	[redacted]	[redacted]
Candesartan, n (%)	[redacted]	[redacted]	[redacted]
Onabotulinumtoxin A, n (%)	[redacted]	[redacted]	[redacted]
Valproic acid, n (%)	[redacted]	[redacted]	[redacted]

Section B: Clarification on cost-effectiveness data

Note: clarification questions on the cost-effectiveness data and model will be forwarded by 17:00 on 28 May 2019 (per the updated timeline)

Section C: Textual clarification and additional points

C1. In the submission, it was stated that for the HALO CM trial (Section B 2.4.2.2 page 43) "**The FAS included all randomised patients who received at least one dose of study drug and had at least *one post-baseline efficacy assessment* for the primary endpoint……..**" In the corresponding sections for the other two trials (HALO EM and FOCUS), it was stated as "……..**at least one dose of study drug and had at least *10 days post-baseline efficacy assessments* for the primary endpoint.**" Please confirm that these two statements (in bold) are correct, and how they differ.

The FAS for the HALO CM trial was erroneously described in the original submission. The FAS included all randomised patients who received at least one dose of study drug and had at least *10 days post-baseline efficacy assessments* for the primary endpoint. This is as reported in the published paper on the HALO CM trial. The FAS was therefore defined in the same way within both HALO trials.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fremanezumab for preventing chronic and episodic migraine [ID1368]

Clarification questions

May 2019

File name	Version	Contains confidential information	Date
Teva clarification response Part B	FINAL_v3.0 with revised confidential information	No	31 October 2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Questions as *per* document submitted on 20 May 2019.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Please explain the sentence of the justification given in Row 2 of Table 57 (page 151) '…and if necessary treatment would be restarted at a later time.' How has treatment re-initiation been considered within this analysis?

Treatment re-initiation has not been considered within this economic analysis. Whilst Teva acknowledges the possibility that some patients may require re-initiation of treatment over the long-term, there are no current clinical data available on which to base any assumptions in this area. Expert opinion gathered by Teva showed that physicians expect to be able to discontinue treatment in some patients who have shown a sufficient response to fremanezumab (as modelled by the positive stopping rule); in line with how they use other preventive medications. The best available estimate was that this would apply to 20% of patients every 52 weeks, and whilst there was an expectation that some patients may require re-initiation of treatment, the experts

consulted did not feel that they were able to provide an estimate of the timescales or the proportion of patients that this may effect. Some experts consulted felt that a higher proportion of responding patients would be able to stop treatment at each assessment, but a conservative value for this assumption was used (20%), in order to try and account for additional usage of fremanezumab that would occur during a second course of therapy.

It is important to note that treatment re-initiation would likely be triggered by changes in disease activity. Such natural history changes in migraine were not included within this model due to a lack of data and the complexity of these changes (for example, the impact of the menopause, as summarised in Table 57 of the submission). As it was not possible to include the natural history changes in migraine, this complicated the ability to include a re-initiation of treatment, as this could not be triggered by changes in disease activity in the model. The modelling was therefore conducted within the limitations of the available data and this is one of the reasons that a 10-year time horizon was used for the model. Within this 10-year horizon, it would be expected that there would be less natural history changes and less requirement for re-initiation of treatment compared to a longer time horizon. Therefore, the 10-year time horizon provides a robust analysis based on the available evidence.

Population, Intervention and comparators

B2. Please provide the source of 67%, the proportion of patients with migraine in the model who are classified as having chronic migraine.

These data are not used to drive <u>any</u> of the calculations in the model and are a legacy from the model originally being programmed to be able to provide combined EM and CM results. However, due to the differences in comparators (onabotulinumtoxin A is licenced only for CM), the EM and CM populations have been presented separately throughout the economic analysis. [redacted]

B3. What proportion of the modelled population are expected to prefer 3-monthly dosing of fremanezumab over monthly dosing?

The expected split between monthly and quarterly dosing of fremanezumab in UK practice is currently unknown. Clinical experts have indicated to Teva that they would expect that some patients will prefer the more infrequent administration offered by the quarterly regimen, whereas others will prefer the regularity of the monthly administration. It is also likely that a proportion of patients may move between the two dosing options. As the cost, efficacy and adverse event profile are equivalent between these two dosing options, the expected preference between them does not impact the cost-effectiveness of fremanezumab. The only exception for this is where patients are not able to self-administer their treatment. This is expected to affect only a very small minority of patients (which was confirmed by clinical experts consulted by Teva), due to the lack of physical disability and the mean age of patients with migraine. It is also possible that in many cases the injection can be assisted by a carer. However, a small proportion of patients may require administration of fremanezumab by a healthcare professional. It is expected that this group will predominantly utilise the quarterly dosing, as this reduces the number of clinic visits needed thereby reducing the burden on this service whilst providing greater convenience for the patient with fewer hospital visits required.

Perspective, time horizon and discounting

B4. Please explain why the model time horizon of 2-years for onabotulinumtoxin A (OBA) (NICE TA260) is not appropriate for fremanezumab.

As migraine is a chronic condition and it is expected that a proportion of patients will remain on fremanezumab treatment for longer than two years ([redacted]), a two year time horizon was not considered appropriate. This was based on the fact that the guidance on the NICE reference case states that the time horizon should be "*Long enough to reflect all important differences in costs or outcomes between the technologies being compared.*" Two years was therefore judged not to meet these criteria and a longer 10-year time horizon was therefore used, as this was judged to be sufficient to meet these requirements and to capture all important

differences in costs and outcomes between technologies; a very small number of patients are projected to remain on treatment beyond 10 years ([redacted]).

Effectiveness (linked to a closer model examination)

B5. PRIORITY: Please elaborate in detail on the derivation of the response rates for each strategy reported in Table 50. These do not match any response rates reported in the clinical outcomes or network meta-analysis (NMA) sections of the clinical chapter. Further, the derivation of the other response rates in the table in worksheet <Config> cells C210:E212 and G210:I212 is unclear; please detail the method used.

The response rates were calculated as described below.

EM (50% response)

Placebo

The 50% response rate for placebo in EM was calculated as the pooled rate for the placebo arms of the trials used in the NMA (Table B5.1).

Table B5.1 50% responder rates for placebo in EM

NMA Source	Responders	Sample Size	Response Rate
Fremanezumab FOCUS (NCT03308968)	[redacted]	[redacted]	[redacted]
Erenumab LIBERTY (NCT03096834)	[redacted]	[redacted]	[redacted]
Combined	[redacted]	[redacted]	[redacted]

Fremanezumab

The odds ratios for fremanezumab monthly treatment and fremanezumab quarterly treatment from the NMA were used to calculate response rates which were weighted by the samples size to get an overall fremanezumab response rate (Table B5.2).

Table B5.2 50% responder rates for fremanezumab monthly and quarterly in EM

Treatment	Odds Ratio vs. Placebo From NMA	Response Rate	Sample Size From NMA
Fremanezumab monthly	[redacted]	[redacted]	[redacted]
Fremanezumab quarterly	[redacted]	[redacted]	[redacted]
Combined		[redacted]	

CM (30% response)

Placebo

The response rate for placebo was calculated as the pooled rate for the placebo arms of the trials used in the NMA (Table B5.3).

Table B5.3 30% responder rates for placebo in CM

NMA Source	Responders	Sample Size	Response Rate
Fremanezumab FOCUS (NCT03308968)	[redacted]	[redacted]	[redacted]
Erenumab Study 295 (NCT02066415)	[redacted]	[redacted]	[redacted]
Combined Placebo	[redacted]	[redacted]	[redacted]

Fremanezumab

The odds ratios for fremanezumab monthly treatment and fremanezumab quarterly treatment from the NMA were used to calculate response rates which were weighted by the samples size to get an overall fremanezumab response rate (Table B5.4).

Table B5.4 30% responder rates for fremanezumab monthly and quarterly in CM

Treatment	Odds Ratio vs. Placebo From NMA	Response Rate	Sample Size From NMA

Fremanezumab monthly	[redacted]	[redacted]	[redacted]
Fremanezumab quarterly	[redacted]	[redacted]	[redacted]
Combined		[redacted]	

Onabotulinumtoxin A

For onabotulinumtoxin A the 30% response rate was calculated as described in question B6.

B6. Please provide the calculation of the conversion of 50% OBA response rate to the 30% response rate.

The calculation of an estimated 30% response rate for onabotulinumtoxin A was done using the following methodology. Firstly, the risk ratios between onabotulinumtoxin A and other treatments (erenumab/fremanezumab) were calculated for the 50% response outcome (as these data are available). These risk ratios were then applied to the known figures for 30% response rate in other treatments (erenumab/fremanezumab) to estimate the response rate in onabotulinumtoxin A whilst accounting for the relative treatment effect between onabotulinumtoxin A and these other treatments. These estimates were then combined as a weighted average based on the trial n numbers to provide the reported estimate for 30% response rate in onabotulinumtoxin A. Alternative approaches were considered, but with the available data the above was considered the most appropriate approach to allow the inclusion of onabotulinumtoxin A whilst using the response threshold (30%) that has been the preference of NICE in previous appraisals. A scenario analysis was included in the submission that utilised a 50% response rate for CM, which was therefore able to use direct data for onabotulinumtoxin A. This scenario analysis resulted in a slightly higher ICER for fremanezumab compared to onabotulinumtoxin A (£17,155 compared to £16,825 in the base case), but did not change the overall cost-effectiveness of fremanezumab. This scenario therefore gives confidence in the approach taken in this analysis and the results produced.

B7. PRIORITY: Please provide further evidence for the selection of the beta binomial distribution above other options for MD dispersion: provide the BIC scores for comparison across the tested distribution alternatives and justify the use of BIC in preference to AIC or BIC and AIC. Goodness of fit results should be shown as R output alongside the respective constants for respective distributions.

Distribution of migraine days

Longitudinal (utilising the week 4, 8, and 12 visits) beta binomial and negative binomial models were fitted to the patient-level monthly migraine day frequency (migraine days *per* 28 days) separately for the EM, HFEM and CM population subgroups. The beta binomial and negative binomial distributions can be described by the mean and an additional parameter accounting for the "spread" of the distribution. For the beta binomial and negative binomial distributions, the "spread" component (sigma) is referred to as the intra class correlation coefficient and the dispersion parameter, respectively. This analysis was primarily concerned with determining which distribution provided a better fit to the observed data and the estimate of the sigma parameter for that distribution.

The probability density function, mean, variance, and intra class correlation coefficient for the beta binomial distribution, with n Bernoulli trails and the two shape parameters, α and β, are given below:

$$f(y \mid n, \alpha, \beta) = \frac{n!}{(n-y)!\,y!} \times \frac{B(y+\alpha, n-y+\beta)}{B(\alpha,\beta)}; \text{where } y \text{ is the number of migraine days}$$

$$\text{where } B(\alpha,\beta) = \frac{\Gamma(\alpha) \times \Gamma(\beta)}{\Gamma(\alpha+\beta)}; \quad \text{where } \Gamma(\cdot) \text{ is the gamma function}$$

$$\text{mean} = n\pi = \frac{n\alpha}{\alpha+\beta}; \quad \text{where } n = 28, \text{and } \pi \text{ is the probability of a migraine day}$$

$$\text{Variance} = \frac{n\alpha\beta(\alpha+\beta+n)}{(\alpha+\beta)^2 \times (\alpha+\beta+1)}$$

$$Variance = n\pi(1-\pi)[1+(n-1)\rho]$$

$$intra\ class\ correlation:\ \rho = \frac{1}{\alpha+\beta+1}$$

The probability density function, mean, variance, and dispersion parameter for the negative binomial distribution (type I) are as follows:

$$f(y|\mu,\varphi) = \frac{Gamma(y+1/\varphi)}{(Gamma(y+1)\times Gamma(1/\varphi))} \times \frac{(\mu\times\varphi)^y}{(\mu*\varphi+1)^{(y+(1/\varphi))}}$$

$$mean = \mu$$

$$variance = \mu(1+\varphi\times\mu)$$

$$dispersion = \varphi$$

The best fitting model for each distribution was determined using the Bayesian information criterion (BIC). Selection between the beta binomial and negative binomial models was determined by both visual inspection and aggregate measures of the error of the predicted distributions versus the observed distribution. Specifically, we compared the mean absolute error and root mean square error from each distribution. These metrics are based on the fitted distribution's density (probability of x migraine days) *versus* the observed proportion (*e.g.* 5% of patients had x migraine days). The metrics are defined as follows:

$$Mean\ absolute\ error = \frac{1}{29}\sum_{t=0}^{28}|y_t-\hat{y}_t|$$

$$Root\ mean\ square\ error = \sqrt{\frac{1}{29}\sum_{t=0}^{28}(y_t-\hat{y}_t)^2}$$

$Where:\ y_t\ is\ the\ observed\ proportion\ for\ t\ migraine\ days;$

$\hat{y}_t\ is\ the\ fitted\ density\ for\ t\ migraine\ days$

We first show the relevant results for the EM MMD distribution models. Thereafter, results are shown for HFEM 8-14 MMD and CM MMD distribution models.

The beta binomial distribution appeared to provide a slightly better fit across populations than the negative binomial distribution.

EM 50% Responder Population

Table B7.1 EM responder sigma parameters and goodness of fit

Distribution	Placebo	Fremanezumab	AIC	BIC
Beta Binomial (Intra class correlation [ρ])	[redacted]	[redacted]	[redacted]	[redacted]
Negative Binomial (Dispersion [φ])	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike information criterion; BIC: Bayesian information criterion

Table B7.2 EM responder – comparative measures of beta binomial and negative binomial model fit

Treatment	Visit	Mean absolute error		Root mean square error	
		Beta binomial	Negative binomial	Beta binomial	Negative binomial
Placebo	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Figure B7.1 EM 50% responder observed MMD by visit overlaid with negative binomial and beta binomial model fit

BB: beta binomial; MMD: monthly migraine days; NB: negative binomial

EM 50% Non-Responder Population

Table B7.3 EM non-responder sigma parameters and goodness of fit

Distribution	Placebo	Fremanezumab	AIC	BIC
Beta Binomial (Intra class correlation [ρ])	[redacted]	[redacted]	[redacted]	[redacted]
Negative Binomial (Dispersion [φ])	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike information criterion; BIC: Bayesian information criterion

Table B7.4 EM non-responder – comparative measures of beta binomial and negative binomial model fit

Treatment	Visit	Mean absolute error		Root mean square error	
		Beta binomial	Negative binomial	Beta binomial	Negative binomial
Placebo	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Figure B7.2 EM 50% non-responder observed MMD by visit overlaid with negative binomial and beta binomial model fit

BB: beta binomial; MMD: monthly migraine days; NB: negative binomial

HFEM 50% Responder Population

Table B7.5 HFEM 50% responder sigma parameters and goodness of fit

Distribution	Placebo	Fremanezumab	AIC	BIC
Beta Binomial (Intra class correlation [ρ])	[redacted]	[redacted]	[redacted]	[redacted]
Negative Binomial (Dispersion [φ])	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike information criterion; BIC: Bayesian information criterion

Table B7.6 HFEM 50% responder – comparative measures of beta binomial and negative binomial model fit

Treatment	Visit	Mean absolute error		Root mean square error	
		Beta binomial	Negative binomial	Beta binomial	Negative binomial
Placebo	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Figure B7.3 HFEM 50% responder observed MMD by visit overlaid with negative binomial and beta binomial model fit

BB: beta binomial; MMD: monthly migraine days; NB: negative binomial

HFEM 50% Non-Responder Population

Table B7.7 HFEM non-responder sigma parameters and goodness of fit

Distribution	Placebo	Fremanezumab	AIC	BIC
Beta Binomial (Intra class correlation [ρ])	[redacted]	[redacted]	[redacted]	[redacted]
Negative Binomial (Dispersion [φ])	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike information criterion; BIC: Bayesian information criterion

Table B7.8 HFEM non-responder – comparative measures of beta binomial and negative binomial model fit

Treatment	Visit	Mean absolute error		Root mean square error	
		Beta binomial	Negative binomial	Beta binomial	Negative binomial
Placebo	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Figure B7.4 HFEM 50% non-responder observed MMD by visit overlaid with negative binomial and beta binomial model fit

BB: beta binomial; MMD: monthly migraine days; NB: negative binomial

CM 30% Responder Population

Table B7.9 CM 30% responder sigma parameters and goodness of fit

Distribution	Placebo	Fremanezumab	AIC	BIC
Beta Binomial (Intra class correlation [ρ])	[redacted]	[redacted]	[redacted]	[redacted]
Negative Binomial (Dispersion [φ])	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike information criterion; BIC: Bayesian information criterion

Table B7.10 CM 30% responder – comparative measures of beta binomial and negative binomial model fit

Treatment	Visit	Mean absolute error		Root mean square error	
		Beta binomial	Negative binomial	Beta binomial	Negative binomial
Placebo	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Figure B7.5 CM 30% responder observed MMD by visit overlaid with negative binomial and beta binomial model fit

BB: beta binomial; MMD: monthly migraine days; NB: negative binomial

CM 30% Non-Responder Population

Table B7.11 CM 30% non-responder sigma parameters and goodness of fit

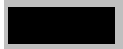
Distribution	Placebo	Fremanezumab	AIC	BIC
Beta Binomial (Intra class correlation [ρ])	[redacted]	[redacted]	[redacted]	[redacted]
Negative Binomial (Dispersion [φ])	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike information criterion; BIC: Bayesian information criterion

Table B7.12 CM 30% non-responder – comparative measures of beta binomial and negative binomial model fit

Treatment	Visit	Mean absolute error		Root mean square error	
		Beta binomial	Negative binomial	Beta binomial	Negative binomial
Placebo	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	Week 4	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Figure B7.5 CM 30% non-responder observed MMD by visit overlaid with negative binomial and beta binomial model fit



BB: beta binomial; MMD: monthly migraine days; NB: negative binomial

B8. Please explain why the increase to full effect (change in MMDs) of fremanezumab and OBA is modelled as a linear increase. Please provide the justification for the longer time frame used for OBA.

The treatment effect is applied relative to the change in MMDs for the best supportive care group, with this group modelled using the data from the placebo arm of the FOCUS trial. Treatment efficacy for active treatments is defined at 12 weeks and the treatment effects at week 4 and 8 are gradually applied proportionally to the reduction in the placebo longitudinal regression models. However, when the placebo curve is flat the model does implement this change in a linear fashion, as the best available estimate for these intermediate time points. These are conservative assumptions, given the rapid onset of action seen in the HALO clinical trials of fremanezumab; but given the lack of similar data for onabotulinumtoxin A were the most appropriate option.

The longer time frame used for onabotulinumtoxin A is due to the fact that the initial assessment period for onabotulinumtoxin A is 24 weeks compared to the 12 weeks of fremanezumab. The MMD reduction data for fremanezumab and onabotulinumtoxin A both use fremanezumab data; therefore, the benefits for fremanezumab are conservative.

B9. In respect of the maintenance of treatment effect, please confirm that as a result of the positive stopping rule, individuals who are 'positively discontinued' [redacted]

As a result of the positive stopping rule, it can be confirmed that patients retain full incremental benefit of treatment *versus* BSC for the remainder of the time horizon (allowing for background mortality and standard *per* cycle discontinuation) and accrue zero treatment costs. As the positive stopping rule is modelled as a subgroup within the "on treatment" patient group, these patients were still subject to the standard *per* cycle discontinuation rate. This ensured that the treatment benefit was not maintained indefinitely (as when patients discontinued they reverted to BSC

MMD values), and was limited in the same way as would have occurred have no positive stopping occurred.

A fuller description of the positive stopping rule is given in this following section to aid understanding of this rule and its implementation. After the initial 12-week assessment, all patients that remained on treatment receive this treatment for 52 weeks. At the end of this time (week 64), all treated patients stop treatment for 12 weeks. After this treatment break (week 76), 80% of patients who received treatment at week 64 resume treatment (with the remaining 20% stopping under the positive stopping rule). The treated patients then receive treatment for another 52 weeks, before another 12-week treatment break (starting week 124 and ending week 136). At week 136, 80% of patients who received treatment at week 124 (start of treatment break) resume treatment (with the remaining 20% stopping under the positive stopping rule). This cycle of 52-week treatment followed by a 12-week assessment period is repeated throughout the model time horizon (base case week 520). After each 12-week assessment, 20% of patients that entered that assessment are stopped from treatment as a 'positive stop'. These patients that are positively stopped maintain their treatment benefit (in terms of MMDs), but no longer incur drug acquisition costs and do still experience standard *per* cycle discontinuation and mortality.

B10. PRIORITY: Please provide scenarios exploring alternative assumptions about the long-term effectiveness of fremanezumab/maintenance of MMD frequency, including the linear return to BSC MMDs over 1-, 3- and 5-year periods.

The requested scenarios are presented in Table B10.1 and Table B10.2 below. It should be noted, however, that there is no available data to suggest that a waning effect occurs with fremanezumab. The available evidence shows that only 2% (38/1888) of patients developed anti-drug antibodies after 12 months of fremanezumab treatment; even in these patients anti-drug antibody titres were low and did not affect the safety or efficacy of fremanezumab treatment. Therefore, anti-drug antibodies would not be expected to reduce the efficacy of fremanezumab over time. In addition, it should be noted that migraine is not a neurodegenerative condition and therefore treatment efficacy can be assumed to not be affected by this.

Based on the available evidence, the most plausible assumption is that there is no waning in the treatment effect over the time horizon of the model. A treatment waning effect has been included within the scenario analyses to provide an analysis of the impact of that assumption; the impact of waning on ICER values was found to be relatively small, which is due to the responder/non-responder analysis, as only the responding patients who remain on treatment will be impacted by this waning.

Table B10.1 EM treatment waning over 1, 3 and 5 years

Scenario	**ICER *versus* BSC**
Waning of treatment effect over 1 year	£14,720
Waning of treatment effect over 3 years	£14,526
Waning of treatment effect over 5 years	£14,392

Table B10.2 CM treatment waning over 1, 3 and 5 years

Scenario	**ICER *versus* BSC**	**ICER *versus* onabotulinumtoxin A**
Waning of treatment effect over 1 year	£12,427	£16,702
Waning of treatment effect over 3 years	£12,273	£16,587
Waning of treatment effect over 5 years	£12,167	£16,503

Health-related quality of life

B11. Please explain the coding used in worksheet <Utilities>, cells E7:G35: '=L7*(1-(-0.05))-0.05'.

The mean of the EQ5D scores was calculated in the logit scale. The regression estimates for EQ5D scores by migraine days need to be transformed from the logit scale. Further, these inverse logit values are estimates of the transformations of the original values, which had been transformed so that all EQ5D values were between zero and one. Thus, they must be transformed back to the original scale. This coding was implemented to conduct this transformation.

B12. PRIORITY: In Section B 3.4.1 (para 1, page 140) it is suggested that utility scores were derived from patients within the FOCUS trial who have failed 3 or more previous migraine treatments; however, later in Section B 3.4.2 (para 3,

page 141) it is stated that the full FOCUS trial population is used. If the base case is not the target model population (3 or more previous migraine treatments failed) then please provide a scenario analysis in which utilities are calculated only from this subgroup. Please also provide more detail behind the justification of the base case preference.

The text at the start of Section B 3.4.1 is relating to the fact that the FOCUS data were the most appropriate data to use for the utilities when compared to the HALO trials and the population of interest for this appraisal (which is stated to be patients who have failed three or more previous migraine preventive treatments). The utility data used within the model is based on the full FOCUS trial population, as stated in Section B 3.4.2. This choice was made as it was determined to be more robust data than was available for the three or more failed previous preventive treatment group, due to the requirements for this data to be split into the 28 MMD states; necessitating the use of the larger dataset.

Within the timescales available, it has not been possible to complete an additional analysis using just the three or more failed previous preventive treatments group. In addition, due to the reasons outlined above, it is not expected that this analysis would provide robust results. The use of utility data from the full trial population is consistent with the approach taken in the ongoing erenumab appraisal, where similar sample size considerations were encountered.

B13. PRIORITY: Please provide the justification and evidence for a separate set of utility values for people on (1) BSC, and (2) off-treatment. Provide also a scenario analysis whereby all patients use the same utility value set, the 'all patients' set.

Only two sets of utility values have been used in the model, an "on treatment" set and an "off treatment" set. This may have been erroneously labelled in some places within the model, but it can be confirmed that the BSC and off-treatment utilities are the same.

The use of separate "on treatment" and "off treatment" utilities is established in the analysis of migraine and is reflective of clinical trial data where active treated patients have improved quality of life compared to placebo patients at the same level

of MMDs. This difference has been justified by reflecting the additional benefits of migraine treatment not captured within the reduction in MMD numbers. This approach was taken within the Botox appraisal and the FAD stated that "*The Committee concluded that although using different utility values within each health state in the botulinum toxin type A and the placebo arm was plausible and better than applying the same utility values within each health state*…" The analysis presented below uses the same utilities for both "on treatment" and "off treatment" within the model, with blended results used (a simple average of the "on treatment" and "off treatment" utilities). These results show that the assumption of a differential impact on utilities has only a minor impact on the ICER values (see Table B13.1 and Table B13.2 below).

Table B13.1 EM blended utility results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£16,142

Table B13.2 CM blended utility results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER *versus* BSC (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
OBA	[redacted]	[redacted]	[redacted]	[redacted]	£7,997	£7,997
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£12,860	£16,517

B14. PRIORITY: Please provide the result of the GAMLSS beta regression with the goodness of fitness measures (BIC) used to select the chosen distribution from the alternatives, and provide deeper discussion of the salient issues. How did the resultant utilities compare to equivalents in the appraisals of OBA and erenumab?

The EQ5D regression analysis used only the mapped EQ5D scores at baseline as the response variable for all patients. Patients in the placebo arm, on average,

experienced an increase in their baseline EQ5D scores over the course of the trial for the same given number of MMDs. An additional analysis was undertaken to obtain more accurate estimates of EQ5D scores for a given number of migraine days for patients that are not participating in a clinical trial.

Parameter estimates and BIC values were compared between the two models in order to gauge the impact of each of the different methods utilised. The first method (transformed model) involved transforming all EQ5D scores so that the range of all scores fell between 0 and 1. The following transformation was utilised:

$$y' = \frac{y - (-0.05)}{1 - (-0.05)};\ \textit{where } y \textit{ is the EQ5D score}$$

The second method (normal model) undertaken was to change to a normal distribution for the regression and not make any changes to the data.

The beta regression coefficient estimates for the transformed baseline mean model are shown in **Table** B14.1. The only predictor used for the sigma model was monthly migraine days.

Table B14.1 Transformed mean baseline EQ5D model using beta distribution

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]				

BIC: Bayesian information criterion; SE: standard error

The coefficient estimates for the mean baseline EQ5D model using a normal distribution (method 2) are shown in **Table**B14.2.

Table B14.2. Mean baseline EQ5D model using a normal distribution

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]				

BIC: Bayesian information criterion; SE: standard error

EQ5D scores in the CEM are based on whether subjects are on or off treatment and the number of migraine days *per* 28 days. Individual patient characteristics are not utilised. Thus, the CEM model only utilises two of the variables (treatment and migraine days) used for the EQ5D regression. Therefore, we used the regression sample averages as values for the remaining predictor variables in order to get estimates for the pertinent regression coefficients. The on treatment EQ5D scores are calculated by adding the on-treatment effect estimated from the longitudinal analysis to the baseline EQ5D regression model. The calculations and the resulting coefficient estimates are shown in Table B14.3.

Table B14.3 Adjustment of regression coefficients based on sample averages

[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

EQ5D: EuroQol five-dimension scale

The mean of the EQ5D scores was calculated in the logit scale. The regression estimates for EQ5D scores by migraine days needs to be transformed from the logit scale. Further, these inverse logit values are estimates of the transformations of the original values, which had been transformed so that all EQ5D values were between zero and one. Thus, they must be transformed back to the original scale.

The utility values reported in the erenumab appraisal were reported (in the ACD) to vary between 0.466 for 28 MMD and 0.784 for 0 MMD. Whereas within the onabotulinumtoxin A appraisal the following utility values were reported (within the additional evidence submission of 24 February 2012).

MMDs	On-treatment	Off-treatment
0-3	0.691	0.669
4-9	0.699	0.638
10-14	0.635	0.565
15-19	0.561	0.550
20-28	0.480	0.507

These values are broadly comparable to those used within this submission. The values in the erenumab appraisal are very similar at low MMD values, with slightly

reduced utilities at the highest MMD states. Due to the banding of MMDs within the onabotulinumtoxin A appraisal, a direct comparison is more difficult. However, the utilities generally show a good level of agreement with those reported in the onabotulinumtoxin A appraisal. This is particularly true in the middle of the MMD range, and at the highest and lowest MMD values the figures from the onabotulinumtoxin A appraisal showed a smaller variation, which is likely, at least in part, to be an artefact of the banding applied to MMDs.

Resource use and costs

B15. PRIORITY: Please provide the method of conversion of resource consumption presented by Vo to the MMD health state resource consumption in Section B 3.5.2 Table 54, page 146.

The resource use data was extracted from the erenumab appraisal, where it was reported as *per* cycle rates with additional information on the rate in the 0 MMD group. As this was the data presented to NICE it was assumed that this was the most appropriate analysis conducted on these data. These data were reported *per* 12-week cycle (cycle length in erenumab model) and so these values were divided by three to produce values *per* 4-week cycle for the fremanezumab model. During the answering of this question, it has been noted that an error had occurred during the imputation of these data into the fremanezumab economic model and the *per* cycle correction had not been applied correctly. Therefore these data have been corrected and all affected analyses updated; corrected versions of all relevant documents have been included with this clarification letter. Teva apologises for this error.

Section C: Textual clarification and additional points

C1. Please supply missing rows of data from Table 63 (DSAs 9-11).

These missing rows directly relate to the numbers in the initial table where the scenarios are defined. These values relate to CM-specific data and are not relevant for EM. However, please see below a revised Table with these rows included.

Scenario	ICER versus BSC
Base case	£13,954

Scenario	ICER versus BSC
1 – 5 year horizon	£22,598
2 – Lifetime horizon	£4,767
3 – Waning of treatment effect over 10 years	£14,202
4 – Lifetime horizon and waning over 10 years	£4,835
5 – Treatment administration costs included for fremanezumab (monthly: £1.85 per cycle)	£14,054
6 – Treatment administration costs included for fremanezumab (quarterly: £0.62 per cycle)	£13,987
7 – Positive stopping rule affects 10% of currently treated patients	£16,620
8 – No positive stopping rule	£20,214
9 – Proportion of patients responding to onabotulinumtoxin A increased to [redacted]%	N/A
10 – Proportion of patients responding to onabotulinumtoxin A increased to [redacted]%	N/A
11– 50% reduction in MMDs used as response threshold in CM	N/A
12 – Impact of lost work days	Dominates
13 – Quarterly fremanezumab dosing	£13,976
14 – Monthly fremanezumab dosing	£13,909

NICE National Institute for Health and Care Excellence

Patient organisation submission

Fremanezumab for preventing chronic and episodic migraine [ID1368]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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

About you	
1.Your name	[redacted]

2. Name of organisation	The Migraine Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Migraine Trust is a patient focussed research driven charity. We provide evidence based information, campaign for and support those affected by migraine in the UK. We are committed to reducing the burden of migraine – on individuals, their families, schools and employers, the health system, the economy and society as a whole. Research is at the heart of our work. We fund and encourage the highest quality of medical research into the causes and treatments for migraine. We believe in advancing knowledge through the dissemination of scientific learning and the sharing of best practice. We provide evidence-based information to empower and educate. We campaign to position migraine as a serious public health issue and promote improved understanding and awareness. Our funding is from legacies, individual donations, events fundraising, corporate partners, trusts and foundations. More information on how we are funded can be found in our annual report and accounts.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	The Trust has taken information gathered from our surveys which seek the views of people living with migraine. We have also spoken to healthcare professionals who support people with migraine. **The chronic migraine survey (n=221)** The survey gathered views from people living with chronic migraine about the impact of migraine on their lives, current medications and new treatments for the prevention of migraine. **Work, health and migraine survey (n=9**61)

carers to include in your submission?	The number of people who responded to the survey who lived with either episodic or chronic was 514 (53%) and 399 (42%) respectively. **What Matters Most to Patients with Headaches and Migraines? (n=116)** A collaborative study between The Migraine Trust and the Headache Service at St George' University NHS Hospital Trust in order to understand the views of patients with migraine and headaches. Nineteen "I statements" produced as a result of a focus group carried out by the Migraine Trust were used as the basis of a semi structured interview during hospital outpatient attendances. Carers or friend's responses were included with the patient's response in order to gain the widest experience. 118 patients agreed to participate with 116 interviews carried out. Thematic analysis of the responses was carried out with codes and themes identified. **Neurological Alliance: Patient Experience survey 2016 (n=1838 people with migraine)** Out of the 7048 responses to the survey, 1,838 answered that they have a migraine condition. Of these 1,359 stated that migraine was their main neurological condition. The Neurological Alliance agreed to share data for the migraine respondents with the Migraine Trust, which was analysed. It is the analysis of just people with migraine responses that will be used in this submission. We have also taken quotes from these surveys from people with migraine who have taken the time to write up their experience of living with migraine.
Living with the condition	
6. What is it like to live with the condition? What do carers	<u>What is migraine?</u> Migraine is a moderate to severe pulsating or throbbing primary headache disorder that can present with or without aura, (visual, sensory, motor, speech, brainstem or retinal symptoms) accompanied with other symptoms such as increased sensitivity to light and/or sound, nausea and/or vomiting and aggravation by physical activity which can last four to 72 hours in adults.

experience when caring for someone with the condition?	Chronic migraine is highly debilitating, it present as migraine for 15 days per month and for more than three consecutive months. Episodic migraine is another migraine sub-type, which is defined as less than 15 headache days per month. For some people there is a steady progression in headache frequency, especially in long term sufferers. This can lead to the migraines becoming so frequent that they cross the threshold of more than 15 days per month and become defined as chronic migraine. Every year between 2.5 and 4.6% of people with episodic migraine experience progression to chronic migraine <u>What is it like to live with the condition?</u> In all of the surveys the areas of a person's day-to-day life most affected were social life, family life, work life/ability to work, and ability to take part in hobbies/leisure activities. Due to the nature and length of time that they are affected, people with chronic migraine spend significantly more time absent from work, school, leisure, home and social activities than episodic migraine patients. Respondents told us that the unpredictable nature of the migraine, both episodic and chronic, prevents people from being able to make plans or commit to family, work or leisure activities. Respondents described the social isolation, depression, loneliness and poor quality of life as a result of missing out on the aforementioned areas of their lives. On rare migraine/headache free days the anxiety of a migraine attack occurring continues to restrict an individual's life and their activities. Inability to attend work, maintain a job, impaired productivity, losing or fear of losing a job due to chronic migraine are commonly occurring themes for the people we spoke to. The high frequency and severity of migraine attacks experienced by chronic migraine sufferers, means that they are regularly unable to spend time with family and fulfilling normal family activities/duties. 65% of respondents to our survey said that chronic migraine has a negative impact on their family and loved ones. Partners and family members become carers to chronic migraine sufferers. Sufferers often cannot be left alone or travel, particularly to new places, unaccompanied in case an attack occurs and they cannot get back. *'A migraine attack takes time away from me and my family.'* *'Not knowing when you are going to have a migraine and if the medication is going to work has an effect on planning any activity and it annoys people if you call off due to migraine. Family suffer as you may have to go to bed*

	and can not be a fully functioning member of the family. The pain at time can be unbearable and this then effects relationships. Side effects of medication make you tired.' *'Difficult to make plans, as may not be able to fulfil. Time off work sick. Can't travel on my own in case unable to get back if I get migraine.'* Employment The work, health and migraine survey found that the fluctuating and unpredictable nature of a headache/migraine disorder was one of the biggest barriers to managing the impact of headache/migraine condition at work for all organization sizes. Additional pressure comes when the chronic migraine sufferer is forced to give up work due to the illness. 50% of the chronic migraine survey respondents said that their condition negatively impacts on their financial circumstances. This is supported by the Work, Heath and Migraine Survey which found that in the United Kingdom, 19% of survey participants have previously lost a job as result of their migraine or headache disorder (*n = 961*). This rate doubles to 38% when we look solely at the survey participants that recognise as having a disability (*n = 320*). With a prevalence of 10 million people living with migraine in the UK, (adults aged 15-69), this would put the number of people considered disabled due to migraine at 3.8 million. 81% of people with either chronic or episodic migraine who answered the work health and migraine survey either agreed or strongly agreed that when their migraine disorder worsened that it would have a negative effect on their employment. The nature of the condition and how sickness policies are currently written, often unfairly penalises people with migraine. The number of short term sickness absence taken to manage the condition means that people with migraine are more likely to trigger disciplinary action. *'I have taken a lot of sick days due to migraine but only recently I've been allowed occasionally to work from home instead to alter my hours around when I can work which is an improvement but I still don't feel my employer understands migraine enough or has enough access to research or resources to put proper support in place.'*

	'My employer's sickness procedure is very aggressive. They have allowed me two additional days sickness before I hit the next sickness trigger, which means I move onto the next level in the sickness procedure, which ultimately could lead to me lose my job.' *'I have face HR based attendance review meetings due to medical absences, some of which were due to both long & short term absences related to migraine.*' '*Trigger sickness policy - formal warning due to taking 8 days off due to migraine in a year'* *'I find it a real struggle coping with chronic migraine and full time but have been refused part time and can't afford to pack up working. Because I am older less chance of getting another job'* *'It's not just work it affects my whole life - time with my children and family life. It's grim but survivable. No other long term health impacts (unless I damage my kidneys through medication over use) just an enormous amount of lost days which puts pressure on everything. There doesn't seem to be a lot of help or answers for that.'* *'I had to give up work because of chronic migraine four years ago. There are days when I feel useless, hopeless and a failure. I feel selfish when I complain about my pain and I miss my life so much.'*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In the chronic migraine survey, 67% of people living with migraine had tried five or more NHS treatments to manage their migraine. There are numerous acute and preventative treatments available for migraine. However many of the current treatments for migraine are drugs that have been developed for other medical conditions that have been repurposed for migraine. They often have unwanted side effects for people with migraine who use them. Fremanezumab is a specific preventative treatment designed for migraine. It is a targeted treatment that is highly specific and as such it has been proven to have a side effect profile comparable to placebo. This is very important as most current proven preventative therapies have severe side effects

	that are commonplace – topiramate for example is very poorly tolerated in > 50% of patients with severe mood distrurbance, cognitive dysfunction, renal calculi etc. Proranalol causes weight gain, fatigue, nightmares, poor circulation etc. The anticnovulsants are teratogenic and sodium valproate causes learning disability in approximately 40% of babies born to mothers taking this medication. Botox is very effective but is hugely demanding of limited healthcare professional resources where there are very few decidated headache nurses or doctors who can administer. There is no standard treatment for migraine, so the choice of medication should always be made on an individual basis. Existing preventative medicine for migraine may not benefit everyone with migraine and side effects or co-existing medical conditions also limit their use. 75% of respondents to the chronic migraine survey had tried over five different medications or treatments for their condition. Only 19% of respondents to our survey were happy with their current treatment for chronic migraine and 58% were not satisfied. People who use acute pain-relief medicine, including codeine, triptans and paracetamol more than two or three times a week or more than 10 days out of the month can set off medication-overuse headaches. This is common amongst people with chronic migraine and can lead to daily headaches. Migraine sufferers can experience intolerable side effects from their medication which impact on their every day life. Respondents to the chronic migraine survey gave details of fatigue, incoherence and weight gain as the most unbearable side effects. For many this limits the number of treatment options available to them. Where patients suffer from multi morbidities the treatment options are limited further due to contraindications and the implications of managing side effects. 54.5% of respondents to the survey suffered from 1 or more other long-term health condition that they are required to take regular medication and/or treatment for.

	Being pregnant or breastfeeding can limit the treatment options available to female chronic migraine sufferers. Since migraine affects three times as many women as men this is a prominent concern amongst sufferers and their clinicians. Injectable treatments, such as the triptans are also generally well tolerated by people with the condition and increase the number of administration options of treatments for people with migraine. The What Matter Most project findings showed that people with migraine, (many of whom were very disabled due to the pain caused by migraine) prioritised the need for better access to migraine specific treatments. 'Effective in lifting the migraine episode. Although as topical no effect on the frequency' 'The preventative medicines have side effects which actually outweigh any positive impact they have on reducing the pain. I fell asleep at my desk at work once because of the side effects. Luckily I was on my own so nobody noticed. I went for years trying one drug and then another but I stopped because of the side effects and the minimal reduction in pain.'
8. Is there an unmet need for patients with this condition?	There is need for more treatments for people living with migraine because: • There are limited migraine specific treatments to prevent migraine. Many of the current treatments are not effective in many people living with the condition. This includes poor tolerance of first line preventative treatments such as topiramate. • Many of the current preventive treatments are not well tolerated by people with migraine. This is in part because many of the current treatments are repurposed drugs used to treat other conditions and people experience unwanted side effects. • Many current preventative treatments often require a person with migraine to use the treatment for a few months before they decide whether it is effective, however the side effects of the

	treatments mean than many people with migraine are unable to tolerate the treatments to the point of it becoming effective. • The lack of targeted and effective treatments for migraine can lead to increased use of medication as people try to need to reduce the pain and severity of migraine. This can lead to the development of medication overuse headache in addition to their migraine. Effective treatments would reduce the frequency and severity of migraine attacks, the use of medications and the development of medication overuse headache. • A need for treatment designed specifically to treat migraine without side effects. • This supports the need for an increase the number of viable and effective alternative treatments for people designed specifically for migraine. • Therefore is a need for an increase in preventative treatments options for people with migraine. '*As I have not responded to taking preventatives, I want to try the Botox injections in the hope it will lead to a reduction in my headache days. Sumatriptan helps to treat the attack but a new drug is required to successfully reduce the number of headache days'* *'My current treatment has reduced the severity of my attacks, however the frequency of attacks has increased over the past while and side effects have worsened meaning another change is on e horizon.'*
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	• It's a preventative treatment that can significantly reduce the frequency and severity of migraine attacks for people with either episodic or chronic migraine. • There is a faster rapidity of onset compared with current preventative treatments. People with migraine will know within the first month whether or not fremanezumab is effective. This is advantageous for both the person with migraine and healthcare professionals. People with migraine will have an improved quality of life faster as they will be able to know quicker whether or not the treatment is effective and partake in their daily lives without the having to overcome side effects of the treatment before it is effective (this is the case of some of the current preventative treatments). Additionally healthcare professionals will have more time to treat patients and write prescriptions for a shorter period of time - this has a potential time and cost saving for the NHS

	• In comparison with the preventative Botox, which requires multiple injections by a trained healthcare professional, fremanezumab is a single monthly or quarterly treatment. • The treatment administered once a month or quarterly and no further prophylactics are needed. There is less need to train healthcare professionals to administer the treatment and set up specific specialist clinics to administer the treatment, unlike Botox. • As a fast, effective and well tolerated preventive treatment fremanezumab is able to reduce the number of headache days and the use of acute treatments for migraine attacks. This has a huge positive impact on people with migraine's general well being and quality of life. • Fremanezumab is well tolerated and given most likely by a healthcare professional; where we know compliance with oral preventative therapies is reported to be less than 20% at 1 year into therapy, this ensures far higher rates of compliance. Fremanezumab has been shown to have definite and good efficacy in a significant proportion of patients, it will be likely complied with and it will be highly likely to be safe. • The reduction in acute treatments and painkillers will also help alleviate the development of headache induced by medication overuse. • Fremanezumab is a preventative treatment developed using the scientific understanding of the pathophysiology of migraine (bench to bedside treatment for migraine). ‘
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	It is felt that there are few disadvantages to the use of fremanezumab as a preventative treatment for migraine. • Some people with migraine may from have trypanophobia (needle phobia) which could be a problem as fremanezumab is administered via an injection • Some may experience mild pain at the injection site and/or an allergic reaction • Although generally well tolerated there is a need for long term studies to understand if there are any long term side effects of fremanezumab. However research has already begun in this area.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who have tried three or four preventative medicines have found that fremanezumab is effective in treating their migraine. Chronic migraine – fewer treatment options for this group of people with migraine and these people are often the most disabled by the condition.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• Migraine can be classed as a disability under the Equality Act 2010 • Women are three times more likely to be affected by migraine and most common in people of working age. Therefore women who already face inequality in the work place are further disadvantaged by migraine. • The 2014 Headache Services report by the APPG on Primary Headache Disorders found that patients in England have non-equivocal access to specialist headache clinics and face barriers accessing appropriate and recommended treatments.

Other issues	
13. Are there any other issues that you would like the committee to consider?	• There is concern about the availability of fremanezumab on the NHS for two reasons. One is the uncertainly around the cost of the drug and whether it will made available on the NHS – we await with much anticipation the outcome of this technology appraisal • The second, if a positive recommendation for this technology appraisal is the outcome, how uniformly will fremanezumab be listed in local CCG formularies to ensure people who would benefit from the treatment have equal opportunity to access the treatment • Given the high prevalence of migraine, the lack of effective preventative treatments without side effects the cost of the new treatments – there is concern whether the NHS will be able to afford the fremanezumab given the huge unmet need • *'Chronic migraine infiltrates all parts of my life. On the odd day when I'm not in pain, I worry about being in pain. Will it be worse the next time? Will I have to stay home from work (again)? Who am I going to let down next? What special occasion am I going to miss out on? How long will my partner put up with taking care of the house? Does he think I'm pretending? The pain varies in intensity each day and I can't predict how I will feel from one day to the next but most often it's a safe bet to assume that I'll be suffering. People don't understand this invisible condition and just because you get up for work each day it doesn't mean you're ok. I rarely feel that I am operating to full capacity. Sometimes I can't think straight or it takes me a little longer than others to process something. I do think it has held me back in my career.'* .
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Fremanezumab is a treatment that has been developed rationally to treat migraine.	

- It has fewer side effects than many of the other current preventative treatments.
- It's rapidity of onset is faster than many other current preventative treatments. This is beneficial to the person with migraine in term of improved quality of life. It is also beneficial to the reducing the cost of NHS prescribing and time with clinicians.
- It requires one injection a month or quarterly. and reduces the frequency and severity of migraine attacks. This also reduces the need for painkillers and risk of developing medication overuse headache.
- The headache community of healthcare professionals and national charities are supporting initiatives and working with the NHS to ensure that people have access to effective treatments for migraine.
-

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Fremanezumab for preventing chronic and episodic migraine [ID1368]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists headache and pain advisory group

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is the professional body that represents neurologists in the UK to 'promote excellent standards of care and champion high-quality education and world-class research in neurology'. It is funded by subscriptions from members. The advisory group members are self-nominated and selected by the elected council members, the Chair is nominated from the members by ABN council
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	• To reduce the impairment and improve disability caused by migraine and improve associated disease-related quality of life for sufferers of migraine • To reduce the number of days affected by 'headache' or 'migraine' • To reduce the duration of migraine attacks • To reduce the impact of other associated functionally disabling "non-headache" symptoms associated with the disorder including aura • To provide a preventative treatment that is well tolerated and safer than existing therapies

or prevent progression or disability.)	To reduce the need for additional acute medications to treat acute attacks
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Both: 1.Reduction in 'headache load' (calculated by headache severity x duration) and/or days with migrainous associated symptoms by ≥ 50% in low frequency episodic (<10 days/month) migraine or >30% in high frequency episodic (10-14 days/month for >3 months) and chronic migraine (≥ 15 headache days/month for >3 months) 2.Significant reported change in patient quality of life measures e.g. a. HIT6 or MIDAS (validated quality of life measure in migraine) b. Functional sales (e.g. functional numeric analogue scale) c. Level of absenteeism from employment where relevant d. Patient reported efficacy e.g. functional numeric analogue scale)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	• As a group, we strongly believe there is a very significant unmet need • Significant 'iceberg' of patients with disabling migraine not accessing appropriate management and only a fraction seen in secondary care • Lack of recognition within healthcare systems of the impact and disability related to migraine • Lack of education in appropriate treatment options and therefore availability to these • Limited effective and targeted preventative pharmacological treatments where side effects do not limit compliance Lack of appropriate resources to manage headache despite high cost to society, the NHS and the individual with greatest costs being indirect and largely discounted in health budget decision making

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Low frequency episodic migraine is usually self-managed in the community or through primary care. Patients with disabling or high frequency migraine are usually referred to secondary care settings and those where the situation is refractory are seen within specialist services which are limited in number and location with often very long waiting lists Treatment is through: 1. Lifestyle, behavioural and psychological modification and education 2. A range of pharmacological options for both acute and preventative treatments. The latter preventative options being mostly re-purposed (betablockers, anti-epileptics, tricyclic anti-depressants and angiotensin converting enzyme inhibitors), having not been designed to target the underlying migraine biology with a range of side effects that are often limiting 3. For chronic migraine, those who remain refractory to standard oral prophylactic medication or drug intolerant the use of injectable techniques such as cranial nerve blocks and botulinum toxin A is an additional option. Neuromodulation devices e.g. vagal nerve stimulators and transcranial magnetic stimulation may be considered although their evidence base needs further growth before place in standard treatment established: use of these are variable with no routine funding in place
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Clinical Guideline 150 (2012 & updates) https://www.nice.org.uk/guidance/cg150 SIGN Guideline 155 - Pharmacological management of Migraine (Feb 2018) http://www.sign.ac.uk/sign-155-migraine.html British Association of Headache (BASH) Guideline – (2010 – in revision & update due to be published Feb 2019) https://www.bash.org.uk/guidelines/
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	Significant variations in headache care occur across the country and in part are determined by access to specialist services. Often episodic migraineurs remain within the community or are managed by primary care. Whilst guidelines exist (NICE CG 150), the application of these are often not seen; for example many patients who should be accessing triptan therapy remaining triptan naïve.

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	• Fremanezumab would bring a novel easily administered once monthly well tolerated treatment to the migraine pathway. The infrequent administration is expected to significantly improve patient compliance and potentially reduce the need for frequent GP review to (1) titrate treatments to their most effective and tolerated dose, and (2) monitor these drugs for commonly occurring and well known side effects (e.g. depression, suicidal ideation, personality change, weight gain, sedation, hypotension, renal calculi, cognitive dysfunction, teratogenic effects) associated with other preventative treatments • The use of new therapies such as Fremanezumab may reduce the burden on acute emergency hospital care by more successfully treating patients with headache disorders and preventing their need for emergency care, where patients with headache represent a high proportion of patients presenting at Accident and Emergency and Acute Medical Assessment Units Fremanezumab opens up a new option for patients in secondary care. As the published studies have looked at episodic as well as chronic migraine patients it is likely that a pool of patients who have failed to find suitable treatments will want to join the pathway which at present has limited resources. Introduction of a new agent that sits best within specialist services will lead to a bottleneck with current specialist resources and greater investment and manpower within these services may be needed.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be a further tool to use within the current pathway, offering the appeal of increased compliance, ease of use and tolerability.
• How does healthcare resource use differ	It may need a better defined treatment pathway definition to determine ‘starting’ and ‘stopping’ criteria. However once treatment is established, Fremanezumab is self-administered and is likely to require less frequent follow up as opposed to treatments such as cranial botulinum toxin therapy which requires three monthly specialist contact.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The introduction of a new biologic agent sits best within specialist services to establish appropriate eligibility (starting criteria), access, monitoring to validate efficacy and safety for continued use and to establish those who no longer need the drug or do not benefit to discontinue therapy (stopping criteria).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• Injection training for patients • Useful to have digital platform e.g. electronic patient record with central monitored records of response accessible by clinicians Facilities: specialist clinic expansion including staff (reception, specialist consultant and nurses, secretarial/admin support), clinic space
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, especially in high frequency and chronic migraine populations and those migraine sufferers intolerant of, or with poor compliance to, conventional preventative treatments.
• Do you expect the technology to increase length of life more than current care?	Improve quality rather than length of life.
• Do you expect the technology to increase health-related quality of	Yes with far better tolerability, appeal of infrequent treatments, patient centred with less requirement for high intensity follow up.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Likely to be more effective in those with chronic migraine (≥ 15 headache days per month for >3 months) and high frequency episodic migraine (10-14 headache days per month for >3 months) as demonstrated in current clinical trials. Likely to be less appropriate in those with low frequency episodic migraine (<10 headache days per month).
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Yes - probably easier. Compared to botulinum toxin for chronic migraine: it does not need the time needed for 31 botulinum toxin injections and the process of toxin disposal and associated consumables. It will still remain a problem for those who are needle phobic. Rapidity of treatment response within the first few months allows potential easier assessment of efficacy. Introduction may be benefited by a Headache nurse specialist led model of care to initiate, monitor and help in patient assessment.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting and stopping criteria would be advisable as this will be a high cost drug and need to safeguard targeted use to the appropriate population and insure outcome monitoring in place to determine suitability of continued treatment. Starting: i) failed 3 standard prophylactic mediation at sufficient dose and for at least 2 months unless reasonable tolerability concern ii) medication overuse addressed iii) compliant with diary monitoring iv) established migraine diagnosis with at least 10 headache days per month (i.e. high frequency episodic migraine and chronic migraine) or those with incapacitating low frequency episodic migraine 4-9 days per month v) if chronic migraine also failed cranial botulinum toxin unless contraindicated Stopping: i) assessment at 3 months after initiating treatment with treatment cessation in patients who do not meet the 30% responder rate in high frequency episodic/chronic state or >50% responder rate in those with low frequency episodic migraine and do not show significant reported change in patient quality of life measures/functional scales (e.g. HIT6, MIDAS). ii) re-evaluation at approximately1 year: consider discontinuation to assess need for ongoing treatment. Current lack of data on relapse rate after discontinuation of treatment to guide long term treatment decisions.

	No additional laboratory testing is required to implement these rules, but patient quality of life measures and headache diaries would need to be routinely monitored
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes: The data from a phase IIb study in episodic migraine showing 75% migraine frequency reduction in 35% of patients compared to 11% on placebo is potentially a step change if sustained effects are seen in longer studies. This approaches the desires of patients to be “cured” of migraine. Data from a phase 3 study in episodic migraine showed that subcutaneous fremanezumab results in a statistically significant 1.3 – 1.5 day reduction in the mean monthly migraine days over a 12 week period when compared to placebo. Data from a phase 3 study in chronic migraine showed that the percentage pf patients with a reduction of at least 50% in the average number of headache days per month was 41% in the monthly fremanezumab group as compared to 18% in the placebo group.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes: It is one of a new class of drugs that are the first preventative agents which targets the underlying biology of migraine. It would appear to offer preventative treatment with limited side effects and with a dosing regimen that is far more attractive to patients and combined this will improve compliance and therein efficacy.

• Is the technology a 'step-change' in the management of the condition?	Potentially yes: although the clinical efficacy in the low frequency episodic migraine groups is similar to current preventive oral medications the tolerability is significantly better and adherence may be at least as good. The drug does not require any monitoring and is self administered thereby likely to significantly increase compliance
• Does the use of the technology address any particular unmet need of the patient population?	Yes, this is a preventative treatment option which is not limited by side effects and daily dosing which restrict compliance.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The very limited side effect profile reported (short term treatment) facilitates compliance and compared to current treatment options this in itself contributes to quality of life as days without headache are not blighted by side effects.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Not entirely - in the phase III clinical trial of episodic and chronic migraine patients were excluded if they had failed treatment on 2 or more standard migraine preventative treatments. In the phase III trial of chronic migraine a minority had previously tried standard preventative treatments: only 30% had previously tried topiramate and 16% had tried Botulinum toxin. In UK clinical practice high cost treatments would not be a 1st line treatment option. More data is also required on whether medication overuse headache affects treatment outcome.

• If not, how could the results be extrapolated to the UK setting?	Likely still applicable although anticipated treatment response may modestly fall as in practise it would be used in those whose migraine state was more resistant
• What, in your view, are the most important outcomes, and were they measured in the trials?	• Reduction in 'headache load' (calculated by headache severity and duration) and/or days with migrainous associated symptoms by ≥ 50% in low frequency episodic migraine or >30% in high frequency episodic and chronic migraine • Significant reported change in patient quality of life measures e.g. o HIT6 or MIDAS (validated quality of life measure in migraine) o Functional scales (e.g. functional numeric analogue scale) o Level of absenteeism from employment where relevant o Patient reported efficacy e.g. functional numeric analogue scale) • % of patients with sustained headache response • % of patients with 75% and 100% response rate In large reported Phase III trials for chronic and episodic migraine response rate was reported based on headache(chronic) or migraine (episodic) days but we would emphasize, particularly in a chronic patient, often a more meaningful measure relates to the 'headache load' (cumulative severity x hrs) as attenuating and shortening headache episodes can have an enormous impact on ability to function. Nonetheless in both these studies the % of patients achieving at least a 50% response rate was presented. In addition both studies used validated quality of life measures (HIT6: chronic; MIDAS episodic) as a secondary outcome measure. 75% headache response was a secondary outcome measure in a phase IIb study of episodic migraine In large Phase II placebo controlled trials patients with episodic migraine receiving fremanezumab experienced an increased number of headache-free days with normal function in work/school/household chore performance and concentration/mental

	fatigue measures compared to their baseline (all $p < 0.005$). An increased number of headache-free days with normal functional performance for some measures was also found in the chronic migraine group in those treated with fremanezumab. Outcomes up to 3 months of treatment have so far been reported : longer term studies are awaited
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	long term treatment efficacy and safety profile
20. Are you aware of any new evidence for the comparator treatment(s) since the	Yes - but no RCT data – all open label observational studies only 1. PREEMPT Severe headache days analysis 2017 https://link.springer.com/article/10.1186/s10194-017-0784-4 2. Real world usage in Europe of Onabotulinum toxin type A in Chronic migraine https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5734384

publication of NICE technology appraisal guidance [TAXXX]?	3. The REPOSE study – Still in preparation/press - Preliminary data 2017 https://link.springer.com/article/10.1186/s10194-017-0802-6 4. The COMPEL study 2018 https://link.springer.com/article/10.1186/s10194-018-0840-8
21. How do data on real-world experience compare with the trial data?	No real world data yet available on Fremanezumab as it is not yet licensed in the UK
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access of patients not yet known to secondary care as previously self-managed in the community or primary care
22b. Consider whether these issues are different from issues with current care and why.	Bringing a new treatment option for episodic migraine with a cohort of patients who are no longer under medical review and will need to accommodate this.
Key messages	

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

- There is an unmet need for patients with episodic and chronic migraine, conditions that result in very high levels of disability across the UK patient population
- Adherence to injectable treatments is much higher than oral medications
- Side effects of Fremanezumab are much less than with oral preventative treatments and treatment is more tolerable than botulinum toxin
- Potentially high levels of high response rate to Fremanezumab in a subset of patients
- Novel mode of action targeting underlying pathogenesis of migraine

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Fremanezumab for preventing chronic and episodic migraine [ID1368]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Association for the Study of Headache

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Association for the Study of Headache (BASH) is the UK society representing clinicians and nurses that have interest in headache disorders and is a registered charity. BASH is a member of the International Headache Society (IHS) and contributes to research in global platform. The organisation is largely funded by the membership fee and meets up regularly to discuss headache services in the UK and various research projects. The exec committee comprises of a Chair, Vice Chair, treasurer, secretary, educational officer and scientific officer in addition to the council elected by its members every two years. The organisation serves the professionals (general practitioners and general physicians) through regular educational meetings that occur two to three times a year in various locations in the United Kingdom.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	• To reduce the severity and frequency of headache in migraine sufferers. • To reduce the number of days with headache on migraine sufferers • To reduce the impact of the disease on activities of daily living including work or household activities. • To reduce the duration of migraine attacks • To reduce other associated symptoms of migraine i.e. nausea, vomiting, sensitivity to light sound and smell. • To reduce need for acute treatment and improve response to treatments used in acute attacks.

or prevent progression or disability.)	• To offer preventive treatment with few side effects and better tolerance.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. To reduce the number of headache days by at least 30% in patients with chronic migraine and 50% in those with episodic migraine. 2. To reduce the number of migraine days (moderate to severe days) to either mild or headache free days by at least 30% in those with chronic migraine and 50% in those with episodic migraine. 3. An improvement in the quality of life score using validated tools like Headache Impact Test-6 (HIT-6) or Migraine Disability Assessment Score (MIDAS). 4. Improvement in patient perceived headache severity and frequency using visual analogue scale.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	• Currently there are no migraine specific preventive treatments. Those currently used are found by chance for migraine prevention and include those used in depression (tricyclic antidepressants), hypertension (propranolol, candesartan), epilepsy (topiramate, sodium valproate). Most of the these drugs are either contra-indicated due to co-morbidities e.g., propranolol in asthma or have extremely poor tolerance e.g., topiramate or have teratogenicity that restricts its use in young fertile females. • Hence the BASH council strongly feels that there is a strong unmet need for new drugs that are migraine specific and have better tolerance and side effect profile. • Migraine is a highly prevalent condition and there are lack of resources to provide comprehensive headache care service in the UK. There is a need for healthcare professionals to be able to manage the condition in the community for which the health services require educational programmes both for the professionals and the public.

	• As a result of all above, many patients who will benefit from preventive treatment do not receive it and those that are prescribed treatment are not monitored to improve their compliance. This results in a high indirect cost to the UK economy in general in addition to impact on the NHS resources.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	1. Patients with low frequency episodic migraine i.e. less than 8 days in a month either do not consult their general practitioner or self-manage with over the counter painkillers and do not receive a formal diagnosis. 2. Patients with high frequency episodic migraine i.e., 8-14 days of headache per month do often consult the general practitioners and are sometime referred to secondary care. The usual treatment strategy is to provide first line preventive treatments including tricyclic antidepressants, beta-blockers, candesartan and topiramate. Those not responsive to treatment are given second line treatments such as pizotifen, clonidine, sodium valproate, venlafaxine, minerals and vitamins (Magnesium and Riboflavin). Many such patients are controlled well while others remain refractory or transform to chronic migraine. 3. Lifestyle measures on diet, regular exercise, timely meals and sleeps could help some people and are usually provided by headache nurses but only in special secondary care centres. Such services are rarely seen at a primary care level. 4. Those with chronic migraine that add up to nearly three quarters of a million in the UK, secondary care referrals are made although specific headache services remains patchy in the UK and most of these patients either remain less optimally treated by the general neurologists or remain refractory to treatment to first and second line treatments. A good proportion of these patients may respond to onabotulinumtoxinA. Those who fail this treatment remain severely disabled as the non-invasive gadgets such as gammacore, transcranial magnetic stimulation, cephaly remains unavailable on the NHS. Some are resorted

	to fairly invasive treatments of IV dihydroergotamine, greater occipital nerve block, occipital nerve stimulator that are extremely expensive and are not available even in many specialised headache centres.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Clinical Guideline 150 (2012 & updates) https://www.nice.org.uk/guidance/cg150 SIGN Guideline 155 - Pharmacological management of Migraine (Feb 2018) http://www.sign.ac.uk/sign-155-migraine.html British Association of Headache (BASH) Guideline – (2010 – in revision & update due to be published Feb 2019) https://www.bash.org.uk/guidelines/
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The neurology services in the UK are well below par compared to the rest of the Europe. Headache services are extremely patchy and only few areas in the UK are able to provide a comprehensive headache care. Most patients are referred to a general neurologist who will provide a screening type of service excluding a secondary pathology and advise first line treatment strategy to primary headache disorders only. Neurologists are extremely busy and oversubscribed and find it hard to provide a detailed consultation required to a complex headache patient. The number of headache nurses have increased but their availability still remain at the secondary care level and restricted to headache centres.
• What impact would the technology have on the current pathway of care?	• Fremanezumab is a migraine specific treatment that has a strong potential for self-administration by patient at home and hence would reduce burden on healthcare resources through less intense monitoring and fewer clinic visits. The side effect profile is quite favourable hence the compliance would be better. • Those who would respond to treatment remain self-caring and would not resort to emergency care at both primary and secondary care level. • Fremanezumab would provide additional option for treatment to those who have failed first line treatments and, in some patients, failing second line options in episodic migraine. Many patients with chronic migraine are treatment refractory and have failed three or more treatments including onabotulinumtoxinA. Fremanezumab would provide a

	valuable option as non-invasive mechanical devices are not available on the NHS and invasive options are either restricted to few centres in the UK as well as are very costly.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is new and would add to the current pathway
• How does healthcare resource use differ between the technology and current care?	The current technology would provide an additional treatment pathway for those refractory to treatment particularly those with chronic migraine. Those that will respond would provide cost-benefit to the NHS through self-care and less need for monitoring and follow up. We will need to define treatment period for identifying non-responders as well as duration for treatment who would respond well as the treatment cannot be continued for indefinite period. Once proved better and cost-effective in health economic modelling it will provide an option in patients with less refractory disease condition and may be first line or second line in those with episodic migraine.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	We feel the technology is best place in secondary care preferably at the headache centres to start with. Building on experience the treatment has a potential for infrequent monitoring at a primary care level in the long run.
• What investment is needed to introduce the technology? (For	• Patients will require injection training that could best be provided through industry support • Need to monitor response through either paper or electronic diaries.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, especially in high frequency and chronic migraine populations and those migraine sufferers intolerant of, or with poor compliance to, conventional preventative treatments.
• Do you expect the technology to increase length of life more than current care?	Better quality of life
• Do you expect the technology to increase health-related quality of life more than current care?	Yes Migraine specific so patient will have more faith on treatment given Less side effect so better health-related outcome Self administration so less supervision by medics.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Likely to be more effective in those with chronic migraine (≥ 15 headache days per month for >3 months) and high frequency episodic migraine (10-14 headache days per month for >3 months) as demonstrated in current clinical trials. Likely to be less appropriate in those with low frequency episodic migraine (<10 headache days per month).

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Much easier as it will be self-administered
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	BASH feels that a three month treatment initially would be adequate to identify responders; those not responding could be stopped (negative stopping rule). Those that are responders could continue the treatment for a year and further continuation should be based on a formal review by the physician (positive stopping rule). We anticipate that no more than two years treatment may be required in the vast majority. As the treatment is expensive, it is reasonable to restrict to those who have failed three treatments, addressed for medication overuse and are prepared to maintain a diary to monitor the effect of treatment. The quality of life should be monitored through validated tools like HIT6 and MIDAS. We feel that the treatment may be more appropriate ahead of Botox in chronic migraine considering the cost of botox, 31 injections as well as need for clinic visits.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes: The data from a phase IIb study in episodic migraine showing 75% migraine frequency reduction in 35% of patients compared to 11% on placebo is potentially a step change if sustained effects are seen in longer studies. This approaches the desires of patients to be “cured” of migraine.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes: First ever migraine specific preventive drug Little or no side effects Self-Administered

• Is the technology a 'step-change' in the management of the condition?	Yes. Although the clinical efficacy is similar to other drugs, the side effect profile and self-administration makes it more favourable.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, this is a preventative treatment option which is not limited by side effects and daily dosing which restrict compliance.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile is comparable to placebo. We do not anticipate this to be an issue although one has to wait for the real life experience.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The trials in episodic migraine excluded patient who had failed more than two treatments and trials in chronic migraine only a few patients were treatment refractory. It is, therefore, not tried well in treatment refractory population that is seen in actual clinical practice where we feel the treatment may be more appropriately placed
• If not, how could the results be extrapolated to the UK setting?	Real life experience will be able to provide a more appropriate clinical data for setting up rules to follow.

• What, in your view, are the most important outcomes, and were they measured in the trials?	• Reduction in either headache days or migraine days by 50% in episodic and 30% in those with chronic migraine to define a responder but data on 75% and 100% response need to be seen in real life. • Improvement in quality of life score using validated tools like HIT6 and MIDAS
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the	Yes mainly for Botox. Mostly real world data. 1. PREEMPT Clinical trials, 2010 Cephalalgia

publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	2. Hull Prospective analysis of Botox in Chronic Migraine – Khalil M et al, Journal of Headache and Pain, 2014 3. Does Medication overuse matter – Ahmed F et al, Springerplus 2015 4. Real world usage in Europe of Onabotulinum toxin type A in Chronic migraine https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5734384 5. The REPOSE study – The Journal of Headache and Pain – January 2019 (in press) 6. The COMPEL study 2018 https://link.springer.com/article/10.1186/s10194-018-0840-8
21. How do data on real-world experience compare with the trial data?	No real world data on Fremanezumab or other MAB available.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to headache services that is extremely patchy. Migraine is more prevalent in females.
22b. Consider whether these issues are different from issues with current care and why.	Identifying those that would be deemed suitable for the treatment would potentially deprive other migraine sufferers that would not fulfil criteria laid down by the NICE.

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • A new treatment that might address the need of some of the refractory patients particularly those with chronic migraine. • Better compliance due to monthly injections. • Side effects profile comparable to placebo and less invasive in comparison to Botox. • Self-administered putting less burden on healthcare resources. • A migraine specific drug.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Fremanezumab for preventing migraine [ID1368]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**David Kernick**
2. Name of organisation	**British Association for Study of Headache**

3. Job title or position	**GPwSI Headache**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ other (they didn't submit one, I don't know if they submitted one etc.) Not yet completed
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce the burden of migraine. To prevent progression of episodic migraine to chronic migraine. Although the definition is arbitrary, there is evidence of structural change in the brain as migraine becomes more frequent. Probably the old term of transitional migraine is more appropriate.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction of 50% headache days in 50% of subjects
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Current agents have limited effectiveness and tolerance. 28% of people will remain on prevention medication at the end of one year. However less than 50% of people with migraine will consult their GP of those likely to benefit, less than 50% will receive prevention
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	The condition is poorly treated in the NHS. As a result 3% of the population have medication overuse headache predominantly from poorly managed migraine.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE British Association for the study of headache SIGN
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathways of care are well-defined.
• What impact would the technology have on the current pathway of care?	Conventional prevention agents would still be drug of first choice. The current technology would add an important option for those in whom burden is problematic.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes but at different points in pathway

• How does healthcare resource use differ between the technology and current care?	A specific mode of action, higher efficacy and lower side effect profile. Effective in the presence of medication overuse headache.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Clinicians with an interest in headache in secondary care or intermediate care settings.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	NHS perspective - for clinical capacity will be needed for follow-up.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes in terms of both effectiveness and tolerability.
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Effective for all of people with migraine
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Additional monitoring will be required. People will need to self administer.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clear rules will be required. On the basis of current evidence and as a first approximation assuming that all MABs have similar characteristics: Stop after three months if migraine days not reduced by 30% Stop annually and review after three months cessation. Evidence shows that there continues to be small improvement at four years but this may be a continued effect of placebo. At five years approximately 30% of people with chronic migraine will still receive benefit from Botox but care taken in extrapolating between Botox and MABs. (Stopping MAB after six months, migraine frequency begins to increase but there will be some people in whom benefit is retained.) 30% of people who do not respond to one MAB will respond to an alternative. One switch at three months would be appropriate.
16. Do you consider that the use of the technology will result in any substantial health-	There will be a considerable reduction in impact upon the health of family.

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Provides a considerable advantage in the way in which migraine is prevented. It is likely to reduce transformation of episodic to chronic migraine and the additional burden of medication overuse headache.
• Is the technology a 'step-change' in the management of the condition?	A significant step change and most important innovation since introduction of Triptans for acute migraine
• Does the use of the technology address any particular unmet need of the patient population?	. The population have invariably failed a number of existing preventers and this technology has been shown to be effective against the background of failed previous interventions.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects appear low and are a significant improvement on existing options.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	50% reduction of headache days in 50% of the population. Effectiveness in the presence failed prevention and also medication overuse headache.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Nil known
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There were a number of useful poster presentations at the international headache society meeting in September this year.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA260]?	No
22. How do data on real-world experience compare with the trial data?	Side effects seem higher in practice.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Where in the treatment pathway for prophylaxis of migraine is fremanezumab likely to be used in clinical practice? After how many treatments?	Will have to follow NICE guidelines i.e. 3 but 4 are more appropriate in a specialist clinic setting.
25. Does the treatment pathway differ according to whether people have chronic or episodic migraine?	No

26. Would you expect any benefit with fremanezumab to be similar for people with chronic migraine and people with episodic migraine?	Due to structural changes benefit is likely to be lower as frequency of headache and duration of that frequency increases.
27. How long would you expect people to receive treatment with fremanezumab for?	Best estimate cautiously drawing on BOTOX experience – 25% at five years
28. Would you expect the benefit of treatment with fremanezumab to continue after treatment has been stopped, and if so, for how long?	This will vary across people. Depending on psycho/social factors and impact of medication overuse headache. Overall benefit will fail off following stopping but trials are limited in duration and there will be a significant number in whom either no treatment is needed or current preventative therapy is effective. An important and unanswered question is should current therapy be reintroduced before or during stopping if deteriates as this may be more effective once frequency has been reduced and psychosocial factors and medication overuse headache addressed.
29. If people experience migraine again once treatment has been stopped, would re-treatment be considered?	See above. I think yes if no side effects previously. Should this be part of the guidance or clinical best practice?

Key messages
25. In up to 5 bullet points, please summarise the key messages of your statement. • the market has been driven by chronic migraine at the expense of appreciating the impact of frequent episodic headache, the overall burden of which is higher than chronic migraine. • a more useful starting point would be to see high-frequency and chronic migraine as failures of management that reflect the fact that a minority of people with migraine enter the healthcare system and when they do so their needs are poorly addressed • the impact of psychosocial factors and medication overuse headache should not be overlooked during the transition to high-frequency migraine • one switch at three months if no response. Stop at one year and re-introduce traditional medication until further evidence is forthcoming • as a first approximation, assume all MABs have similar characteristics for longer term modelling requirements.

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Patient expert statement

Fremanezumab for preventing migraine [ID1368]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Chani Montaque**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Migraine Trust
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☒ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Historically, living with chronic migraine has been somewhat of a journey. During my University Studies I found it scaled between manageable to out-of-control, excruciating migraines leaving me sick, tired and exhausted. I considered dropping out of University in second year, but decided to persevere with my studies. After leaving University and starting my first job, my migraines abated and became manageable, almost infrequent. For 2 years things carried this way, until I started a very busy and stressful, but rewarding and challenging, Hospital job in 2014. From there they turned chronic again: unbearable pain, dizziness, vomiting, sensitivity to light. I triggered the sickness policy which added to the stress, and considered leaving numerous time but I liked my work. I I didn't do so until 2017. I felt the Hospital Trust were open to suggestion: in 2016 I worked 3 days a week, working a flexible pattern, doing more hours if I could but making up a previously lost day to sickness the next week to stop me triggering on the sickness policy. Living with condition felt very disabling at times. I was unable to commit to social or family visits because of Migraine. I was missed for promotion because of migraine. I developed bad anxiety and depression with suicidal

	thoughts at one point, because of the uncertainty of migraine onset and unable to deal with the terrible pain the headaches bring. I would lay in a dark room for days on end. There was financial pressure with dropping my hours at one point. However, since being under the care of [redacted] in [redacted], I have a good management plan and feel well looked-after: trialling said drug, nerve block in 2017 and I am now on Candestartan to good effect. Historically I have tried: Topiramate (which was not well-tolerated and triggered mental health relapse), amitriptylene and prolpanolol. I have Naproxen and Frovatriptan as well as anti-sickness for acute attacks.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I think patients want either this drug or nerve blocks or botox, as there are many success stories in the media. However, I feel finding the right treatment plan is a trial and error process, as one medication will not necessarily have the same results from one person to another. I think people complain at the long wait to see a Consultant or poor management at Primary care level. However, my experiences have been positive and I have been able to access everything I need (albeit the wait to see a Consultant! But everyone has to wait).
10. Is there an unmet need for patients with this condition?	I would say mental health support could be better in consultations, but I realise there are time pressures alongside the volume of patients, and all mental health services I accessed via my GP. I continue to see a private psycho-therapist, but realise most people do not have the means for this. I think group support could be a good thing for people to seek peer support, I know charities do this sort of outreach work but I am not aware of any in my area. I have recently joined online forums (Reddit and Migraine Buddy App) which gives good support. I feel the headache/neurology service is well-staffed in my area, with two nurse specialists at the end of the telephone who are so helpful, kind, patient and informative. They also administer nerve blocks, taking pressure off some of the clinics. I realise this is not the same for every patient experience. Some patient see a general neurologist rather than a headache specialist, but I think it is important to see a headache specialist for timely diagnosis and a management plan. The drug provides a unique solution in that is specifically targets the metabolic components of migraine.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Self-inject, long-lasting prophylaxis of migraine. It has worked for a lot of people so far.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The time the medication is taken to the actual effect on migraines vary from person to person, but there is a 'lag-time' for most treatments.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those with a long-term health condition, memory problems or long-term mental health problems as it is done once every 3 months (?), so they don't have to think about taking tablets everyday.
Equality	
14. Are there any potential equality issues that should be	**Migraine can be classed as a Disability under the Equality Act which was helpful guidance for my employer regards making resonable adjustments. I know that many employers dismiss migraine as a trivial problem, and many sufferers do not know that it can be classified as such**

taken into account when considering this condition and the technology?	**to help them.**
Other issues	
15. Are there any other issues that you would like the committee to consider?	Clinical trials have been positive; so far it is the only drug that acts specifically against migraine proponents; it has had much positive impact upon the daily lives of sufferers. Treatment needs to be cost-effective to the NHS but balancing this so there is not an unfair advantage to the service user, whom ultimately the NHS serves.
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement: • Timely access to a neurologist/headache specialist for diagnosis and management • Access to specialist support groups/mental health/counselling support as needed • Trial of said drug and access to all, for those meet the criteria for administration • •	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Fremanezumab for preventing migraine [ID1368]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Scott Bruce**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? X a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	OUCH (UK)
4. Did your nominating organisation submit a submission?	☐ yes, they did **X** no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X** other (they didn't submit one, I don't know if they submitted one etc.) **OUCH(UK) as a headache charity whos focus is on Cluster Headache, we deferred to Migraine Trusts very accurate submission on patient experiences and offered no further comment at the time.**

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	X I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: X I am drawing on others' experiences. Please specify how this information was gathered: **Our Patient Cohort are participating in the clinical Trials – Evidence of its effectiveness is gathered from their experiences**
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Migraine and Headache Disorders are disabling and destroy lives particularly at chronic end of the scale of the condition. Any Migraine episode however has a daily effect on the patient.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Patents are let down by the availability of treatment options for Migraine and Headache disorders particularly for those who can't self medicate The treatments available are often off label prescription or Triptans which have side effects leaving patients feeling washed out after aborting an attack.
10. Is there an unmet need for patients with this condition?	Yes – a long lasting treatment with minimal side effects. The removal of daily drug taking to control the condition
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	It revolutionises the condition, giving the patients back their lives, allowing them the freedom of not having to take daily or multiple daily doses of powerful drugs.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Side Effects, with the relative new ness of the drugs being taken, people are adjusting to the side effects of this new treatment option.
Patient population	
13. Are there any groups of patients who might benefit	Chronic and headache sufferers whom have tried multiple treatment steps and have had little or no effect.

more or less from the technology than others? If so, please describe them and explain why.	Episodic and irregular sufferers of the condition may benefit from the treatment however existing medication may be more cost effective in these instances. This treatment would be of benefit where the standard pharmalogical treatments are proving difficult to control the condition, and should be considered prior to surgical interventions.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None**
Other issues	
15. Are there any other issues that you would like the committee to consider?	None
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement: • This Treatment option should be considered for Chronic Headache Patients • When condition is not brought under control by existing pharmalogical treatment plans	

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Fremanezumab for preventing migraine

A Single Technology Appraisal

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU

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Date completed

15/07/2019

Source of funding

This report was commissioned by the NIHR Systematic Reviews Programme as project number 18/54/15.

Declared competing interests of the authors

Mark Cossburn declares education and training funding from Allergan and conference funding from Novartis.

Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR SR Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows	Bello S, Griffin E, Farmer C, Nikram E, Robinson S, Packman D, Salmon A, Cossburn M, Melendez-Torres GJ, Crathorne L. Fremanezumab for preventing migraine: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2019.
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Contributions of the authors	Segun Bello provided overall project management, acted as lead systematic reviewer, critiqued the company's clinical effectiveness evidence and contributed to the writing of the report. Ed Griffin acted as health economic project lead, led the company's economic evaluation and contributed to writing of the report. Caroline Farmer acted as systematic reviewer, critiqued the company's clinical effectiveness evidence and contributed to the writing of the report. Elham Nikram acted as lead modeller, critiqued the company's economic evaluation, and contributed to the writing of the report. Sophie Robinson acted as lead information scientist on this project, critiqued the literature searches performed by the company, and contributed to the writing of the report. David Packman and Andrew Salmon acted as a modeller and critiqued the company's economic evaluation. Mark Cossburn provided expert clinical advice to the ERG on migraine and its management and reviewed the draft report. G.J. Melendez-Torres critiqued the company's clinical effectiveness evidence and contributed to the writing of the report, and acted as co-project director. Louise Crathorne critiqued the company's review of cost-effectiveness evidence, contributed to the writing of the report, and acted as co-project director.

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Abbreviations

AE	adverse event
AMA	American Medical Association
ANCOVA	analysis of covariance
BASH	British Association for the Study of Headache
BSC	best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CGRP	calcitonin gene-related peptide
CI	confidence interval
CM	chronic migraine
CS	company submission
CSR	clinical study report
DP	decision problem
EM	episodic migraine
EMA	European Medicines Agency
ERG	Evidence Review Group
EQ-5D	EuroQol-5 Dimension
FAS	full analysis set
HDPM	headache days per month
HFEM	high-frequency episodic migraine
HIT-6	six-item headache impact test
HRG	Healthcare Research Group
HRQoL	health-related quality of life
HS	health state
ICER	incremental cost-effectiveness ratio
IHS	International Headache Society
ICHD-3	The international classification of headache disorders, 3rd edition
IPD	individual patient data
IQR	interquartile range
ITC	indirect treatment comparison
ITT	intention to treat
LFEM	low-frequency episodic migraine
LSM	least squares mean

MD	mean difference
MeSH	medical subject heading
MFEM	moderate frequency episodic migraine
MID	minimally important difference
MIDAS	migraine disability assessment
mITT	modified intention to treat
MMD	monthly migraine days
MMRM	mixed-effects, repeated-measures
MOH	medication overuse headache
MSQoL	migraine-specific quality of life questionnaire
NA	not applicable
NHS	National Health Service
NHSE	National Health Service England
NHx	natural history
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
OBA	onabotulinum toxin A
OLE	open label extension
ONS	Office for National Statistics
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PRO	patient reported outcomes
PRISMA	preferred reporting items for systematic reviews and meta-analysis
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	systematic literature review

SMPC	summary of product characteristics
SoC	standard of care
TA	Technology Appraisal
Tx	treatment
VAS	visual analogue scale
WTP	willingness to pay

1 Summary

1.1 Critique of the decision problem in the company submission

The National Institute for Health and Care Excellence (NICE) final scope defines the population of interest as 'adults with chronic or episodic migraine' while the company submission (CS) focused on a subgroup of adults with chronic or episodic migraine who have used three or more preventative therapies, thereby positioning fremanezumab as a fourth line option in the migraine preventative treatment pathway. This narrowed population also informed the company's economic model. Furthermore, the Evidence Review Group (ERG) considered that the exchangeability of the population in the key FOCUS trial and the population in UK clinical practice [redacted] Reasons for stopping preventative therapies vary, which may influence how people progress to different lines of therapy in the pathway. There is no evidence on whether the types of therapy received by people with migraine may affect the subsequent treatment effect. The FOCUS trial setup [redacted] and therefore, this is a key uncertainty in the applicability of the FOCUS data to the UK target population.

There was a slight difference between the fremanezumab dosage regimens used in the trials and the licensed dosage. The difference involved a loading dose of 675 mg for [redacted] whereas the licence stipulates 225 mg as the starting dosage for all monthly regimens.

As a consequence of the narrower population, [redacted] (topiramate, propranolol and amitriptyline) used as first, second and third lines of preventative therapies in the migraine preventive treatment pathway [redacted].
[redacted]

The outcomes were in line with the final scope. The company asserted that data for the indirect treatment comparison (ITC) was available in comparator treatments only for absolute change from baseline in monthly migraine days (MMD) and response rates. As a result, only two outcomes were considered in the indirect treatment comparison (ITC):

- The mean MMD
- The proportion of participants with ≥50% reduction in average monthly migraine days.

There were indications however, that some outcomes involved in the ITC were not reported. For example, [redacted] featured in the ITC, but this was not mentioned in the main text of the appraisal.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company presented a systematic literature review (SLR) involving a broad population of adults ≥18 years with migraine or medication overuse headache. Four key trials were included from the SLR: the HALO EM involving people with episodic migraine (EM), the HALO CM involving people with chronic migraine (CM), the HALO extension and the FOCUS trial involving a combination of people with EM and CM. The NICE final scope described the population as 'adults with chronic or episodic migraine', while the company submission focused on a subgroup of EM and CM populations who have used three or more preventative therapies. Thus, the company considered only the FOCUS trial to be directly relevant to the population of interest, because patients in the HALO trials have used only one or none of the classes of drugs. While there were no UK centres involved in the HALO trials,

[redacted]

In the HALO EM trial, people in both fremanezumab groups (monthly and quarterly administrations) had about one and half fewer MMDs on average compared to the placebo group, and nearly half demonstrated ≥ 50% reduction in MMDs compared to less than a third of participants on placebo. In the HALO CM trial, participants on both fremanezumab regimens experienced about 1.7 fewer MMDs on average compared to placebo, and also about a third of participants on fremanezumab had ≥ 50% reduction in MMDs compared to a fifth of people receiving placebo. [redacted]

For the EM subgroup of the FOCUS trial, people on either of the fremanezumab regimens (monthly and quarterly administrations) also experienced [redacted] This was [redacted] in the EM population who had used three or more preventative therapies. The [redacted] of EM patients on either of the fremanezumab regimens [redacted] in the placebo group. This was [redacted] EM subgroup who have used three or more preventative therapies. EM patients who have used three or fewer drugs and who were on either of the fremanezumab regimens also [redacted] use of any acute headache

medication versus placebo, on average. Similarly, the same population [redacted] monthly headache hours of at least moderate severity compared to placebo.

For the CM subgroup of the FOCUS trial, people on either fremanezumab regimens experienced about 3.2-3.8 fewer MMDs compared to placebo. This was [redacted] for the CM population who have used three or more preventative therapies. The [redacted] of CM patients on either fremanezumab regimen [redacted] in fremanezumab groups [redacted] in the placebo group. This was [redacted] in the CM population who have used three or more preventative therapies. Also, CM patients on fremanezumab who have used three or more therapies, [redacted] use of any acute headache medication and [redacted] monthly headache hours of at least moderate severity compared to placebo, on average.

There was no direct head-to-head evidence comparing fremanezumab to any of the comparators. The ITC containing a network of fremanezumab, erenumab and OBA and placebo, showed there was no statistically significant advantages between either of the two fremanezumab dosing regimens and OBA, though both dosing regimens of fremanezumab were numerically superior to OBA in terms of percentage of patients with at least 50% reduction in monthly average number of migraine days [redacted]

The quality of life outcomes for the EM population who have used three or more therapies demonstrated [redacted] on migraine disability assessment (MIDAS), six-item headache impact test (HIT-6) and migraine-specific quality of life questionnaire (MSQoL) for both fremanezumab groups compared to placebo. [redacted] in the corresponding CM population on fremanezumab compared to placebo for MIDAS and HIT-6. However, for the MSQoL the role function-preventive and the emotional function domains of the MSQoL [redacted] for the fremanezumab quarterly group.

During 12 weeks of treatment, the proportion of participants with at least one adverse event (AE) was significantly higher in both fremanezumab groups for both HALO EM and CM populations compared to placebo but [redacted] This distribution was [redacted] treatment-related AEs. All groups in the HALO EM, HALO CM and FOCUS had serious adverse events (SAEs) and AEs leading to study discontinuation of [redacted].

[redacted] The AE profile reported for the FOCUS population [redacted] HALO EM and

HALO CM population. AEs reported for the HALO extension lacked placebo comparison but [redacted] in both fremanezumab groups, [redacted] had at least one treatment-related AE, about [redacted] had at least one SAE, while about [redacted] had at least one AE leading to study discontinuation at 12 months.

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

The company conducted a SLR broadly aligned with NICE scope. The ERG considered that the evidence presented was narrower than the SLR conducted. The ERG deemed the company's search strategies generally disorganised and were not confident that all relevant records would have been picked up in the search results for example, additional phase II trials were found for fremanezumab and considered relevant to the SLR inclusion criteria but were omitted in the CS. It was unclear whether the company's search strategies did not locate these phase II trials or whether the company deliberately omitted them without justification. The evidence presented in the CS for fremanezumab is adequate only for the population subgroup proposed by the company i.e. people who have previously used three or more preventative therapies. Also, the company provided very little or, in most cases, no relevant outcome data for comparators which hindered more extensive comparative appraisal of the evidence. Furthermore, limited information describing the study selection, data extraction and quality assessment, restricted ERG's ability to evaluate the quality of the SLR process.

The company identified four randomised controlled trials (RCTs), three of which compared the efficacy and safety of two (quarterly and monthly) fremanezumab regimens and placebo. The company considered only one trial (FOCUS) as relevant to the population of interest. The ERG agreed that the HALO trials are not homogenous with the FOCUS trial with regards to the number of previous therapies used by the underlying participant population. Thus, pooling these trials would have been inappropriate. The ERG considered the FOCUS trial as more relevant to the UK population.

There is no direct evidence comparing fremanezumab and the main comparator OBA. Thus, only ITC evidence was presented in the CS. The company documented to have conducted a feasibility assessment for conducting ITC only for change in MMDs and responder rates, though it appeared that additional ITCs were undertaken and not reported. It is unclear whether the company was interested in only these outcomes for the ITC as other outcomes in the NICE scope were not involved. Details of the feasibility assessment were not reported. Thus, ITC analyses were provided only for two clinical outcomes in the CM subgroup who have used three or more preventative therapies. The ERG considered the ITC methods

broadly appropriate. The company however, did not justify the selection of outcomes used in the ITC as other outcomes reported in the key FOCUS trial were left out. Findings from the ITC were verified and confirmed to be reasonable by the ERG. Though the networks used to estimate the ITC were sparse, the ERG was satisfied that additional relevant trials to inform the network were not available.

Overall, the ERG agrees that the evidence provided in the FOCUS trial [redacted] fremanezumab monthly and quarterly regimens [redacted] placebo, with [redacted] in outcomes and [redacted] in the population who have used three or more preventative therapies. However, the ERG has less confidence in the precision of the outcome estimates because of the [redacted], which was demonstrated in the [redacted] reported, especially for the EM subgroup who have used three or more preventative therapies.

1.4 Summary of cost-effectiveness evidence submitted by the company

The company performed a literature review to identify cost-effectiveness evaluations of prophylactic interventions used to treat people (aged 18 years-plus) with migraine. No prior economic evaluations of fremanezumab in the specified population were identified. Three economic evaluations evaluating OBA were identified; two reported the economic model developed for the NICE appraisal of OBA (TA260). The included cost-effectiveness studies were summarised and critically appraised using the Philips checklist. The company also presented an SLR of utilities and healthcare resource utilisation and costs No relevant studies reporting health-related quality of life or healthcare resource use and cost data in sufficient detail were identified, although the National Health and Wellness Survey provided some information regarding healthcare resource use for people with migraine.

The company developed a cost-effectiveness model to simulate the cost and benefit accrual of people with episodic and chronic migraine (separately) over a 10-year time horizon; results for an 'all migraine' population were not presented. Fremanezumab was compared to a strategy of BSC, and additionally compared to OBA in in the chronic migraine analysis. The model handled responders and on-responders to treatment separately (including BSC) using a decision-tree, costs and benefits thereafter using a 28-day cycle health state transition model where state occupancy was determined by statistical distributions about a changing mean frequency of monthly migraine days (MMDs). Treatment response (in trial) was defined as a reduction in MMDs from baseline of at least 50% for EM and 30% for CM at Week 12 in trials (at 24 weeks for OBA). The mean and statistical distribution were based on an analysis of individual patient data not provided to the ERG and therefore not verified.

A number of rules were applied to the model to deal with issues arising from long-term prediction based on short-term evidence: (a) patients were at risk of death from background all-cause mortality, which did not differ by treatment strategy; (b) a small and constant proportion of patients discontinued prophylactic treatment every model cycle ([redacted] per cycle); (c) after a year of uninterrupted prophylaxis [redacted] of responders discontinued due to adequate and sustained effect through a three-month period of assessment (the positive stopping rule). For these people the full treatment effect was sustained indefinitely. Cost and utilities were exclusive to each of the 29 possible MMD health states, thereby linking cost and utility accrual directly to treatment effect. Future costs and benefits were discounted at the standard rates, and the analyses were conducted from a NHS and Personal Social Services (PSS) payer perspective.

The modelled populations were adults with ≥4 to <15 MDs per month (episodic migraine) with ≥3 prior prophylactic treatments used; and adults with ≥15 MDs per month (chronic migraine) with ≥3 prior prophylactic treatments used. This is a narrower population that the EMA license for fremanezumab (prophylaxis of migraine in adults who have at least four migraine days *per* month [1]), and is also a subgroup of the population of the scope issued by NICE, which is simply adults with chronic or episodic migraine. The company did not present an analysis for a combined all migraine population. The population of the key supporting trial, FOCUS, was aligned with the modelled population for estimates of effect size, but not in respect to utility estimation (≥2 prior prophylactic treatments used) or resource consumption (no prior medication use specified). Outcomes from the HALO trial, used to inform the assumptions of sustained long-term effect and long-term discontinuation, did not align to the intended ≥3 prior prophylactic population. Mean starting age was [redacted] years depending on the migraine classification, aging to [redacted] by the end of the modelled period, and [redacted].

Responder rates were calculated using a combination of placebo arms from trials included in ITCs. For EM, proportions used for 50% responder rates in placebo arms drew from FOCUS and from the LIBERTY trial of erenumab; and for CM, proportions used for 30% placebo responder rates from FOCUS. Odds ratios from ITCs were applied to placebo response rates to generate response rates for fremanezumab. The estimation of the 30% responder rate for OBA used the odds ratios generated from the ITC for a 50% responder rate to known estimates for 30% responder rates in placebo and fremanezumab to 'impute' an estimate for the number of people who would have been classified as responding at a 30% threshold. In the EM analysis [redacted] responded to fremanezumab and [redacted] to BSC. In the CM analysis [redacted] responded to fremanezumab, [redacted] to OBA, and [redacted] to BSC.

Responders to fremanezumab in the EM analysis maintained a mean reduction in MMDs relative to baseline of [redacted] days, compared to [redacted] days relative to baseline for responders to BSC. Non-responders to fremanezumab maintained a mean reduction relative to baseline of [redacted] MMDs, compared to [redacted] relative to baseline for responders to BSC, although this seems an unlikely trial outcome. Responders to fremanezumab/OBA in the CM analysis maintained a mean reduction in MMDs relative to baseline of [redacted], compared to [redacted] relative to baseline for responders to BSC. Non-responders to fremanezumab/OBA maintained a mean reduction relative to baseline of [redacted], compared to [redacted] relative to baseline for responders to BSC. For responders the onset of effect was fast, based on an exponential rate of MMD reduction per cycle; onset for non-responders was linear.

The modelling of costs and benefits after the 12-week assessment is very important to the cost-effectiveness of the prophylactics. There is no randomised trial evidence to support the assumptions of this period, which is 98% of the 10-year time horizon, so there is very large uncertainty introduced from extrapolation. Data from the one-year open label extension of the HALO trial provides some evidence, albeit non-comparative, but even so strong assumptions are necessary around treatment effect size, changes in the natural history of the condition; and the long-term safety of prophylactics.

HRQoL data collected from the FOCUS trial population (≥2 prior prophylactic therapies) using the migraine specific MSQ was mapped to the EQ5D scale. Respondents were from the US and Europe, aged between 18 and 70 years. MSQ data was preferred to data collected directly using the EQ5D because it captured HRQoL over the previous four weeks rather than just the day of the clinic visit. The mapping technique did not adjust for patient characteristics between the source dataset (International Burden of Migraine Study; IBMS). Utility estimates were produced separately for an on- and off- treatment set using the responses at baseline, and Week 4 and 12, respectively. For the MMD range 0-28, the utility scores ranged [redacted] for people on prophylactic treatment; and [redacted] for those off treatment or receiving BSC. The company did not cite evidence to support the justification that this treatment benefit is not captured within the MMD benefit, but noted precedence and these estimates as derived from RCT evidence. For reference, the UK population norm for people aged 35-44 years is 0.91 (University of York, UK Population Norms for EQ-5D). Taking into account baseline MMD health state distribution, the mean utility at baseline for EM responders was [redacted] fremanezumab, and [redacted] BSC; [redacted] and [redacted] respectively for non-responders. Baseline scores in the CM analysis were lower: [redacted] fremanezumab/OBA and [redacted] BSC for responders, and [redacted] fremanezumab/OBA and [redacted] BSC for non-responders. Given the stability of long-term effectiveness arising from the company's preferred assumptions, utilities post-baseline stabilised within the first year of the model

horizon. Whilst the utility of non-responders returned to baseline, EM responders to fremanezumab improved their utility to [redacted] by the end of the first year, a little better than responders to BSC whose utility increased to [redacted]. The utility of CM responders to fremanezumab increased to [redacted] by the end of the first year (OBA = [redacted]), again, a greater improvement that responders to BSC, at [redacted].

Fremanezumab costs £415.38 per 28-day treatment cycle, also one model cycle, and did not attract an administration costs, just a small one-off cost of training patients to self-administer (all patients were assumed to manage this). The 28-day and 12-week dosing schedules were assumed to be cost equivalent (in contrast to effectiveness). The cost of OBA was £276.40 per 12-week treatment cycle, equal to three model cycles. Every administration required 30 minutes of neurologist time (£85.50), there were no training costs. A small monitoring cost was applied for equal for both prophylactic strategies. There was zero active treatment cost applied to BSC, and the acute medications used in this setting were also assumed as applicable to the prophylactic strategies. Prophylactic treatment costs declined through the time horizon as discontinuation persisted, but these costs also decline annually as 20% of remaining responders discontinued treatment following a positive assessment for [short-term] sustained response. Other included healthcare resources identified by the company as supportive of the condition were: GP visits, emergency department visits, hospitalisations, nurse practitioner consultations, neurologist consultations, and triptan consumption. Unit costs were obtained from the most recent NHS reference cost schedule and the PSSRU handbook. Healthcare resource consumption estimates drew from the National Health and Wellbeing Survey 2017 and were based on health system contacts following headaches - rather than specifically migraines - in the previous six months. The company noted this was the same source used for the ongoing appraisal of erenumab (ID1188). Regardless, the measurement of MHDs may lead to underestimation of resource use and thereby favour the least effective treatment strategies. Costs associated with adverse events were not considered.

The company base case for EM found that over 10 years the average cost per person of fremanezumab was [redacted]; some [redacted] more than the cost of BSC ([redacted] of the cost was accumulated after one year, [redacted] after two years, [redacted] after five years). Fremanezumab QALYs were [redacted], a gain of [redacted] QALYs over BSC through the ten-year horizon ([redacted] after 1 year, [redacted] after two years and [redacted] after five years). The ICER was £13,954 per QALY gained. The company base case for CM found that over 10 years the average cost per person of fremanezumab was [redacted], some [redacted] more than BSC and [redacted] more than OBA. Fremanezumab QALYs over ten years were [redacted], a gain of [redacted]

QALYs over BSC. The same pattern of incremental QALYs being gained ahead of costs was observed in CM as seen in EM. The ICER for fremanezumab versus BSC was £11,825 per QALY gained; and for fremanezumab versus OBA was £16,227 per QALY gained. Results using the company base case assumptions and parameters support the company conclusion that over 10 years fremanezumab is cost-effective in episodic migraine versus BSC, and chronic migraine versus BSC and OBA. The company's tests for stability in the ICERs towards changes in the input parameters led to their conclusion that the ICERs are stable. The PSA of the EM analysis found that in [redacted] of simulations fell below £20,000 per QALY gained, and [redacted] below £30,000 per QALY gained. The respective predictions for CM were [redacted] and [redacted] versus BSC, and [redacted] and [redacted] versus OBA.

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

The structure of the cost-effectiveness searches was poor, which is likely to produce ill-defined search results. There were poorly presented, hard to follow, were limited in ways that are not evidence-based, and deviated from recognised and validated economics or health utilities filter. The ERG cannot be confident that all relevant records would have been picked up in the search results.

The model structure was restrictive since it did not allow for natural history modelling. An individual patient simulation would have been more appropriate, providing a framework attuned to alternative assumptions concerning long-term outcomes. It was, however, structurally similar to the models of NICE TA260[2] for OBA and the ongoing appraisal of erenumab (NICE ID1188). Fremanezumab was modelled using a subgroup of adults with CM or EM who have used three or more preventative therapies; this subgroup was narrower than specified in the NICE final scope and narrower than the marketing authorisation. Effectiveness, utility, and resource use parameters were estimated from multiple different populations, creating inconsistencies, in particular the extent of prior prophylactic treatment. The modelling of OBA contrasted its licence, since the positive stopping rule was defined in terms of headache not migraine, and discontinuation was not implemented as headache/migraine frequency fell below the definition of CM. A 10-year time horizon was a plausible compromise to capture most long-term treatment effects on a background of increasing uncertainty in terms of the extrapolation of short-term evidence.

Response rates, effect size, positive and negative stopping, and a utility premium for prophylaxis drove QALY differences between fremanezumab versus comparators. Response rates were derived from an ITC, noted for some inconsistency in the number of placebo responders. The division of the BSC strategy by response was unnecessary and

concerning given that [redacted] was attributed to non-responders of BSC but not non-responders to prophylaxis, in contrast to expectation from the FOCUS trial. This approach was unexplained and may underestimate the effect of BSC, favouring fremanezumab. Clarity and completeness was a wider concern, especially in respect to responder and non-responder effect sizes, the calculation of which were neither presented nor published.

Prediction of long-term outcomes was the foremost problem with the submitted model. There was a heavy reliance on strong assumptions and expert clinical opinion in the absence of quality evidence beyond 12 weeks. The 10-year time horizon brought into focus the key assumptions which singularly and together may introduce significant bias:

- prophylactic discontinuation: the HALO open-label observation extended unchanged for nine years, excluding any provision for long term safety and potentially overestimating time on treatment;
- positive stopping: application to 20% of patients, and sustained full treatment effect is highly uncertain and optimistic (at Week 64 alone 14.6% of fremanezumab patients were modelled to retain full effect with no treatment cost);
- natural history of migraine: not accounted for and of unknown impact on the cost-effectiveness of prophylaxis, but relevant to this population as known to change with the onset of menopause.

In an additional analysis the ERG tested the cost-effectiveness of fremanezumab versus BSC in chronic migraine in a scenario of effect waning for effect for positive stoppers of fremanezumab, and responders to BSC, coupled with fremanezumab re-initiation after a loss of half the full effect. ICERs versus BSC were observed to increase in the region of 20%.

The selection of MSQoL data collected in FOCUS in favour of EQ5D data for utility estimation was reasonable despite probable inaccuracy introduced through mapping, however the ERG was concerned about underestimation, especially in the CM range. A comparison with NICE TA260[2] supports this concern. This and the application of a higher utility set to patients on prophylaxis may bias QALY gain in favour of fremanezumab. Three scenario analyses were run and found that all base case ICERs were sensitive to inflated utilities and removal of the prophylaxis utility premium.

Resource modelling was broadly appropriate. The ERG believed that the assumption of 100% self-administration is unlikely but noted a minimal impact on the ICER. There was some concern that resource consumption rates were based on a study of a general migraine population, and that they were based on headaches not migraines. Therefore consumption

rates may have been underestimated, which would introduce a small conservative bias. Whilst the exclusion of adverse events may be acceptable in the context of evidence collected in short-term trials, the ERG are concerned that the impact of as yet unknown long-term safety is not included in the model.

Company base case parameters and assumptions give rise to the conclusion that fremanezumab is cost-effective versus BSC for both the episodic and chronic conditions. ICERs were £13,954 and £11,825 per QALY gained, respectively. Incremental costs were gained early and incremental QALYs gained relatively late as a consequence of low long-term discontinuation and positive stopping rule effect of benefit with no cost. Probabilistic sensitivity analysis (PSA) findings were consistent with the deterministic findings, but QALY variation shows sensitivity to the effectiveness variables. PSA simulations of the episodic migraine analysis predicted a [redacted] probability of fremanezumab being cost-effective versus BSC at the £20,000 threshold. Slightly fewer QALYs are gained in the CM analysis, at similar cost, so the predicted probability of fremanezumab being the more cost effective than BSC decreased to [redacted] (same threshold). The comparison versus OBA was deeply flawed but the respective probability lower mainly due to smaller QALY gain ([redacted]). The subgroup analysis of high frequency EM, based on alternative effect size estimates, produced similar incremental costs and QALYs, and therefore ICER, to the analysis of episodic migraine. This outcome was subject to uncertainty as the main analyses, although the company did not present sensitivity analyses specific to the subgroup.

With regard to the validity of results, the ERG found that the utility calculation contained a small error, and the intended three month assessment period to be implemented as two months. These were corrected and a revised set of results produced. The ERG was concerned with redundant content and code, unnecessarily formula complexity, absent/poor labelling, and overly brief method description hindered model validation. Also, the absence in the model of separate calculation sheets for responders and non-responders added complexity to model validation. External validation of model outputs from the company were not presented, and the one-way uncertainty parameters did not include the key effectiveness inputs, leading to an optimistic conclusion of ICER stability.

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

1.6.1 Strengths

- The SLR conducted was generally broad.
- The evidence presented in the submission for fremanezumab was informed by data analysed from a well conducted randomised controlled trial. The company also envisaged potential baseline group imbalance hence the adoption of the analysis of covariance (ANCOVA) for the subgroups analysed.
- The population in the key FOCUS trial was broadly representative of UK population.
- The evidence provided by the key FOCUS trial was high quality.
- The treatment effect of fremanezumab in FOCUS was consistent and stable across subgroups.
- The ITC methods were appropriate, and estimates reported were confirmed to be accurate.
- Extended follow up for adverse events profile up to one year.

1.6.2 Weaknesses and areas of uncertainty

- The population proposed by the company was narrower than the population described in the NICE scope; thus the evidence presented was adequate only for the population those who have used three or more preventative therapies.
- There was no direct head-to-head evidence between fremanezumab and comparators of interest.
- Only one outcome, the MMD and its derivatives, was involved in the ITC.
- The FOCUS trial was randomised but not stratified for the EM/CM subgroups which may have explained the trend for imbalance in the subgroups. The EM and CM subgroups also lack adequate power thus, explaining the wide 95% confidence intervals reported for some of the outcomes.
- The ITC network was sparse.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG identified two areas for correction following a review of the company model for coding and implementation error; (i) correction of coding for averaging of cycle level utility; and (ii) correction of assessment period length and alignment with 24-week treatment cycles to produce a 48-week treatment year. The impact on the ICERs of the two corrections were not large and did not increase deterministic ICERs above the £20,000 per QALY threshold.

2 Background

2.1 Critique of company's description of underlying health problem

Migraine is a disorder of the neurological system recognised as one of the top 10 causes of disability globally,[3] especially among adults in their prime productive age.[4] Migraine is a form of headache that may cause unilateral pain in the muscles of the head, preventing individuals from performing their daily activities.

Migraine affects about 15% of the global population and may coexist with other conditions such as neck pain, depression and anxiety.[5] The prevalence of migraine in the UK population is also similar to the global prevalence and affects more women than men (ratio 3:1) and increases through early life with a peak at around 30-40 years.[4;6] The company submission (CS) states that "….restricting access to migraine therapies will disadvantage women to a greater extent than men. There are no other equality factors that require consideration in this appraisal" (CS, p. 23). The Evidence Review Group (ERG) noted that migraine is also more prevalent among persons in the productive age group, among Caucasians, and among the lower socioeconomic class.[7] The CS also states that "Migraine prevalence has been shown to rise through early adult life with a peak at 30 to 40 years" (CS, p. 16) and that "Furthermore, it is recognised that the prevalence and frequency of migraine attacks decrease with age" (CS, p. 16). The ERG noted that while the frequency of migraine decreases with age in an individual, the prevalence actually rises with age and peaks at 30-40 years before tailing off.[4]

Migraine has been classified by the International Headache Society based on the frequency of headache days per month.[5] The CS states that "The definitions of the International Headache Society (IHS) (ICHD-3 criteria) are the most widely accepted, and these define EM as headaches occurring on less than 15 days per month. Whereas CM comprises headache occurring on 15 or more days per month for more than three months, which exhibits migraine characteristics on at least eight days per month" (CS, p. 13). The ERG noted that people with headaches occurring on 15 or more days but for less than three months are not represented in the definitions. Clinical advice to the ERG confirmed that it is not a relevant clinical problem considering the length of time people wait to see their GP and a specialist which will almost always exceed three months. Also the company enrolled episodic migraine (EM) patients with a monthly headache frequency of ≥6 but <15 days, and chronic migraine (CM) patients with a monthly headache frequency of ≥ 15 but only for a history of an equivalent of one month. A headache with migraine characteristics is further defined depending on whether or not there is associated aura. The CS states that "These guidelines define a migraine attack (without aura) as a headache lasting at least four hours

that includes at least two of the following characteristics (unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity) and at least one of the following characteristics (nausea/vomiting, photophobia and phonophobia). For classification as "migraine with aura" it is required that one or more aura symptoms has at least three of the following characteristics (at least one aura symptom spreads gradually over ≥5 minutes; two or more aura symptoms occur in succession; each individual aura symptom lasts 5–60 minutes; at least one aura symptom is unilateral; at least one aura symptom is positive; the aura is accompanied, or followed within 60 minutes, by headache)" (CS, p. 13). For EM, the company used a cut-off of ≥4 days of headaches that should demonstrate migraine characteristic and a monthly headache days frequency of ≥6 in both HALO and FOCUS trials. Thus, EM with monthly headache days frequency of <6 were excluded from the trials.

Lipton et al. proposes several health states based on the assumption that migraine exists on a continuum ranging from: persons with no migraine; individuals with low frequency episodic migraine (LFEM) with a monthly headache days frequency of <9; high frequency episodic migraine (HFEM) with a monthly headache days frequency of 10-14; through to CM with a monthly headache days frequency of ≥15.[8;9] Silberstein et al. also suggested a further subgrouping of EM into LFEM (monthly headache days frequency of <4), moderate frequency episodic migraine (MFEM) with monthly headache days frequency of 4-9, and HFEM with a monthly headache days frequency of 10-14.[10]

Migraine is an important cause of disability during attacks and also between attacks. The CS reports that "UK results from two large multinational surveys show that 88% of CM patients reported very severe disability, whereas for EM this was 20-24% (Table 3)" (CS, p. 17). The ERG noted that the study population from the references may not be representative of EM or CM patients as they were derived from a survey of respondents from a pool of pre-registered panellists who expressed interest in completing health-related surveys for some compensation. Data from a clinically enrolled migraine population reported a severe migraine disability assessment (MIDAS) grade of 59.8% and 32.6% in CM and EM respectively.[11] Thus, both clinic and population-based studies have shown that the CM population have greater headache-related disability compared to the EM population.

The CS asserts that "…patients with HFEM were more closely aligned to patients with CM regarding headache-related disability outcomes and impact on daily life than to patients with LFEM" (CS, p. 17). The clinical expert to the ERG stated that although people with HFEM have more disability, they are biologically distinct from the CM population in imaging studies and that the categorisation into LFEM and HFEM is more clinically relevant. The ERG noted

that the definition of HFEM used in the reference quoted was 10-14 headache days per month whereas the company adopted a definition of 8-14 headache days per month in their analysis. The clinical expert to the ERG considered the definition of 10–14 headache days per month to be more reflective of clinical practice. Thus, the company's population of HFEM in the FOCUS subgroup analysis may not be comparable with the CM population in the literature and in clinical practice.

The CS states that "In the UK, the annual direct costs per person with migraine have been estimated to be £736.58 for EM and £3,160.67 for CM in 2010" (CS, p. 18) and also presented evidence for the disparity in the resource use between EM and CM. The evidence presented was from the US setting and may not be applicable to the UK, but may represent a general trend in the disparity between the economic burdens of CM compared to EM.

ERG comment:

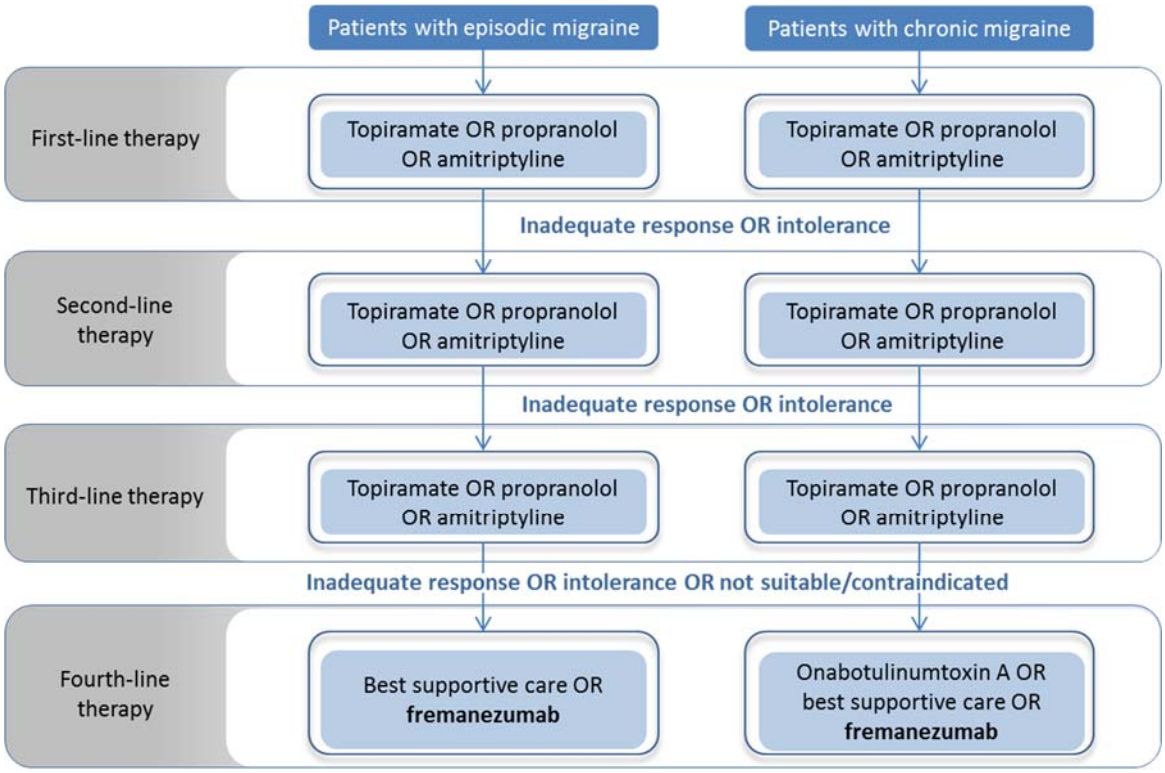
The company's description of the disease area and burden is appropriate and broadly representative of the literature. The ERG noted a deviation in the headache frequency inclusion criteria for CM which was stated as ≥15 within 28 days run-in period for the HALO and FOCUS trials, as opposed to more than three consecutive months stated in the literature. The criteria for classifying participants according to migraine severity may thus be questionable given that the monthly headache frequencies in migraine fluctuates. The baseline observations taken within the 28-day run-in period would further influence some trial outcomes for example, the proportion of participants who have had ≥ 50% reduction in monthly migraine days (MMD). Clinical advice to the ERG however, indicated that this may not have an appreciable impact on the evidence for all practical purposes, given that the populations in the trials have, on average, a long standing history of migraine up to 19 years, and the participants' status were likely known prior to trial onset and would likely have been under treating physician monitoring. The definition of HFEM used in the subgroup analysis also deviates from the literature. The clinical expert to the ERG confirmed that there is no firm consensus on what constitutes HFEM but preferably used 11-14 headache days per month in their own practice.

2.2 Critique of company's overview of current service provision

The CS states that the treatment pathway is based on NICE G150 (Figure 1). In the NICE treatment pathway presented, topiramate or propranolol or amitriptyline may be used interchangeably as first, second or third line of migraine prevention for both EM and CM. The CS also states that "For chronic migraine, TA260 adds OBA as an option for patients who have previously used three other preventive therapies" (CS, p. 21). NICE guidance TA260[2]

recommends OBA for people with CM who have not responded to or are intolerant of, three prior pharmacological prophylaxis therapies. Thus, the company argues that anti-calcitonin gene-related peptide (anti-CGRP) therapies, such as fremanezumab, would be expected to fit in as an alternative option to OBA. The pathway also places fremanezumab as a fourth line prophylaxis for people with EM who have not responded to topiramate, propranolol and amitriptyline (Figure 1).

Figure 1: NICE preventive treatment pathways for patients with migraine (including proposed positioning of fremanezumab)



Source: CS, p. 21.

The CS also noted that the British Association for the Study of Headache (BASH) guidelines differed from the NICE guidance in that topiramate is specifically recommended as a second-line therapy in the BASH guidelines and only amitriptyline and beta blockers are recommended as first-line options.[6;12] Also, the CS states that "Gabapentin, which is not recommended by NICE, is included as a third-line treatment in the BASH guidelines" (CS, p. 21). The ERG noted that although gabapentin is recommended in the BASH guidelines as a third-line option, the guidelines recognise that the evidence for efficacy is not robust as was similarly stated in the NICE guidance.

ERG comment:

The company's overview of the current service provision is appropriate and relevant to the decision problem. The FOCUS trial population consisted of people who have previously used between two or more of four clusters (clusters A-D) while the HALO trial population had previously used a maximum of one or none of these four clusters. Two of these clusters (cluster A and B, CS, Appendix L, p. 5) are not included in the treatment pathway and not recommended by NICE, although cluster A drugs are also anticonvulsant drugs like topiramate. The guidance for the comparator OBA (TA260[2]) recommended OBA after patients have previously used three or more pharmacological therapies without restrictions to specific therapies. Therefore, there is uncertainty about the role of these two classes of drugs. Clinical advice to the ERG confirmed that the classes of migraine prevention drugs typically used in the UK include the anticonvulsants, the antidepressants and the antihypertensive drugs and that the drugs in clusters A and B are rarely used in the UK. The clinical expert to the ERG also stated that the classes of drugs previously received by the trial participants are probably less important and that the only evidence available on previous drug use impacting the course of migraine is with the regular use of analgesics, particularly opiate based drugs and barbiturates which can induce medication overuse headache.

3 Critique of company's definition of decision problem

3.1 Population

The final scope defined a population of adults with chronic migraine (CM) or episodic migraine (EM). The marketing authorization indication was for preventing migraine in adults with at least four migraine days per month. The population (people who have used three or more prior preventative treatments) for which the company seeks a recommendation is narrower than the population specified in the NICE scope. Two trials (HALO trials) enrolling adults aged between 18 and 70 years old with migraine onset at age ≤50 years, supported the marketing authorisation application. These trials enrolled people with EM (headaches ≥6 and ≤14 days, and migraine days ≥4 per month). The trials also enrolled people with CM (headaches on ≥15 days and migraine on ≥8 days per month). Similar headache criteria were used for enrolling participants into the FOCUS trial. The EM population with monthly headaches <6 would have been excluded from the trial population. Additional restrictive inclusion criteria were used for the FOCUS trial population which was described by the company as "inadequate response to two to four classes of prior preventive migraine medications within the past 10 years (defined as a lack of a clinically meaningful improvement after at least three months of therapy, intolerance to the treatment or contraindication/unsuitability for a treatment)" (CS, p. 29)..

None of the participants from the HALO trials were from the UK. The HALO trial populations are thus, not representative of the UK population. The FOCUS trials included participants from the UK, enrolling people from six UK centres out of 113.

The subgroups for which the company seeks a NICE recommendation (i.e. used three or more medications) is narrower than the population specified in the scope. Both HALO trials included adults with migraine for at least 12 months for the EM and CM population. The FOCUS trial included adults with migraine and inadequate response to two to four classes of prior preventive treatments.

ERG comment:

The characteristics of the population of the HALO and FOCUS trial participants are broadly similar to the population of persons with migraine in the UK in terms of age, disease duration, frequency of headache and the number of preventative therapies used, as confirmed by the clinical expert to the ERG. However, persons outside of the clinical trial enrolment age range (young persons aged between 16 and 18 years and persons aged 70 years-plus) are seen in headache clinics especially in a secondary care setting. The

proportion of older persons aged 70 years-plus may be as high as 15% although this proportion is said to vary according to how metropolitan the setting is.

Although the trials have excluded patients with headache frequency <6 headache days per month, this may be justified because the clinical expert to the ERG suggested that the preventative strategy is adopted for more disabling migraine or more frequent attacks. The ERG noted substantial differences in the preventative therapies used in the FOCUS trial population who have used three or more prior preventative therapies, when compared to the preventative therapies used in UK clinical practice. It is unclear whether types of therapy received by people with migraine may affect subsequent treatment efficacy. Clinical advice to the ERG suggested that reasons for stopping preventative therapies vary (including both tolerability and contraindication issues), which may influence how people progress to different lines in the pathway. Furthermore, there is no evidence on how these factors may impact on treatment effects at later lines of therapy thus, it is a key uncertainty on how the FOCUS population compares to the UK target population.

The CS described fremanezumab as "…a fully humanised anti-CGRP monoclonal antibody developed for the preventive treatment of migraine. Fremanezumab potently and selectively binds to both isoforms of CGRP (α and β), whilst its design ensures that the antibody does not cross react with CGRPs' closely related family members. Fremanezumab differs from erenumab, another monoclonal anti-CGRP developed for migraine prevention, in the fact that the latter targets the CGRP receptor, giving both antibodies differences in mechanism of action" (CS, p. 11). This matches the description in the final scope. The CS reports that that calcitonin gene-related peptide (CGRP) levels are elevated during a migraine attack and that fremanezumab acts by binding to both isoforms of CGRP, thus interfering with its ability to bind to its receptor and preventing signalling.

Fremanezumb is licensed by the European Medicines Agency (EMA) for the prevention of migraine in adults who have at least four migraine days per month. Fremanezumab is administered by subcutaneous injection at a dose of 225 mg monthly or 675 mg quarterly. In the HALO CM trial and the FOCUS CM subgroup, a loading dose of 675 mg fremanezumab for the monthly regimen was administered which is not in line with the marketing authorization. It appears that none of the CM population on the fremanezumab monthly regimen was commenced on the 225 mg dose.

ERG comment:

The ERG had concerns about the difference between the licensed dose and the dose administered in the HALO and the FOCUS trials for the CM population on the

fremanezumab monthly regimen. It is unclear whether the licensed starting dose of 225 mg would have a similar clinical effect compared to the evidence provided for the loading dose of 675 mg in the trials.

3.2 Comparators

The comparators considered by the company were fewer than the comparators listed in the NICE scope. The scope stated that: “Established clinical management for migraine prevention without fremanezumab, including oral preventive treatments (such as topiramate, propranolol, amitriptyline), OBA, erenumab (subject to ongoing NICE appraisal), and best supportive care.” The company considered only OBA and best supportive care appropriate for comparison with fremanezumab in the CM population who have used three or more preventative therapies included. These were considered as established clinical management for migraine prevention without fremanezumab. The company argued that erenumab is not an appropriate comparator for the EM and CM population who have used three or more preventative treatments, as erenumab is not considered standard practice in the UK. Nevertheless, erenumab data from Study 295 was included in the indirect comparison to strengthen the network.

ERG comment:

The ERG agreed that for the proposed positioning of fremanezumab (after three prior use of preventative therapies), OBA and best supportive care are appropriate comparators. Oral preventive treatments are recommended lower down in the first, second and third line of preventative therapies in the treatment pathway. Erenumab is yet to be recommended by NICE as at the time of company submission.

3.3 Outcomes

Table 1 compares the outcomes in the NICE scope and the outcomes reported by the company.

Table 1: Outcomes in NICE scope and company submission

Outcome (NICE scope)	Corresponding outcome in the company submission	ERG comment
Frequency of headache days per month	Mean headache days of at least moderate severity	Only moderate severity headaches was reported
Frequency of migraine days per month	Mean monthly migraine days	Presented
Severity of headaches and migraines	Mean headache days of at least moderate severity Mean monthly headache hours of at least moderate severity	Presented for severity of headaches but not for migraine severity
Number of cumulative hours of headache or migraine on headache or migraine days	Mean monthly headache hours of at least moderate severity	Presented
Reduction in acute pharmacological medication	Mean monthly days of use of any acute headache medication	Presented
Adverse effects of treatment	Adverse events, treatment-related adverse events, serious adverse events, adverse events leading to study discontinuation	Presented
Health-related quality of life	MIDAS, HIT-6 and MSQoL scores	Presented

Abbreviations: ERG, Evidence Review Group; HIT-6, Six-Item Headache Impact Test; MIDAS, Migraine Disability Assessment; MSQoL, Migraine-Specific Quality of Life Questionnaire.

ERG comment:

All outcomes were reported in the CS for fremanezumab trials and for the subgroup population proposed by the company. The CS reported the following outcomes for OBA (whole population) from the PREEMPT trials (CS, Appendix D, p. 330): change from baseline in headache days, migraine days, cumulative headache hours on headache days, migraine episodes, acute medication use severe (≥60) HIT-6 score and also 50% responder rates. The outcomes reported for erenumab Study 295 whole population included: change from baseline in monthly migraine days, ≥ 50% responder rate, ≥ 75% responder rate and change from baseline in acute medication use. The outcomes analysed in the ITC, however, included only absolute change from baseline in monthly migraine days (MMDs) and its derivatives: the reduction in MMDs and the proportion of participants who had at least 50% reduction in MMDs. The company argued for use of only these outcomes in the NMA stating that "These outcomes were chosen as those were the best comparable evidence between treatments exists, and as these inputs were required for the economic model" (CS, p. 94). The ERG noted that the feasibility assessment for outcomes used for the indirect comparison was based on baseline characteristics and as described below, it appears additional ITCs were undertaken that were not reported.

3.4 Other relevant factors

The company reports a wider societal impact of migraine arguing that "Overall, indirect costs (such as absenteeism) account for more than 90% of the total cost of migraine" (CS, p. 19) and that "This impact is particularly important for migraine due to its prevalence in adults of working age" (CS, p. 19). The company also noted that: "Migraine is a condition that is more common in women" (CS, p. 23). In addition, the ERG highlight that migraine is more common among lower income earners.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

4.1.1.1 Clinical effectiveness search (Search C)

The company presented a literature search protocol to support its review of clinical effectiveness. The same searches were also used to inform the NMA, see Section 4.4.1. This protocol included systematic searches of key biomedical databases using a literature search strategy, and a search of grey literature sources. The literature searches were carried out for the period 1995 - February 2018 and were updated in November 2018. It is not clear why this date range was used or why the searches have not been updated more recently.

The search strategy was applied in the following bibliographic databases: Medline and Embase (Elsevier at Embase.com) and Cochrane Library (Wiley). A wide range of grey literature sources including clinical trials registries were also searched.

The bibliographic database searching used a search strategy that took the following form:

1. Controlled index and free text terms for migraine AND
2. Controlled index and free text terms for either topiramate, botulinum toxin, amitriptyline, valproic acid, gabapentin, propranolol, atenolol, bisoprolol, metoprolol, flunarizine, fremanezumab, erenumab, eptinezumab, or galcanezumab AND
3. Some free text terms related to efficacy, migraine/headache days or adverse events; OR a range of terms related to costs, economics, health utilities or quality of life (from the health utilities search detailed in section 5.1.1) AND
4. Free text terms related to a range of study types such as RCT, observational study AND
5. Limit to humans.

4.1.1.2 Epidemiological search (search A)

Teva also presented a search for epidemiology which was carried out for the period 2007 – February 2018 and updated in October 2018.

The bibliographic database searching used a search strategy that took the following form:

1. Some free text terms for epidemiology (no controlled index terms were used); OR some controlled index and free text terms for clinical guidelines or pathways terms

(not a recognised filter); OR some free text terms for treatment pattern or unmet need AND

2. Controlled index and free text terms for migraine AND
3. Some free text terms for a number of European countries
4. Limit to humans.

The literature search strategies for searches C and A are poorly conducted and reported, to the extent that it is likely that relevant papers will have been missed.

- The layout and presentation of the search strategies is very confusing, this affects the transparency and reproducibility of the searches and it is very hard to follow what has been done.

- The search strategies are not consistent in their use of key techniques such as truncation of words to include different endings (e.g. migraine should have been truncated as migrain* to include migraines and migrainous, but this was not done). This is poor methodology and some relevant papers are likely to have been omitted.

- The drug name 'Ajovy' has been omitted from the search strategy, even in the November 2018 update searches, by which time the drug name was approved by the FDA (in September 2018)[13] and should have been included as a search term. The Emtree drug term Fremanezumab/ was also not used in the searches, so any articles indexed in this way could have been omitted.

- The search strategies use free text search terms, but are not consistent in their use of controlled index terms such as Medical Subject Headings (MeSH). This is poor practice and as a result some relevant papers are very likely to have been omitted. The Cochrane Library searches do not include any MESH terms at all which is very poor practice.

- The terms used for study types are not validated search filters, which is likely to result in missing relevant papers. It is unclear why the company did not use tested study type filters such as those by SIGN[14] or CADTH[15]. The Cochrane Library searches use these same study type terms even though this is unnecessary since the database only contains RCTs and systematic reviews; this is likely to have led to exclusion of relevant search results.

- The limit to humans is not a validated method of limiting search results. The human filter from the Cochrane Handbook[16] should be used but was not, which is likely to result in missing relevant papers.

- The geographical limits used are not comprehensive, nor do they use any controlled index terms such as MeSH; it is very likely that these limits will have excluded a number of relevant records that do not have a specific country name in the title or abstract. The decision to limit to certain countries and not others (e.g. not Australia or Canada, not NHS) is not justified in the text.

- We do not have access to Embase.com so are unable to test the searches but the value of searching Medline and Embase simultaneously with one strategy is debatable since these databases use different indexing terms (Emtree for Embase and MeSH for Medline).

- The company did not search Medline-in-Process or PubMed as part of the searches. It is standard practice to do this in order to capture papers that have been added but not yet indexed in Medline. In clarification, the company stated that their searches of Embase.com would have picked up in-Process papers. However our investigations have shown that there is a delay of up to two weeks between papers being added to PubMed and then going into Embase.com. So any very recently published papers could have been omitted from the search results. We are unable to fully test this as we do not have access to Embase.com.

- Numbers in the PRISMA diagrams do not tally with the results: grey literature searches yielded 977 results (Table 3) but the PRISMA for search C (Figure 1) reports 1,022 ‘records from other sources’ with no explanation of where these have come from. In clarification the company stated that these were grey literature search results but the figures are not consistent and the source of the additional records is unclear. An additional six results are listed as ‘Records manually added’ in the PRISMA but it is not clear what these records are, or how they were identified.

- It is unclear why Search C included terms for economics as well as for clinical effectiveness; since the economics searches were carried out elsewhere (Search D see Section 5.1.1), including these terms in search C will just have made the results even more broad and confused.

- Clinical trials searching was poor, the drug name was not included in the search terms used.

- It does not appear that any forward or backward citation chasing (of references from the final included papers) has been done.

ERG comment:

The structure of these searches is poor, the search questions are not clearly defined and different concepts have been mixed in a disorganised way (e.g. economics or adverse events in search C; epidemiology or treatment patterns in search A), which is likely to produce very broad and ill-defined search results. Searches of this type would usually be conducted on the Population and Intervention facets but in this case Outcome terms have also been used, thus narrowing and confusing the results but not targeting those of interest. Searches have been limited in ways that are not evidence-based, e.g. without the use of a recognised and validated RCT filter[16].

The company has included searching for adverse events with some of the other search terms in the clinical effectiveness searches (Search C). However these searches were limited by study design and it is possible that limiting to certain study types (RCTs and observational studies) means that papers reporting adverse events (e.g. cross-sectional, case series) may have been missed.

The poor quality of these searches means that the ERG could not be at all confident that all relevant records would have been picked up in the search results. Our concerns were such that we ran our own search, for migraine and fremanezumab only, in Medline, Medline-in-Process, Embase and Cochrane, without any human or study type filters (see Appendix 1). This identified a number of additional papers, including several that report on two Phase IIb studies (one in EM [NCT02025556] and one in CM [NCT02021773]) that were not in the CS. Both trials are placebo-controlled RCTs [17-24].

4.1.2 Inclusion criteria

While the ERG considered that the inclusion and exclusion criteria for the clinical effectiveness SLR, as specified in the CS Appendix (p. 4 and 22-23) is broadly aligned with the NICE scope; the company only included a subset of the evidence relevant to the inclusion criteria.

The inclusion and exclusion criteria for the company's SLR of clinical effectiveness evidence are summarised in Table 2, alongside discrepancies noted by the ERG between the inclusion criteria and the evidence presented in the CS.

Table 2: Inclusion/Exclusion Criteria for the SLR of Clinical Effectiveness Evidence

SLR Inclusion criteria		Evidence presented in the CS
Population	Adults (aged ≥18 years) with migraine[≠] or MOH[∞]	Adults (aged ≥18 years) with migraine
Intervention/ comparators	• Topiramate • OBA • Amitriptyline • Divalproex/valproate • Gabapentin • Propranolol • Fremanezumab • Erenumab • Eptinezumab • Galcanezumab	• Fremanezumab • Best supportive care • Onabotulinumtoxin A (OBA)* • Erenumab^
Outcomes	• Clinical efficacy • HRQoL (including generic and migraine-specific instruments and functioning) • Safety • Adherence	• Clinical efficacy • HRQoL (migraine-specific instruments and functioning) • Safety
Study types	RCTs and observational trials – Phase III RCTs for all treatments, Phase II for anti-CGRPs only	Phase III RCTs
Species	Human studies only	No discrepancy
Language	Abstracts in English	No discrepancy
Geographical	No geographical limit	No discrepancy
Exclusion criteria		
Publication types	Case studies and case series	No discrepancy
Timeframe	Published before 1996	No discrepancy

Abbreviations: CS, company submission; CGRP, calcitonin gene-related peptide; HRQoL, health-related quality of life; MMD, monthly migraine days; MOH, medicine overuse headache; OBA, onabotulinum toxin A; PROs, patient reported outcomes; RCTs, randomised controlled trials; SLR, systematic literature review.

Notes: [≠] Migraine was defined as patients with either episodic (<15 days headache per month) or chronic (headache ≥15 days per month for more than 3 months and migraine on ≥8 days per month) migraine

∞ At clarification, the company clarified that no patients with MOH were in included evidence

*Data for OBA in the main submission is presented for two outcomes in the fourth line population only. In the appendix (appendix D, p. 329 – 330), data for the full trial populations of PREEMPT[25;26] are presented, however with the exception of ≥50% response rates, all outcomes were continuous and were provided without accompanying variance data. At clarification, standard errors were provided for one outcome (MMDs) during Weeks 9-12.

[^]Data for erenumab is presented in the appendix of the CS (appendix D, p. 328 – 330) for 4 outcomes [change in MMDs, ≥50% response rate, ≥75% response rate, and acute medication use] for participants with no previous, ≥1, and ≥2 previous prophylactic therapies. However, the three continuous outcomes were not accompanied by variance data. At clarification, standard errors were provided for one outcome (MMDs) during weeks 9-12.

Source: CS Appendix D, p. 22-23.

In particular, the ERG identified three discrepancies between the inclusion/exclusion criteria of the SLR and the evidence reported in the CS, which were considered to be important to this submission:

(a) The company places greater emphasis on clinical outcome data in the fourth line population. Notably, the ITC analysis was conducted only with this patient population, based on evidence from a subgroup population in the FOCUS trial

(b) Evidence for comparator interventions used to treat migraine was limited to a subset of evidence for OBA that was used to inform the NMA, or was incompletely reported. Evidence for comparator interventions (specified in the NICE scope) that are currently not used in the fourth line population in the UK was not reported

(c) Evidence from phase II trials for fremanezumab, which met inclusion criteria for this submission and the company's SLR, was not included.

Further discussion of these discrepancies is included below.

The company stated in their submission that evidence from a subgroup of the FOCUS trial, including participants who had previously received three or more prophylactic therapies for migraine, was more relevant to their submission than the remaining body of evidence. While evidence from earlier in the treatment pathway is reported in the CS, derived from the HALO trials and the main FOCUS population, this evidence was stated to be of less importance, and was not included in the company's ITC.

The decision to limit the target population to fourth line altered the evidence that was included for potential comparators to fremanezumab. Contrary to the SLR inclusion criteria, evidence for oral preventative medicines, including amitriptyline and topiramate, was not included in the CS (p.8). Moreover, evidence is incompletely reported for the fourth line population: evidence for OBA in the CS was scantily reported, such that evidence in the full participant population from the PREEMPT trial[25;26] was reported in the appendix without variance data (Appendix D, p. 329-330), and evidence in the fourth line population was limited to two outcomes only (those that were considered in the company's ITC).

At the time of this appraisal, erenumab is also currently under consideration as a fourth-line therapy for migraine, however evidence for this comparator was also scantily reported in the CS. Evidence from Study 295[27] was reported for four outcomes in the appendix of the CS (Appendix D, p. 328-329) without variance data. The CS stated that the exclusion of evidence for erenumab from the CS was because it was "not a comparator of interest for this appraisal" (CS, p. 94), presumably because approval for erenumab was pending at the time the CS was submitted to NICE. This decision has since been upheld by communications with NICE (communication 24/05/2019).

It is unclear why the company did not report evidence from Phase II trials in this submission. As reported in Section 4.1.1, the ERG conducted an additional literature search to identify

additional trials of fremanezumab not included in the CS, which identified two Phase II, placebo-controlled RCTs evaluating fremanezumab. These trials are summarised in Table 3, and were both considered by the ERG to meet the inclusion criteria for the SLR. In addition, three publications were identified that reported pooled data from the phase II trials and the HALO trials included in the CS, suggesting that the phase II trials may be sufficiently similar in design to HALO. Phase II trials for any anti-CGRP therapy were eligible for inclusion in this SLR, however no such evidence was reported in the CS.

Table 3: Phase II Trials Evaluating Fremanezumab

	Phase II EM	Phase II CM
Study Design and Sample Size	Multicentre, double-blind, placebo-controlled RCT conducted in the US N=297	Multicentre, double-blind, placebo-controlled RCT conducted in the US N=264
Trial ID	NCT02025556	NCT02021773
Population	Adults who had migraine headaches 8-14 days per month	Adults who have chronic migraine
Intervention/ Comparison	Fremanezumab 225mg vs. Fremanezumab 675mg vs. placebo	Fremanezumab 675/225 mg (675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles) vs. Fremanezumab 900mg vs. placebo
Outcomes	• Change from baseline in migraine days • Change from baseline in headache days • Safety and tolerability	• Change from baseline in the number of headache hours • Safety and tolerability
Publications	• Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet neurol. 2015;14(11):1081-90. • Silberstein SD, Rapoport AM, Loupe PS, Aycardi E, McDonald M, Yang R, et al. The Effect of Beginning Treatment With Fremanezumab on Headache and Associated Symptoms in the Randomized Phase 2 Study of High Frequency Episodic Migraine: Post-Hoc Analyses on the First 3 Weeks of Treatment. Headache. 2019;59(3):383-93.	• Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015;14(11):1091–100. • Bigal ME, Dodick DW, Krymchantowski AV, VanderPluym JH, Tepper SJ, Aycardi E, et al. TEV-48125 for the preventive treatment of chronic migraine: efficacy at early time points. Neurology. 2016;87(1):41–8.
Additional publications	<u>The following trials analysed pooled data from the two trials</u>: • Cohen JM, Dodick DW, Yang R, Newman LC, Li T, Aycardi E, et al. Fremanezumab as Add-On Treatment for Patients Treated With Other Migraine Preventive Medicines. Headache. 2017;57(9):1375-84. • Halker Singh RB, Aycardi E, Bigal ME, Loupe PS, McDonald M, Dodick DW. Sustained reductions in migraine days, moderate-to-severe headache days and days with acute medication use for HFEM and CM patients taking fremanezumab: Post-hoc analyses from phase 2 trials. Cephalalgia. 2019;39(1):52-60. • VanderPluym J, Dodick DW, Lipton RB, Ma Y, Loupe PS, Bigal ME. Fremanezumab for preventive treatment of migraine: Functional status on headache-free days. Neurology. 2018;91(12):e1152-e65.	

Abbreviations: CM, chronic migraine; ERG, Evidence Review Group; EM, episodic migraine; RCT, .randomised controlled trial.
Source: additional literature search conducted by the ERG.

A number of other discrepancies in the SLR inclusion criteria were noted by the ERG. It is unclear from the CS whether only full-text publications were eligible for inclusion in the SLR, or whether conference abstracts were also eligible. In an additional literature search to identify trials evaluating OBA, which may have been missed or excluded from the company's search strategy (see Section 4.4.1), the ERG identified several conference abstracts[28-32] reporting evidence from a comparison between fremanezumab and placebo in patients who had previously received OBA. Based on the SLR inclusion criteria stated by the company, the ERG also consider that evidence from these abstracts should have been included in the CS. Further, the company do not provide a rationale for restricting the inclusion of observational trials to anti-CGRP interventions only (i.e. fremanezumab, erenumab, and galcanezumab). Crucially, this decision may have led to the exclusion of phase II trials for OBA as fourth line therapy, which may have provided comparative clinical efficacy and safety evidence.

The SLR specified that participants with medication overuse headache (MOH) were eligible for inclusion. People with MOH are rarely seen in UK practice, due to the reduced use of opioid therapy in the UK compared with other countries. At clarification the company stated that no studies included in the SLR recruited people with MOH, however two thirds of participants in the FOCUS trial were stated to have 'medication overuse status' ([redacted]). The ERG were unclear about whether this referred to the number of participants who had experienced MOH in the past, or whether this number of participants developed this during the trial.

ERG comment:

Contrary to the NICE scope, the CS omits evidence for comparator interventions used prior to fourth line therapy, and thus limits the focus of this submission to the fourth line population. However, even in this population, the ERG considered that evidence was scantily reported and may exclude key relevant evidence. In particular, the ERG were troubled by the limited evidence presented for OBA, which is currently available as fourth line therapy for people with chronic migraine. As a consequence of this omission from the CS, the ERG considered that it was not possible to fully evaluate the relative clinical efficacy and safety of fremanezumab and OBA in the target population. The ERG also noted that the evidence for fremanezumab in the fourth-line population is derived from a subgroup of the FOCUS trial, and therefore does not retain randomisation.

4.1.3 Critique of data extraction

Limited details of screening and data extraction methods are provided in the CS (Appendix D, p.4). A two-stage screening process was adopted, with a first-pass screening based on titles and abstracts followed by a second-pass screening for full-text publications. One reviewer screened publications at the title/abstract level, and two independent reviewers screened publications at full-text. A random selection of excluded studies was verified by a third reviewer. References for the excluded studies were reported in the appendix, but the individual reasons for exclusion were not reported. A PRISMA diagram depicting the inclusion and exclusion of publications in the clinical SLR is provided in the CS (Appendix D, p. 24). The PRISMA represents the flow of evidence for a larger SLR conducted by the company, from which evidence meeting the inclusion criteria for the CS were included. As a consequence, the reasons for exclusion summarised in the PRISMA diagram are not wholly relevant to the CS, as these numbers do not account for publications included in the SLR that are not relevant for the CS. The PRISMA ends with 441 articles included in the SLR, from which a subset was selected to be included in the current CS. The methods in which these articles were selected was not reported. Issues with the PRISMA diagram and number of studies included/excluded were also highlighted in Section 4.1.1.

Data extraction of the included studies was conducted, but no details were provided about the methodology used. At clarification, the company stated that data extraction was performed in standardised data extraction tables in Microsoft Excel, which contained information about the PICOS information specified in the protocol. No further details were reported about the number of reviewers used and whether quality assurance of data extraction was conducted.

ERG comment:

The ERG judged that the screening process described by in the CS is of limited quality. Standard methodology for the conduct of SLRs for STA submissions typically involves two independent reviewers to screen records at both the title/abstract and full-text levels, due to the risk that records may be missed due to human error. It is also unclear how discrepancies between reviewers at full-text level were handled, and the proportion of records that were verified by the third reviewer is also not reported. The PRISMA diagram reported in the CS is not specific to this appraisal and to the inclusion/exclusion criteria for the SLR. The methods by which articles were selected for inclusion in the CS is therefore unclear.

No information was provided about the data extraction process in the CS, although it was stated by the company at clarification that a standardised template was used. The methods

of data extraction, including the way in which the quality of data extraction was assured, was not reported. It was not possible, therefore, for the ERG to determine whether data extraction was conducted appropriately.

Overall, the ERG considered that there is an unknown risk of bias associated with the SLR process, which may impact on the way in which publications were included and excluded, and the quality of the data that was extracted.

4.1.4 Quality assessment

Two tables reporting different approaches to evaluating the quality assessment of the three included trials were reported in the CS. these reported quality appraisal as conducted using the JADAD scale (reported in Appendix D, p. 325), and the Cochrane risk of bias tool for randomised trials (RoB 2; reported in Appendix D, p. 326-327).

ERG comment:

The JADAD scale is an inadequate method of evaluating the quality of the included trials. This is because it does not consider the potential of bias from allocation concealment procedures (a significant potential source of bias in RCTs), and the ratings place more emphasis on the reporting of evidence than on the conduct of trials. Scoring of the JADAD scale also lacks transparency (Cochrane Handbook[33]). Consequently, the JADAD scale is not reproduced or considered further in this report.

The Cochrane RoB 2 tool considers the principal areas for identifying risk of bias in RCTs; although the company's appraisal is not conducted per outcome, as is recommended practice (Cochrane Handbook[33]). No introduction to the appraisal was included in the CS, and the methods for evaluating risk of bias in each were not reported. Overall the ERG considered that this approach is adequate, however, due to the lack of information provided in the CS about the way in which quality assessment was performed and quality assured, the ERG are unable to evaluate whether it was conducted appropriately.

4.1.5 Evidence synthesis

No qualitative synthesis or pairwise meta-analysis of evidence from the HALO and FOCUS trials was reported in the CS. Evidence for the three trials is presented separately in the report, without a qualitative comparison of the data. The company state that any synthesis of the trials would be inappropriate, given the separation of EM and CM populations in the HALO trials, when they are combined in FOCUS (CS, p. 93); although the ERG noted that evidence from the FOCUS trial is nevertheless presented separately for EM and CM patients in the CS. The company further stated that participants in the HALO trials were treated

earlier in the treatment pathway, and cannot be combined with evidence from patients in FOCUS who had received at least three previous lines of prophylactic therapy. The company do not provide a clinical rationale for why line of therapy may vary the treatment effect of fremanezumab and so would prevent pooling, although this decision is consistent with their decision to target the submission on the fourth line population only.

The CS reported the findings of two ITCs, integrating evidence from participants with CM in the FOCUS trial, but not with participants with EM, or with evidence from the HALO trials. The ITCs compared fremanezumab with placebo and OBA in patients with CM for two key clinical outcomes: monthly migraine days (MMDs) and the proportion of patients with at least 50% reduction in their monthly average number of migraine days. The company stated that these outcomes were chosen as they contained the "best comparable evidence" (CS p. 94). The CS reported that no ITC was conducted for EM as "no relevant comparators with appropriate efficacy data were available" (CS, p. 94). No qualitative synthesis was reported for outcomes and populations for whom ITC was not conducted. Further details of the methods used in the ITCs is reported in Section 4.4.1.

ERG comment:

The company provided evidence from two ITC analyses comparing fremanezumab with OBA, via placebo, in participants with CM. The analyses were conducted using evidence from fourth-line population data only, and for two outcomes (the change in MMDs and for a ≥50% response rate). At clarification, the company stated that ITC was not conducted for patients with EM, as the analyses were limited to the fourth-line population, and there is no established fourth-line treatment for EM. Therefore, evidence for the effectiveness of fremanezumab for EM in the submission is limited to data from the FOCUS trial.

The feasibility assessment that determined the selection of evidence and outcomes was not fully reported in the CS, and therefore the rationale for not including evidence for other outcomes could not be evaluated by the ERG. The ERG was concerned that no pairwise meta-analysis or qualitative synthesis was presented in the CS where ITC was determined not to be feasible. The ERG considered this to therefore undermine the quantity of evidence for fremanezumab in the target population. The company provided no rationale for why the effect of treatment is likely to vary across lines of treatment, and clinical advice to the ERG stated that there is no established clinical rationale for this. Ultimately, the ERG considered that the decision by the company to restrict the evidence in this submission to a limited number of analyses in the fourth-line population has reduced the quantity and quality of available evidence for fremanezumab in EM and CM.

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

4.2.1 Excluded studies

As discussed in Section 4.1.1, the PRISMA diagram provided in the CS (Appendix D, p. 24) shows the flow of publications through a larger SLR performed by the company using broader inclusion/exclusion criteria than those relevant to this submission. The figures presented in the PRISMA therefore do not represent the number of publications that were excluded at title/abstract and full text screening according to the inclusion/exclusion criteria of this SLR. An excluded studies table was provided in the CS, however this was also specific to broader inclusion/exclusion criteria. As a consequence, it was not possible for the ERG to scrutinise the number of exclusions from the SLR, and the reasons given for these.

ERG comment:

Due to the lack of relevant information provided in the CS, it was not possible for the ERG to evaluate the quality of the exclusion process for this SLR. The ERG were therefore unable to evaluate whether evidence relevant to this submission has been missed in screening.

4.2.2 Included studies

Three placebo-controlled RCTs evaluating fremanezumab in participants with migraine were included in the SLR: HALO EM (evaluating fremanezumab in participants with episodic migraine), HALO CM (evaluating fremanezumab in participants with chronic migraine), and FOCUS (evaluating fremanezumab in a combined population of participants with episodic and chronic migraine). In all three trials, monthly and quarterly administrations of fremanezumab were evaluated in separate trial arms. Evidence from a 12-month randomised comparison of monthly and quarterly administrations of fremanezumab was also presented (HALO Extension), which was an extension phase to HALO EM and HALO CM. An overview of the three RCTs is provided in Table 4.

Details of the trial populations, interventions, and outcomes are provided in Sections 4.2.2.1 to 4.2.2.4. The results of the trials are reported in Section 4.2.4.

Table 4: Overview of Trials Included in the Clinical Effectiveness SLR

	HALO EM	HALO CM	HALO Extension	FOCUS EM	FOCUS CM
Design, follow-up	Phase III, multicentre, randomised, double-blind, parallel-group trial. Follow-up = 16 weeks		Double-blind 12-month extension phase (population includes some patients from HALO) Follow-up = 1 year	Phase IIIb, multicentre, randomised, double-blind, parallel-group trial Follow-up = 16 weeks	
Trial registration	NCT02629861	NCT02621931	NR	NCT03308968	
Setting, geography	International study in 9 countries (USA, Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain)	International study in 9 countries (USA, Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain)	NR	International study in 14 countries (USA, Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK)	
Population	Adults aged 18-70 years with episodic migraine	Adults aged 18-70 years with chronic migraine	Adults aged 18-70 years with episodic or chronic migraine	Adults aged 18-70 years with episodic migraine	Adults aged 18-70 years with chronic migraine
Sample size	N=875	N=1130	EM: N = 780 CM: N = 1110	N=329	N=509
Comparison	Fremanezumab monthly vs. Fremanezumab quarterly vs. placebo	Fremanezumab monthly vs. Fremanezumab quarterly vs. placebo	Fremanezumab monthly vs. Fremanezumab quarterly	Fremanezumab monthly vs. Fremanezumab quarterly vs. placebo	Fremanezumab monthly vs. Fremanezumab quarterly vs. placebo

Abbreviations: CM, chronic migraine; EM, episodic migraine; NR, not reported; SLR, systematic literature review.
Source: CS, p. 28-33.

ERG comment:

All three trials included in the SLR were considered to be consistent with the SLR inclusion criteria and the NICE scope, although the company assert that the HALO trials are less relevant for targeting fremanezumab in the fourth-line population.

4.2.2.1 Study design

A summary of the study designs used in the three included trials and the HALO extension is presented in Table 5.

The three trials were double-blind, parallel-group, placebo-controlled trials conducted in multiple centres internationally. Randomisation and blinding procedures between the trials

appear similar, although factors by which participants were stratified varied (see discussion in Section 4.2.4.1.1, 4.2.4.2.1 & 4.2.4.4.1).

The majority of treating centres for the HALO trials were in the US (HALO EM = 88/136; 64.7%; HALO CM = 87/132; 65.9%), whereas less than one-third of treating centres in FOCUS were based in the US (30/113; 26.5%), and the remainder were based in Europe (83/113; 73.5%). None of the participants included in the HALO trials were based in the UK. The number of participants in FOCUS that were based in the UK was not reported in the CS, although the CS reported that 6/113 (5.3%) of sites used in the FOCUS were in the UK. The geography of centres used in the HALO extension was not reported, although likely included many of the centres used in the HALO trials.

Notably, FOCUS was a considerably smaller trial (EM N=329; CM N=509) than the main HALO EM (N=875) and HALO CM (N=1130) trials. All three trials met their target sample size according to the power calculations reported (CS, p 38-40), although (as opposed to the HALO trials) the criteria used to calculate power in the FOCUS trial combined patients with EM and CM into the same treatment group. When EM and CM populations are analysed separately, FOCUS is underpowered to detect an effect; although the ERG noted that assumptions in the power calculation were reached comfortably, which adds greater confidence in the findings. Power calculations used to target additional recruitment for the HALO extension were not reported.

In the HALO-extension, participants in the original HALO EM and HALO CM trials were eligible to opt into a 12-month extension to evaluate the long-term efficacy and safety of fremanezumab. New participants were also recruited to the extension phase, and were subject to the same eligibility criteria as the main trial. Participants who participated in the original trial and who received fremanezumab continued on the same dosing schedule; while placebo participants and new participants were randomly assigned to either monthly or quarterly fremanezumab. Treatment with fremanezumab was delivered open label in the extension, although participants were blinded to the dose (monthly or quarterly administration) that they were receiving for the first three-months.

A lead-in phase of 28 days was used to establish baseline severity in both the HALO and FOCUS trials. Follow-up in the main trials was 12 weeks. Longer-term data, at 12 months (15 months for those in the original trials) is provided by the HALO extension. An open-label extension phase is also underway for FOCUS, which will evaluate the longer-term efficacy and safety of fremanezumab; however, the results of this extension will not be available until late 2019 (CS, p. 112).

Table 5: Study Design of Trials Included in the Clinical Effectiveness SLR

	HALO EM	HALO CM	HALO Extension	FOCUS EM	FOCUS CM
Design	Phase III, multicentre, randomised, double-blind, parallel-group trial to 16 weeks. Patients were randomised 1:1:1: to fremanezumab monthly, fremanezumab quarterly, and placebo. A 28-day lead in phase was used to determine eligibility and baseline outcome data.		3-month double-blind period, followed by a 12-month open label phase: patients could opt in from the main trial, and additional patients were recruited. Unclear if the same lead in phase was used to determine eligibility and baseline severity of newly recruited participants.	Phase IIIb, multicentre, randomised, double-blind, parallel-group trial to 16 weeks. A 28-day lead in phase was used to determine eligibility and baseline outcome data.	
Locations	136 centres in nine countries (United States (n=88), Canada (n=5), Czech Republic (n=6), Finland (n=3), Israel (n=6), Japan (n=12), Poland (n=5), Russian Federation (n=7), Spain (n=4))	132 sites in nine countries (United States (n=87), Canada (n=4), Czech Republic (n=6), Finland (n=3), Israel (n=4), Japan (n=12), Poland (n=5), Russian Federation (n=7), Spain (n=4))	NR. Multicentre, international.	113 sites in nine countries (United States (n=30), Belgium (n=4), Czech Republic (n=10), Denmark (n=5), Finland (n=6), France (n=6), Germany (n=12), Italy (n=2), Netherlands (n=4), Poland (n=9), Spain (n=11), Sweden (n=5), Switzerland (n=3), United Kingdom (n=6))	
Sample size	N=875	N=1130	EM: N = 780 (including 119 new patients) CM: N = 1110 (including 193 new patients)	N=329	N=509

	HALO EM	HALO CM	HALO Extension	FOCUS EM	FOCUS CM
Intervention	• Fremanezumab monthly n=290 • Fremanezumab quarterly n=291	• Fremanezumab monthly n=379 • Fremanezumab quarterly n=376	• Fremanezumab monthly EM n=386; CM n=559 • Fremanezumab quarterly EM n=394; CM n=551	• Fremanezumab monthly n=110 • Fremanezumab quarterly n=107	• Fremanezumab monthly n=173 • Fremanezumab quarterly n=169
Comparator	Placebo n=294	Placebo n=375	NA	Placebo n=112	Placebo n=167
Power calculation	The target sample size for this trial was calculated to be at least 768 total patients (256 patients per treatment group); based on having at least 90% power to detect a 1.6 difference in migraine days between active and placebo arms and assuming a common SD of 5.2 days and a 12% discontinuation rate	The target sample size for this trial was calculated to be at least 1020 total patients (340 patients *per* treatment group); based on having at least 90% power to detect a 1.7 difference in migraine days between active and placebo arms and assuming a common SD of 6.3 days and a 15% discontinuation rate.	NR	The target sample size for this trial was calculated to be at least 804 total patients (268 patients *per* treatment group*); based on having at least 90% power to detect a 1.8 difference in migraine days between active and placebo arms and assuming a common SD of 6.0 days and a 12% discontinuation rate.	

Abbreviations: CM, chronic migraine; EM, episodic migraine; NA, not applicable; NR, not reported; SD, standard deviation; SLR, systematic literature review.
Notes: *With each treatment group comprised of both EM and CM participants.
Source: CS, p. 28-33.

ERG comment:

The ERG considered that the design of the trials included in the CS are relevant for the SLR inclusion criteria. The trials evaluated the clinical efficacy of fremanezumab as relative to placebo, and/or as a comparison between monthly and quarterly fremanezumab. No head-to-head evidence is presented in the CS, and thus a direct comparison of the relative efficacy and safety of fremanezumab compared to other available treatments for migraine is not presented.

The ERG considered the follow-up of the main trials and the HALO extension to be appropriate for demonstrating the short- and medium-term efficacy and safety of fremanezumab. However, the ERG considered that the lack of evidence for fremanezumab beyond 12-months is a key limitation of the submission, as it does not capture the pattern of long-term use of fremanezumab (including use of positive stopping rules), and the possibility of a waning in treatment effect, which clinical advice to the ERG suggests is likely (see Section 5.2.6).

The ERG noted that recruitment for the FOCUS trial was powered only when CM and EM populations are combined, and therefore the trial may have been underpowered for evaluating these groups separately. Some confidence is introduced, however, by the fact that assumptions of effect size and discontinuation were met comfortably. This is a key limitation of the evidence, as much of the clinical efficacy and safety data for fremanezumab from the FOCUS trial are presented separately for CM and EM patients, including the evidence used to inform the company's ITC analysis.

4.2.2.2 Population characteristics

Key population inclusion criteria for the included trials are reported in Table 6; criteria for the definition of EM and CM are reported in Table 7. The inclusion criteria for the HALO extension were the same as those used in the main trials.

In general, the ERG considered that the population inclusion criteria used in the trials were consistent with the inclusion criteria for the SLR. Criteria for the definition of EM and CM were also consistent with UK practice, although clinical advice to the ERG is that there is no established definition of HFEM.

Notably, and as discussed previously, the HALO and FOCUS trials restricted inclusion on the basis of line of treatment: the HALO trials excluded participants who had received two or more prior lines of preventative therapy (as defined by medication groupings, see Table 6), while the FOCUS trial only included participants who had received two to four prior lines of

preventative therapy (as defined by different medication groupings). The HALO trials determined line of treatment based on four medication clusters:

- cluster A: divalproex sodium and sodium valproate
- cluster B: flunarizine and pizotifen
- cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine
- cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol.

Participants were excluded from the HALO trials if they had received medications in two or more clusters. Notably, however, these clusters did not include topiramate or OBA, and so the ERG considered it possible that a minority of participants included in the trials may have previously received three preventative therapies for migraine, including a medication in one of the clusters, plus both topiramate and OBA. At clarification, the company submitted data suggested that 21.3% (186/875) of participants in HALO-EM and 35.3% (399/1130) of participants in HALO-CM had received between one and three preventative therapies, including OBA, topiramate, or other.

The CS states that ineligibility in the FOCUS trial was determined by having previously used two to four classes of preventative therapies, defined as:

- beta-blockers (propranolol, metoprolol, atenolol, and bisopropol)
- anticonvulsants (topiramate)
- tricyclics (amitriptyline)
- calcium channel blocker (flunarizine)
- angiotensin II receptor antagonist (candesartan)
- OBA
- valproic acid.

The clusters used in FOCUS overlapped with those used for HALO, but were extended to include angiotensin II receptor antagonists, topiramate, and OBA. There were also some alterations in the specific drugs that were included within each class.

As noted in Section 4.1.2, participants with ‘other migraine disorder’, described elsewhere in the CS as ‘medication overuse headache’ (MOH) were also eligible for inclusion in the trials (CS p.48). At clarification, the company advised that no participants recruited to any of the included trials were classified as having MOH. However, the majority of participants in the FOCUS trial who had previously used ≥3 preventative therapies for migraine were identified

by the company as having overused acute medication status ([redacted]). The ERG are unsure whether this refers to participants who have previously been classified as having MOH and have resolved this, or whether they developed MOH during the trial. Clinical advice to the ERG is that MOH complicates treatment of migraine as it changes the nature of the headaches people experience. People with MOH are also seen rarely in clinical practice in the UK as compared to the US, due to variation in the prescription of opiates. As it is unclear whether 'medication overuse status' refers to present or previous MOH, it is unclear whether this may affect the applicability of the evidence included.

Trial inclusion is limited to those between the ages of 18 and 70 years. This excluded people aged between 16 and 18 years, who are treated in adult services in the UK, and older adults, who may constitute a significant minority of people with migraine treated in the UK (clinical advice to the ERG suggests approximately 15% of people will be over age 70 years, although this will vary by region). Clinical advice to the ERG is that evidence from the included trials may be generalised to people between 16 and 18 years of age, although may be less appropriate for people over 70 years of age, due to variation in metabolism.

Population inclusion criteria for the HALO and FOCUS trials, aside from criterion for line of treatment, were generally comparable.

Table 6: Population Inclusion/Exclusion Criteria of the Included Trials

	HALO EM and HALO CM	FOCUS
Inclusion criteria	• Aged 18 to 70 years • Migraine onset at or prior to age 50 • History of migraine based on ICHD-3 beta criteria or clinical judgement suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for at least 12 months prior to screening • Meets trial criteria for EM or CM (see Table 7) • ~85% diary compliance • Not using preventive medications (i.e. at least 5 half-lives have passed since last use) or using no more than 1 preventive medication for migraine [f]or other medical conditions (e.g. propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to beginning the 28-day run-in period	• Aged 18 to 70 years • Migraine onset at or prior to age 50 • History of migraine based on ICHD-3 beta criteria or clinical judgement suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for at least 12 months prior to screening • Meets trial criteria for CM or EM (see Table 7) • ~85% diary compliance • Documented inadequate response to 2 to 4 classes of prior preventive migraine medications within the past 10 years (defined as a lack of a clinically meaningful improvement after at least 3 months of therapy, intolerance to the treatment or contraindication/unsuitability for a treatment) Classes as follows: o beta-blockers (propranolol, metoprolol, atenolol, and bisopropol) o anticonvulsants (topiramate) o tricyclics (amitriptyline)

	HALO EM and HALO CM	FOCUS
		o calcium channel blocker (flunarizine) o angiotensin II receptor antagonist (candesartan) o OBA o valproic acid. • At least 5 half-lives of prophylactic medications must have passed prior to start of trial
Exclusion criteria	• A lack of efficacy after ≥3 months of treatment of at least two of four classes of preventive medications: o Cluster A: divalproex sodium and sodium valproate o Cluster B: flunarizine and pizotifen o Cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine o Cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol • Use of OBA during previous 4 months before screening • Use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during previous two months prior to screening • Use of opioid or barbiturate medications on more than four days during the 28-day run-in period • Any prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or TEV-48125) • Clinically significant haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator • History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [e.g. cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or	• Use of OBA during previous 3 months before screening • Use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during previous two months prior to screening • Use of opioid or barbiturate medications on more than four days during run-in period • The patient uses triptans/ergots as preventive therapies for migraine. • Patient uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. • Any prior exposure to a monoclonal antibody targeting the CGRP pathway • The patient suffers from unremitting headaches, defined as having headaches for more than 80% of the time he/she is awake, and less than 4 days without headache per month. Daily headache is acceptable if patient has headaches 80% or less of the time he/she is awake on most days • Clinically significant haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator • History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [e.g. cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism • Evidence or medical history of clinically significant psychiatric issues that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this

HALO EM and HALO CM	FOCUS
thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism Evidence or medical history of clinically significant psychiatric issues, including any suicide attempt in the past, or suicidal ideation with a specific plan in the past 2 years	study including major depression, panic disorder, or generalized anxiety disorder, any suicide attempt in the past or suicidal ideation with a specific plan the past two years prior to screening or current suicidal ideation • The patient has a history of alcohol abuse during the 2 years prior to screening. • The patient has a history of drug abuse during the past 2 years or drug dependence during the past 5 years

Abbreviations: CGRP, calcitonin gene-related peptide; CM, chronic migraine; EM, episodic migraine; ICHD-3, The international; classification of headache disorders, 3rd edition; OBA, onabotulinum toxin A.
Source: CS, Table 8, 29-33; Appendix L, p3-11.

Table 7: Criteria for Episodic and Chronic Migraine used in the Included Trials

	HALO Trials	FOCUS
Episodic migraine (EM)	• Patient fulfils the following criteria for EM in prospectively collected baseline information during the 28-day run-in period: o headache occurring on ≥6 and ≤14 days, on ≥4 days, fulfilling any of the following: o ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura o ICHD-3 criteria B and C for 1.2 Migraine with aura o Probable migraine (a migraine subtype where only 1 migraine criterion is missing) o The patient used a triptan or ergot derivative to treat an established headache	
Chronic migraine (CM)	• Patient fulfils the following criteria for CM in prospectively collected baseline information during the 28-day run-in period: o headache occurring on ≥15 days, on ≥8 days, fulfilling any of the following: o ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura o ICHD-3 criteria B and C for 1.2 Migraine with aura o The patient used a triptan or ergot derivative to treat established headache	• Patient fulfils the following criteria for CM in prospectively collected baseline information during the 28-day run-in period: o headache occurring on ≥15 days, on ≥8 days, fulfilling any of the following: o ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura o ICHD-3 criteria B and C for 1.2 Migraine with aura o Probable migraine (a migraine subtype where only 1 migraine criterion is missing) o The patient used a triptan or ergot derivative to treat

Abbreviations: CM, chronic migraine; EM, episodic migraine; ICHD-3, The international classification of headache disorders 3rd edition.
Source: CS, Appendix L p 3-11.

ERG comment:

Aside from the line of treatment participants received in the trials, population inclusion criteria were comparable between the HALO and FOCUS trials, and were generally consistent with the SLR inclusion criteria.

The ERG considered it unlikely that there would be significant implications of defining prior line of treatment based on clusters of therapies, rather than on individual medicines. However, it was not clear whether there would be a difference in treatment effect between participants in the studies who have experienced different treatment pathways. Moreover, in both studies participants were permitted to have previously received OBA: at clarification, the company reported that amongst participants in FOCUS who had received ≥3 prior therapies, 33/127 (26.0%) of participants with EM and 138/293 (47.1%) of participants with CM had previously received OBA. As the company wish to position fremanezumab as an alternative to OBA, this means that a significant minority of participants in the key trial are at a different position in the treatment pathway. The ERG also noted that there is an overlap in the populations treated in HALO and FOCUS, with a minority of participants in HALO having previously received between one and three treatments.

It is unclear from the CS whether a significant number of participants in the FOCUS trial developed MOH during the trial. If true, this could affect the generalisability of the treatment effect to the UK population, although the ERG were unable to determine from the information provided in the CS and at clarification if this was the case. All exclusions from the trials were considered to be appropriate, although clinical advice to the ERG is that the evidence may be less generalisable to people with migraine over the age of 70 years.

4.2.2.3 Intervention characteristics

Intervention characteristics used in the included trials are summarised in Table 8 below.

In all trials, participants with EM received a dose of 675 mg of fremanezumab; either in one quarterly administration, or as in three monthly administrations of 225 mg. Participants with EM received a dose of 900 mg of fremanezumab; either in one quarterly administration, or in a dose of 675 mg at baseline, followed by two monthly administrations of 225 mg. The ERG noted that the initial dose of 675 mg used for CM participants on monthly treatment exceeded the marketing authorisation for fremanezumab. A matching placebo (not described) was arranged to blind participants to treatment allocation, and was delivered using the same schedule in both trials.

All trials employed a 28-day lead-in phase to washout non-permitted medications and to establish baseline disease severity. Participants were permitted to use one other preventative therapy for migraine during the HALO trials, providing that the dose had been stable for two months: the CS reports that 421/2005 (21.0%) of participants were receiving another preventative medication during the lead-in phase, although the proportion of participants who continued on medication during the trial is not reported. No other preventative therapies for migraine were permitted during, or in the lead-in phase of, the FOCUS trial. Acute headache pain relief medications were permitted during both the HALO and FOCUS trials, although there was a restriction on the extent that these could be used during the lead-in phase in both trials. Use of opioids (including codeine) was restricted to no more than four days during the lead-in phase; in addition, use of barbiturates and medications containing butalbital were not permitted for more than four days in the lead-in phase. Acute pain medication was used frequently by patients during the lead-in phase; between a mean of 7-15 out of 28 days across groups in HALO and FOCUS. However, the proportion of participants using pain medication was not reported. No information is provided in the CS about background medication used by patients in HALO and FOCUS during the trial period, although the mean number of monthly days using acute headache medication was reported as an outcome in both HALO and FOCUS trials.

For the HALO extension phase, dosing of fremanezumab was the same as used in the main trials. No information on background care was reported for the HALO extension phase.

ERG comment:

The dose and schedule of fremanezumab evaluated in the included trials is consistent with the NICE scope, and is consistent between the HALO and FOCUS trials. The ERG noted that the use of a concurrent preventative therapy for migraine by 21% of participants in the HALO trials may introduce a risk of performance bias. In addition, the ERG noted that limited information was provided in the CS to describe the background care received by participants during the treatment phase, beyond descriptions of non-permitted intervention criteria specified in the inclusion criteria for the trials.

Table 8: Intervention Characteristics of the Included Trials

	HALO EM	HALO CM	FOCUS EM	FOCUS CM
Lead-in Phase (28 days)	182/875 (20.8%) of patients used another preventative therapy during lead-in phase Use of OBA, devices such as nerve blocks and transcranial magnetic stimulation, opioids and barbiturates were not permitted at timepoints prior to the start of the trial. Patients reported using acute headache medication a mean of 7.7 - 7.8 days (SD 3.4 – 3.7) during the lead in phase, of which 6.1 – 7.1 days (SD 3.0 – 3.1) were migraine-specific medications	239/1130 (21.2%) of patients used another preventative therapy during lead-in phase Use of OBA, devices such as nerve blocks and transcranial magnetic stimulation, opioids and barbiturates were not permitted at timepoints prior to the start of the trial. Patients reported using acute headache medication a mean of 13.0 – 13.1 days (SD 6.8-7.2), of which 10.7-11.3 days (SD 6.0 – 6.3) were migraine-specific medications	No other preventative therapies for migraine were permitted during the trial At least five half-lives of prior preventive migraine therapies must have passed. Use of OBA, devices such as nerve blocks and transcranial magnetic stimulation, opioids and barbiturates were not permitted at timepoints prior to the start of the trial. Patients reported using acute headache medication a mean of 8.5 – 9.3 days (SD 2.9 – 3.4) during the lead in phase	No other preventative therapies for migraine were permitted during the trial At least five half-lives of prior preventive migraine therapies must have passed. Use of OBA, devices such as nerve blocks and transcranial magnetic stimulation, opioids and barbiturates were not permitted at timepoints prior to the start of the trial. Patients reported using acute headache medication a mean of 14.1 – 15.0 days (SD 6.1 – 7.2) during the lead in phase)

	HALO EM	HALO CM	FOCUS EM	FOCUS CM
Intervention (12 weeks)	• Fremanezumab monthly n=290 (one 225mg fremanezumab injection (1.5mL) and two 1.5mL placebo injections at baseline; one 225mg fremanezumab injection (1.5mL) at weeks 4 & 8) • Fremanezumab quarterly n=291 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 1.5mL placebo injection at weeks 4 & 8)	• Fremanezumab monthly n=379 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 225mg fremanezumab injection (1.5mL) at weeks 4&8) • Fremanezumab quarterly n=376 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 1.5mL placebo injection at weeks 4&8)	• Fremanezumab monthly n=110 (one 225mg fremanezumab injection (1.5mL) and two 1.5mL placebo injections at baseline; one 225mg fremanezumab injection (1.5mL) at weeks 4 & 8) • Fremanezumab quarterly n=107 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 1.5mL placebo injection) at weeks 4 & 8	• Fremanezumab monthly n=173 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 225mg fremanezumab injection (1.5mL) at weeks 4 & 8) • Fremanezumab quarterly n=169 (675mg (three 225mg injections [1.5mL]) fremanezumab at baseline; one 1.5mL placebo injection at weeks 4 & 8)
Comparator	Placebo n=294 (three 1.5mL placebo injections at baseline; one 1.5mL placebo injection at weeks 4 & 8)	Placebo n=375 (three 1.5mL placebo injections at baseline; one 1.5mL placebo injection at weeks 4 & 8)	Placebo n=112 (three 1.5mL placebo injections at baseline; one 1.5mL placebo injection at weeks 4 & 8)	Placebo n=167 (three 1.5mL placebo injections at baseline; one 1.5mL placebo injection at weeks 4 & 8)

	HALO EM	HALO CM	FOCUS EM	FOCUS CM
Background Care	An unknown proportion of participants were allowed to continue use of one preventive migraine medication during the trial, if dosing had been stable for ≥2 months. It is possible that the proportion of participants is the same as the; proportion of participants who received preventative medications during the lead-in phase (21%) Acute headache medications were permitted, and evaluated as an outcome of the trial	Merge with HALO EM	Acute headache medications and drugs to treat adverse events were permitted, and evaluated as an outcome of the trial	Merge with FOCUS EM

Abbreviations: CM, chronic migraine; EM, episodic migraine; SD, standard deviation; OBA, onabotulinum toxin A.
Source: CS, Table 8 p. 29-33.

4.2.2.4 Outcome assessment

The outcomes evaluated in the included trials are summarised in Table 9, and methods of statistical analysis used to analyse the trial data are reported in Table 10.

All trials evaluated the mean change in monthly migraine days (MMDs), monthly headache hours, mean change in the monthly use of acute headache medication, and the proportion of participants who experienced a 50% reduction in MMDs at 12 weeks. As its primary outcome, HALO CM also evaluated the change in headache days of at least moderate severity at 12 weeks; this outcome was prioritised in a change to the study protocol (as reported on clinicaltrials.gov on June 12, 2017). All clinical outcomes were evaluated using participants' diary entries: participants completed daily electronic diaries of their symptoms. The distinction between headache and migraine used in the trials is not specified, and it's unclear if this was based on participants' judgement (i.e. in their diaries) and/or whether established criteria were used to guide this. While headaches are a part of the migraine disease, and are included in the definition of chronic migraine, clinical advice to the ERG is that to classify as a migraine, headaches must meet specific criteria, including criteria such as: duration of four to 72 hours; unilateral, pulsating pain; of at least moderate severity; interfere with routine activities; and be accompanied by nausea, vomiting, photophobia, or phonophobia. The CS did not provide detail on the methods of assessing HRQoL and functional outcomes, although participants were stated to be seen by trial personnel at screening and baseline, followed by weeks four, eight, and twelve and/or discontinuation (HALO EM and HALO CM) or weeks four, eight, twelve, sixteen, and twenty and/or discontinuation (FOCUS; CS p. 32).

With regards to HRQoL, the three main trials all evaluated the Migraine-Specific Quality of Life Questionnaire (MSQoL). In participants with EM, HALO EM and FOCUS also evaluated the Migraine Disability Assessment (MIDAS), while in participants with CM, HALO CM and FOCUS evaluated the six-item Headache Impact Test (HIT-6). HRQoL as evaluated by generic tools was not reported in the CS, and no HRQoL outcomes were evaluated in the HALO extension. The CS did not report validated minimally important differences (MIDs) for the three scales. The ERG was able to identify MIDs for the MSQoL and HIT-6 (reported in Table 9).

Measures of AEs were consistent across the trials, and were assessed as: any AE; treatment-related AEs; SAEs; discontinuation due to AEs; and any AE experienced by more than 2% of any group.

In addition to pre-planned subgroup analyses and those specified in the review protocol, additional subgroup analyses were also performed in FOCUS. These analyses evaluated the clinical efficacy of fremanezumab for participants who have previously received three or more preventative therapies (in line with the company's target population for fremanezumab), and participants with HFEM. In HALO, subgroup analyses were reported only for two outcomes: monthly average number of migraine days and the monthly average number of headache days of at least moderate severity. No evidence from subgroup analyses of the HALO extension data were presented in the CS.

Table 9: Outcomes Evaluated in the Included Trials

	HALO EM	HALO CM	HALO Extension	FOCUS EM	FOCUS CM
Final follow-up	**12 weeks**	**12 weeks**	**1 year**	**12 weeks**	**12 weeks**
Clinical Efficacy	• Mean change from baseline in **MMDs** • Mean change from baseline in monthly average number of days of **use of any acute headache medication** • Patients with at least **50% reduction from baseline in MMDs** • Patients with at least **75% reduction from baseline in MMDs** • Mean change from baseline in **monthly average number of headache days** • Mean change from baseline in **monthly average number of headache hours** of any severity • Mean change from baseline in **monthly average number of headache hours** of at least moderate severity	• Mean change from baseline in **monthly average number of headache days** of at least moderate severity • Mean change from baseline in **MMDs** • Mean change from baseline in monthly average number of days of **use of any acute headache medication** • Patients with at least **50% reduction from baseline in MMDs** • Mean change from baseline in **monthly average number of headache hours** of any severity • Mean change from baseline in **monthly average number of headache hours** of at least moderate severity	• Mean change from baseline in **MMDs** • Mean change from baseline in **monthly average number of headache days** of at least moderate severity • Patients with at least **50% reduction from baseline in MMDs** • Mean change from baseline in monthly average number of days of **use of any acute headache medication** • Mean change from baseline in **monthly average number of headache hours** of at least moderate severity	• Mean change from baseline in **MMDs** • Mean change from baseline in monthly average number of days of **use of any acute headache medication** • Patients with at least **50% reduction from baseline in MMDs** • Mean change from baseline in **monthly average number of headache hours** of any severity • Mean change from baseline in **monthly average number of headache hours** of at least moderate severity	• Mean change from baseline in **MMDs** • Mean change from baseline in monthly average number of days of **use of any acute headache medication** • Patients with at least **50% reduction from baseline in MMDs** • Mean change from baseline in **monthly average number of headache hours** of any severity • Mean change from baseline in **monthly average number of headache hours** of at least moderate severity

	HALO EM	HALO CM	HALO Extension	FOCUS EM	FOCUS CM
Final follow-up	**12 weeks**	**12 weeks**	**1 year**	**12 weeks**	**12 weeks**
Adherence	The total number of subcutaneous injections and their locations were recorded at each dosing visit			NR	NR
HRQoL	All trials used the Migraine-Specific Quality of Life Questionnaire (MSQoL). The MSQoL measures the degree to which performance of normal activities is limited by migraine (Role Function-Restrictive domain comprising 7 items), the degree to which performance of normal activities is prevented by migraine (Role Function-Preventive domain comprising 4 items), and the emotional effects of migraine (Emotional Function domain comprising 3 items). Scores range from 0 to 100, with higher scores indicating better health-related quality of life. Recommended MIDs [34] are 3.2 for role function restrictive, 4.6 for role function preventative, and 7.5 for emotional function				
Function	Migraine Disability Assessment (MIDAS). Scored as: little or no disability, 0-5; mild disability, 6-10; moderate disability, 11-20; severe disability, >20. The ERG could not identify an established MID for this scale.	Six-Item Headache Impact Test (HIT-6). Scored as: little to no impact 36-49; moderate impact 50-55; substantial impact 56-59); severe impact 60-78. Recommended MID is 2.3[35]	None	Migraine Disability Assessment (MIDAS). Scored as: little or no disability, 0-5; mild disability, 6-10; moderate disability, 11-20; severe disability, >20. The ERG could not identify an established MID for this scale.	Six-Item Headache Impact Test (HIT-6). Scored as: little to no impact 36-49; moderate impact 50-55; substantial impact 56-59); severe impact 60-78. Recommended MID is 2.3[35]
Adverse Events	The same AE outcomes were evaluated in all of the included trials: • Number of patients with ≥1 AE • Number of patients with ≥1 treatment-related AE • Number of patients with ≥1 SAE • Number of patients with ≥1 AE leading to discontinuation • Number of patients with ≥1 AE of special interest • Death • AEs of special interest^ experienced by >2%≠ of any treatment group				
*Planned Subgroup analyses**	• Patients receiving or not receiving concomitant preventive treatment • Patients with past topiramate use for migraine • Patients with past OBA use for migraine • Age groups (18-45 years; >45 years) • Race groups (Caucasian; non-Caucasian) • Sex		None reported	• Special treatment failure group (patients with inadequate response to valproic acid plus two to three other migraine preventive medications) • Age groups (18-45 years; >45 years) • Sex • Region (North America; Europe) • Migraine classification (CM; EM) • Valproic acid failure (yes; no)	

	HALO EM	HALO CM	HALO Extension	FOCUS EM	FOCUS CM
Final follow-up	**12 weeks**	**12 weeks**	**1 year**	**12 weeks**	**12 weeks**
Additional Analyses	• Patients with past topiramate and/or OBA use			• HFEM • Patients who have previously received 3 or more classes of preventative migraine treatment • Patients with HFEM who have previously received 3 or more classes of preventative migraine treatment	

Abbreviations: AE, adverse event; ALT, Alanine transaminase; AST, Aspartate transaminase; CM, chronic migraine; CS, company submission; EM, episodic migraine; ERG, Evidence Review Group; HFEM, high-frequency episodic migraine; HIT-6,six-item headache impact test; HRQoL, health-related quality of life; INR, international normalised ratio; MID, minimally important difference; MIDAS, migraine disability assessment; MMDs, mean monthly migraine days; MSQoL, migraine-specific quality of life questionnaire; NR, not reported; OBA, onabotulinum toxin A; SAE, serious adverse event; ULN, upper limit of normal.

Notes: * Note that within HALO EM and HALO CM, all pre-planned subgroup analyses were stated to have been conducted for 2 outcomes only: monthly average number of migraine days and the monthly average number of headache days of at least moderate severity.

^Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions.

≠The CS reports that data for AEs experienced by ≥5% of any treatment group was also assessed (p.101), but the data was not reported in the CS.

Source: CS, p. 29-33, 52; 74-93; clarification question A26.

The statistical analytic approach used in the included trials is summarised in Table 10 below.

The sample size calculations were intended to result in 90% power to detect a difference in migraine days between fremanezumab and placebo; defined as 1.6 days (SD 5.2) in HALO EM, 1.7 days (SD 6.3) in HALO CM, and 1.8 days (SD 6.0) in FOCUS. A discontinuation rate of 12% was estimated for HALO EM and FOCUS, while 15% was estimated for HALO CM. It's not clear from the CS how these assumptions were derived, although the publications for the HALO trials[36;37] report that the assumptions were based on the earlier phase II trials of fremanezumab.

Methods used to handle missing data and to analyse outcomes were broadly appropriate, although the ERG noted that covariates included in inferential analyses varied within each trial, without explanation. The ERG also noted that where baseline differences were noted in the FOCUS trial, these factors were not consistently included as covariates in analyses. Some of the appendices of the HALO CSRs were not provided to the ERG, nor was the full CSR for FOCUS, and therefore it is unclear whether further analyses were conducted and not reported. ANCOVA methods used to analyse secondary outcomes in the three trials were described as "similar" (CS p. 42, p.44, p.46) to those used in the analysis of the primary outcomes; the ERG were able to confirm that the same methods were used in the HALO trials, but were unable to confirm this for FOCUS as the CSR was not provided to the ERG.

Table 10: Statistical Analysis Used in the Included Trials

	HALO EM	HALO CM	HALO Extension	FOCUS
Sample Size	The sample size was calculated based on having at least 90% power to detect a difference of 1.6 in migraine days between treatment and placebo arms, at an alpha level of 0.05, and assuming a common SD of 5.2 days. Based on these assumptions, it was calculated that a sample size of 768 patients (256 patients per treatment group) was required, allowing for a discontinuation rate of 12%	The sample size was calculated based on having at least 90% power to detect a difference of 1.7 in migraine days between treatment and placebo arms, at an alpha level of 0.05, and assuming a common SD of 6.3 days. Based on these assumptions, it was calculated that a sample size of 1020 patients (340 patients per treatment group) was required, allowing for a discontinuation rate of 15%	NR	The sample size was calculated based on having at least 90% power to detect a difference of 1.8 in migraine days between treatment and placebo arms, at an alpha level of 0.05, and assuming a common SD of 6.0 days. Based on these assumptions, it was calculated that a sample size of 804 patients (268 patients per treatment group) was required, allowing for a discontinuation rate of 12%
Analysis Sets	**ITT**: All patients (N=875) **FAS**: All randomised patients who received at least 1 dose of the study drug and had at least 10 days of post-baseline efficacy assessments for the primary endpoint (N=865) **Safety set**: All patients who received treatment (N=874)	**ITT**: All patients (N=1130) **FAS**: All randomised patients who received at least 1 dose of the study drug and had at least 10 days of post-baseline efficacy assessments for the primary endpoint (N=1121) **Safety set**: All patients who received treatment (N=1130)	**FAS**: All randomised patients who received at least 1 dose of the study drug and had at least 10 days of post-baseline efficacy assessments for the primary endpoint (N=1868) **Safety set**: All patients who received treatment (N=1866).	**ITT**: All patients (N=838) **mITT**: All randomised patients who received at least 1 dose of the study drug and had at least 10 days of post-baseline efficacy assessments for the primary endpoint (N=837) **Safety set**: All patients who received treatment (N=838)
Missing Data	• Patients in active treatment groups who discontinued because of adverse events or lack of efficacy were assigned to the placebo group • If patient had ≥10 days of data for a month, number of days/hours was prorated to 28 days for that month, and a multiple imputation method was also conducted as a sensitivity analysis • If a patient had <10 days data for a month, the monthly number of days of efficacy variables was considered missing before the multiple imputation procedure		NR	• For patients who withdrew from the trial, their safety data at the early termination visit was excluded from the by-visit summaries but was included in the last assessment summaries. • If patient had ≥10 days of data for a month, number of days/hours was prorated to 28 days for that month, and a multiple imputation method was also conducted as a sensitivity analysis • If patient had <10 days data for a month, the monthly number

	HALO EM	HALO CM	HALO Extension	FOCUS
				of days of efficacy variables was considered missing before the multiple imputation procedure • In terms of weekly variables, patients with three or more days of electronic headache diary data for a week had their number of days of efficacy variables prorated to seven days for that week. For patients with less than three days of data, these variables were considered as missing for that week
Statistical Analysis	Statistical analysis of the primary outcome was conducted by analysis of covariance (ANCOVA), which included treatment, sex, region, and baseline preventive migraine medication use as fixed effects and the baseline number of migraine days and years since onset of migraine as covariates. The CS reports that an ANCOVA "similar" to this was used for secondary outcomes, but this was not described. It is unclear from the CS which ANCOVA method was used to analyse subgroups. A Cochran Mantel-Haenszel test stratified by baseline preventive migraine medication use was used for analysing the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days. The Wilcoxon rank-sum test was performed as the primary analysis if there was deviation from normality as assessed by the Shapiro-Wilk test. A mixed-effects, repeated measures (MMRM) analysis was implemented as a sensitivity analysis to estimate the mean change from baseline in the monthly average number of migraine days for the overall 3-month treatment period and for each month. The MMRM analysis included baseline value, treatment, sex, region, baseline preventive migraine medication use (yes/no), years since onset of migraines, month, and treatment month interaction as fixed effects and patient in the repeated statement as a random effect.	NR	Statistical analysis of the primary outcome was conducted by analysis of covariance (ANCOVA), which included treatment, sex, region, inadequate response to valproic acid (and 2 to 3 other classes of migraine preventive medications), migraine classification (CM or EM), and treatment-by-migraine classification interaction as fixed effects and the baseline number of migraine days and years since onset of migraine as covariates. The CS reports that an ANCOVA "similar" to this was used for secondary outcomes, but this was not described. It is unclear from the CS which ANCOVA method was used to analyse subgroups. A hierarchical logistic regression model was used for analysing the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days, with the following effects: treatment, sex, region, inadequate response to valproic acid

HALO EM	HALO CM	HALO Extension	FOCUS
			(and two to three other classes of migraine preventive medications) and migraine classification (CM or EM). A mixed-effects, repeated-measures (MMRM) analysis was implemented as a sensitivity analysis to estimate the mean change from baseline in the monthly average number of migraine days for the overall 3-month treatment period and for each month

Abbreviations: CM, chronic migraine; EM, episodic migraine; FAS, full analysis set; ITT, intention-to-treat; mITT, modified intention-to-treat; NR, not reported; SD, standard deviation.
Source: HALO EM CSR p. 52-53; HALO CM CSR p.57-58.

ERG comment:

Overall, the ERG considered that the outcomes evaluated were appropriate for judging the clinical efficacy and safety of fremanezumab, and are consistent with the inclusion criteria for the SLR. Outcome evaluations were based on participants' diaries, in which participants recorded the duration and severity of symptoms. The ERG acknowledged that this method was the most feasible for evaluating the outcome of therapies for migraine; however, the ERG also noted that this method is subjective and may be susceptible to bias.

Clinical efficacy outcomes in HALO CM evaluating migraine of at least moderate severity were added to the protocol for the trial following the start of recruitment, and therefore may be at a risk of bias (see Section 4.2.3). In addition, a threshold of ≥50% reduction in mean monthly migraine days (MMDs) was reported as an outcome in the CS, however, it is unclear how this threshold was selected. According to the trial CSRs[38;39], a reduction of 75% and 100% was also evaluated in the HALO trials (data at ≥75% threshold was reported in the CS for participants in HALO-EM, though not HALO-CM), and may have been evaluated in FOCUS, although the ERG have no access to the FOCUS CSR to determine this. Whilst the company provided no clinical justification for the selection of thresholds evaluated, the ERG identified evidence that multiple thresholds were evaluated, and generally the ERG considered the use of thresholds to introduce bias in assessing treatment response, clinical advice to the ERG is nevertheless that a ≥50% reduction in migraine days would be a clinically meaningful change to patients.

HRQoL outcomes evaluated using generic tools were not reported in the CS for any of the included trials; however, the ERG identified HRQoL data evaluated using EQ-5D VAS in the HALO trial CSRs. As the CSR for the FOCUS trial was not provided with this submission, it's unclear whether a generic measure of HRQoL was also evaluated for FOCUS. As generic methods for evaluating HRQoL are favoured where possible, and for completeness, the ERG has reproduced the EQ-5D VAS data in this report. However, the ERG noted that the company have argued that generic HRQoL outcomes do not represent the full impact of EM and CM on people's quality of life. This view has been upheld by clinical advice to the ERG; who advised that migraine-specific HRQoL tools will evaluate the impact of migraine quality of life in greater depth, and will identify some impacts of migraine that would not be picked up by generic tools (for example, the ability to work but have reduced productivity).

Methods for statistical analysis used in the included trials were generally appropriate, although the ERG were concerned with variations in covariates used in the multipredictor

analyses within each trial. In addition, statistical methods used in the HALO extension phase were not reported.

4.2.3 Quality assessment

The findings of the quality assessment using the Cochrane risk of bias tool 2.0 as conducted by the company is reproduced in Table 11. No quality assessment was provided for the extension phase of the HALO trials. The company's quality assessment concluded that all three trials were at a low risk of bias, with no risks of bias identified across any tool items. Additional columns have been added to Table 11 to summarise the ERG's commentary on the company's quality assessment.

Table 11: Quality Assessment of the Included Trials: Cochrane Risk of Bias (RoB) Tool 2.0

Domain	Question	HALO EM	HALO EM ERG comment	HALO CM	HALO CM ERG comment	FOCUS	FOCUS ERG comment
Random-isation	Was the allocation sequence random?	Y	Y: the ERG agreed with the company assessment	Y	Y: the ERG agreed with the company assessment	Y	Y: the ERG agreed with the company assessment
	Was the allocation sequence concealed until participants were recruited and assigned to interventions?	PY	PY: the ERG agreed with the company assessment	PY	PY: the ERG agreed with the company assessment	PY	PY: the ERG agreed with the company assessment
	Were there baseline imbalances that suggest a problem with the randomisation process?	N	N: the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment
	Risk of bias judgement	Low	Low	Low	Low	Low	Low
	What is the predicted direction of bias arising from the randomisation process?	NA	NA	NA	NA	NA	NA
Deviations from intended interventions	Were participants aware of their assigned intervention during the trial?	N	N the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment
	Were carers and trial personnel aware of participants' assigned intervention during the trial?	N	N: the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment	N	N: the ERG agreeds with the company assessment
	Were there deviations from the intended intervention beyond what would be expected in usual practice?	NI	U: the company state that no information is available to assess this, which was also the case for the ERG. Consequently, the ERG considered this item should be rated as unclear.	NI	U: the company state that no information is available to assess this, which was also the case for the ERG. Consequently, the ERG considered this item should be rated as unclear.	NI	U: the company state that no information is available to assess this, which was also the case for the ERG. Consequently, the ERG considered this item should be

Domain	Question	HALO EM	HALO EM ERG comment	HALO CM	HALO CM ERG comment	FOCUS	FOCUS ERG comment
							rated as unclear.
	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	NA	U: the company state that no information is available to assess this, which was also the case for the ERG. Consequently, the ERG considered this item should be rated as unclear.	NA	U: the company state that no information is available to assess this, which was also the case for the ERG. Consequently, the ERG considered this item should be rated as unclear.	NA	U: the company state that no information is available to assess this, which was also the case for the ERG. Consequently, the ERG considered this item should be rated as unclear.
	Were any participants analysed in a group different from the one to which they were assigned?	N	N: the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment	PN	PN: the ERG agreed with the company assessment
	Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	NA	NA	NA	NA	NA	NA
	Risk of bias judgement	Low	Low	Low	Low	Low	Low
	What is the predicted direction of bias due to deviations from intended interventions?	NA	NA	NA	NA	NA	NA
Missing outcome data	Were outcome data available for all, or nearly all, participants randomised?	Y	Y: the ERG agreed with the company assessment	Y	Y: the ERG agreed with the company assessment	Y	Y: the ERG agreed with the company assessment

Domain	Question	HALO EM	HALO EM ERG comment	HALO CM	HALO CM ERG comment	FOCUS	FOCUS ERG comment
	Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	Y	Y: the ERG agreed with the company assessment	Y	Y: the ERG agreed with the company assessment	Y	Y: the ERG agreed with the company assessment
	Is there evidence that results were robust to the presence of missing outcome data?	Y	Y: the ERG agreed with the company assessment	Y	Y: the ERG agreed with the company assessment	Y	Y: the ERG agreed with the company assessment
Risk of bias judgement		Low	Low	Low	Low	Low	Low
	What is the predicted direction of bias due to missing outcome data?	NA	NA	NA	NA	NA	NA
Measure-ment of the outcome	Were outcome assessors aware of the intervention received by study participants?	N	N: the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment
	Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	NA	NA	NA	NA	NA	NA
Risk of bias judgement		Low	Low	Low	Low	Low	Low
	What is the predicted direction of bias due to measurement of the outcome?	NA	NA	NA	NA	NA	NA
Selection of the reported result	Are the reported outcome data likely to have been selected on the basis of the results, from…						
	... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	PN: the ERG agreed with the company assessment	PN	PN: the ERG agreed with the company assessment	N	PN: the ERG agreed with the company assessment
	... multiple analyses of the data?	PN	PN: the ERG agreed with the company assessment	PN	PN: the ERG agreed with the company assessment	N	N: the ERG agreed with the company assessment
Risk of bias judgement		Low	Low	Low	Low	Low	Low

Domain	Question	HALO EM	HALO EM ERG comment	HALO CM	HALO CM ERG comment	FOCUS	FOCUS ERG comment
	What is the predicted direction of bias due to selection of the reported result?	NA	NA	NA	NA	NA	NA
Overall bias	Risk of bias judgement	Low	Low	Low	Low	Low	Low
	What is the overall predicted direction of bias for this outcome?	NA	NA	NA	NA	NA	Unclear

Abbreviations: CM, chronic migraine; EM, episodic migraine; ERG, Evidence Review Group; N: no; NA, not applicable; NI, no information; NR, not reported in the CS; PN, probably no; PY, probably yes; U, Unclear; Y: Yes.
Source: CS, p. 47-49; Appendix D 326-327.

Table 12: ERG Quality Assessment of the HALO EM and CM Extension

Domain	Question	HALO EM Extension	HALO CM Extension
Randomisation	Was the allocation sequence random?	Yes: stated to be 'randomised', no further details provided.	Yes: stated to be 'randomised', no further details provided.
	Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Unclear: no details on allocation concealment were reported	Unclear: no details on allocation concealment were reported
	Were there baseline imbalances that suggest a problem with the randomisation process?	NR: baseline characteristics for participants as they entered the trial were not reported, except for baseline outcome scores, which were presented separately	NR: baseline characteristics for participants as they entered the trial were not reported, except for baseline outcome scores, which were presented separately
	Risk of bias judgement	Unclear	Unclear
	What is the predicted direction of bias arising from the randomisation process?	NA	NA
Deviations from intended interventions	Were participants aware of their assigned intervention during the trial?	Yes: participants were aware that they were receiving fremanezumab, although were blinded to the dosing schedule they were receiving (monthly or quarterly)	Yes: participants were aware that they were receiving fremanezumab, although were blinded to the dosing schedule they were receiving (monthly or quarterly)
	Were carers and trial personnel aware of participants' assigned intervention during the trial?	Yes: carers and personnel were aware that participants were receiving fremanezumab, although were blinded to the dosing schedule they were receiving (monthly or quarterly)	Yes: carers and personnel were aware that participants were receiving fremanezumab, although were blinded to the dosing schedule they were receiving (monthly or quarterly)

Domain	Question	HALO EM Extension	HALO CM Extension
	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Unclear: the CS reports the proportion of acute medication participants were using, but no further details about background care was reported. Adherence information was also not reported, although the CS states that 23.9% of participants from both the HALO-EM and HALO-CM trials discontinued from the trial for all causes.	Unclear: the CS reports the proportion of acute medication participants were using, but no further details about background care was reported. Adherence information was also not reported, although the CS states that 23.9% of participants from both the HALO-EM and HALO-CM trials discontinued from the trial for all causes.
	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	NA	NA
	Were any participants analysed in a group different from the one to which they were assigned?	Unclear: no information reported	Unclear: no information reported
	Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	Unclear: no information reported	Unclear: no information reported
	Risk of bias judgement	High	High
	What is the predicted direction of bias due to deviations from intended interventions?	Unclear	Unclear
Missing outcome data	Were outcome data available for all, or nearly all, participants randomised?	Yes/No: Data for nearly all participants (775/780; 99.4%) was available at 1 month, but by 12 months data for 27.1% of participants (211/780) was missing (CS, p. 70)	Yes/No: Data for nearly all participants (1103/1110; 99.4%) was available at 1 month, but by 12 months data for 21.7% of participants (241/1110) was missing (CS, p. 70)

Domain	Question	HALO EM Extension	HALO CM Extension
	Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	NA/Yes; for the principle purposes of this submission, there was no comparator to fremanezumab and therefore this item is NA. Proportions of missing participants were comparable between quarterly and monthly administrations, and between newly treated and active rollover participants	NA/Yes; for the principle purposes of this submission, there was no comparator to fremanezumab and therefore this item is NA. Proportions of missing participants were comparable between quarterly and monthly administrations, and between newly treated and active rollover participants
	Is there evidence that results were robust to the presence of missing outcome data?	No: the CS does not include discussion of the missing data in the HALO extension phase, and no additional analyses to determine robustness of the data were provided	No: the CS does not include discussion of the missing data in the HALO extension phase, and no additional analyses to determine robustness of the data were provided
	Risk of bias judgement	Low risk for 1, 3, and 6 months follow-up, high risk for 12 months follow-up	Low risk for 1, 3, and 6 months follow-up, high risk for 12 months follow-up
	What is the predicted direction of bias due to missing outcome data?	Unclear. If a significant proportion of missing participants discontinued the trial due to lack of efficacy or intolerance, this may amplify the treatment effect	Unclear. If a significant proportion of missing participants discontinued the trial due to lack of efficacy or intolerance, this may amplify the treatment effect
Measurement of the outcome	Were outcome assessors aware of the intervention received by study participants?	Yes, but were blinded to treatment schedule (monthly or quarterly administration)	Yes, but were blinded to treatment schedule (monthly or quarterly administration)
	Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	Yes: clinical outcome data was based on participant reporting in daily diaries, which may be prone to bias	Yes: clinical outcome data was based on participant reporting in daily diaries, which may be prone to bias
	Risk of bias judgement	High	High
	What is the predicted direction of bias due to measurement of the outcome?	Unclear	Unclear

Domain	Question	HALO EM Extension	HALO CM Extension
Selection of the reported results		Are the reported outcome data likely to have been selected on the basis of the results, from…	
	... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Unclear: full information about the outcomes evaluated in the HALO extension phase is not reported in the CS. A subset of the outcomes that were reported for the main trial were reported for the extension phase, and it's unclear if this is because fewer outcomes were evaluated or whether a selection were reported only.	Unclear: full information about the outcomes evaluated in the HALO extension phase is not reported in the CS. A subset of the outcomes that were reported for the main trial were reported for the extension phase, and it's unclear if this is because fewer outcomes were evaluated or whether a selection were reported only.
	... multiple analyses of the data?	Unclear: it is stated in the CS that the same methods of analysis were used to analyse the data, although it's unclear if ITT data was available for the extension and not reported (this was requested at clarification but was not provided).	Unclear: it is stated in the CS that the same methods of analysis were used to analyse the data, although it's unclear if ITT data was available for the extension and not reported (this was requested at clarification but was not provided).
	Risk of bias judgement	Unclear	Unclear
	What is the predicted direction of bias due to selection of the reported result?	Unclear	Unclear
Overall bias	Risk of bias judgement	Very high: due to multiple unclear ratings of bias across domains, lack of blinding, lack of information about background care, and concerns about missing data at 12 months	Very high: due to multiple unclear ratings of bias across domains, lack of blinding, lack of information about background care, and concerns about missing data at 12 months
	What is the overall predicted direction of bias for this outcome?	Unclear	Unclear

Abbreviations: CM: Chronic migraine; EM: Episodic migraine; ERG, Evidence Review Group; ITT, intention-to-treat; NA, not applicable.

ERG comment:

For the most part, the ERG agreed with the company's quality appraisal of HALO-EM, HALO-CM and FOCUS. All three trials employed double-blind, randomised designs, with appropriate methods for group allocation and blinding. Adherence to treatment was also high. However, the ERG was concerned that limited information was provided about the delivery of background care received by participants across the three trials. The extent to which participants were using acute medications during the trial was reported as a trial outcome across the trials; however, there was a lack of clarity about the proportion of participants using other preventative therapies in the HALO trials. Furthermore, the use of other therapies used in the standard care of patients with migraine (such as psychological therapies) were not reported. As the HALO trials in particular reported a strong placebo effect, it would be useful to know what concomitant care was being provided to participants in the trials. The company appraisal rated the respective items in the checklist as 'no information', which the ERG has changed to 'unclear'.

The ERG were concerned about the risk of reporting bias in the CS for the three trials, as there was a lack of clarity about the selection and use of covariates in multivariate analyses (see Section 4.2.2.4), and the selection and reporting of outcomes. For example, the CS reports evidence for the ≥50% reduction in migraine days threshold for HALO CM, but not ≥30%, ≥75%, or ≥100%. The 75% and 100% thresholds were both planned outcomes for the trial (HALO CM CSR[39]). The company provided the full trial CSRs for both the HALO EM[38] and HALO CM[39] trials, and a subset of the trial CSR for FOCUS[40] displaying outcome data, and therefore the ERG did not downgrade for reporting bias. However due to the lack of clarity about the methods for analysis, the ERG considered this item in the checklist should be rated as 'unclear'.

The ERG was concerned that a quality appraisal for the extension phase of the HALO trials was not reported in the CS, and considered this to be a significant omission from the CS. The ERG conducted this assessment, based on the information available in the CS, and determined the results to be at a high risk of bias due to the trial being open label, the subjectivity of outcome assessment, a lack of information about baseline characteristics and background care, and missing data at 12-month follow-up. Overall, the ERG considered HALO-EM, HALO-CM, and FOCUS to all be at low risk of bias, but identified the lack of clarity about background care and statistical analysis as areas of uncertainty. The ERG considered the open label extension to HALO-CM and HALO-EM to be at very high risk of bias.

4.2.4 Clinical effectiveness of the technology of interest

4.2.4.1 HALO EM

4.2.4.1.1 Baseline characteristics

The baseline characteristics of participants included in the HALO-EM trial are reported in Table 13. Baseline characteristics were not reported for population subgroups.

Participants in the HALO-EM trial were aged between 18 and 70 years, with a mean age of between 41.1 – 42.9 (SD 11.4 – 12.7) across trial arms. The majority of participants (84.8%, 742/875) were female, and had been diagnosed with migraines between one and 65 years prior to the trial (mean 19.9 – 20.7; SD 11.9 – 12.9). The line of treatment of participants in the trial was not reported in the CS, although at clarification the company submitted that 21.3% (186/875) of participants in the trial had previously received between one and three preventative therapies, which may include OBA or topiramate. The CS reported that 19.2% (168/875) of participants had previously received topiramate. The CS further reported that 20.8% (182/875) of participants were receiving another preventative therapy for migraine in the run-up period to the trial. Evidence from the trial CSR[38] (p. 99) suggests that most of these participants continued their preventative therapy during the main trial ([redacted]).

Assessment of disease severity at baseline, as reported in the CS, was based on participants' reports during the run-in phase of the trial (28 days). During this period participants reported a mean of 8.9 – 9.2 migraine days (range 3 – 17; SD 2.6 – 2.7), and a mean of 6.8 – 7.2 moderate or severe headache days (range 0 – 16; SD 2.9 – 3.1). Participants reported using acute headache medication on 7.7 – 7.8 days (range 0 – 16; SD 3.4 – 3.7), and acute migraine-specific medications on 6.1 – 7.1 days (range 1 – 14; SD 3.0 – 3.1). Mean migraine disability assessment scores ranged between 37.3 – 41.7 across arms (range 0 – 306; SD 27.6 – 33.2). Typically MIDAS scores are not reported as a total, but rather are averaged over the 5 items for each respondent[41]. Averaging this mean total score would correspond to a severity rating of 7.5 – 8.3, which would correspond with mild disability (Grade II).

Generally participant characteristics at baseline were similar across trial arms except for one outcome, where the mean number of acute migraine-specific headache medications received by participants during the run-in phase were significantly higher in the placebo arm than in the monthly fremanezumab arm (7.1 [SD 3.0] vs. 6.1 [SD 3.1]; p <.01). There was no significant difference between quarterly fremanezumab and placebo (6.6 [SD 3.1] vs. 7.1 [SD 3.0]; p=0.17) or quarterly and monthly fremanezumab (6.6 [SD 3.1] vs. 6.1 [SD 3.1];

p=0.16). This outcome was only reported for half (437/875, 49.9%) of all participants, however the CS does not provide an explanation for the missing data.

Table 13: Baseline Characteristics of Patients Included in HALO-EM

HALO EM Baseline characteristic	Placebo (n=294)	Fremanezumab quarterly (n=291)	Fremanezumab monthly (n=290)
Age, years			
Mean (SD)	41.3 (12.0)	41.1 (11.4)	42.9 (12.7)
Median (range)	41.0 (18-70)	42.0 (18-69)	43.0 (18-70)
Sex, n (%)			
Male	47 (16)	40 (14)	46 (16)
Female	247 (84)	251 (86)	244 (84)
Weight, kg			
Mean (SD)	75.3 (16.0)	74.2 (15.4)	72.1 (15.8)
Median (range)	74.3 (43-118)	73.0 (45-120)	69.3 (45-119)
Time since initial migraine diagnosis, years			
Mean (SD)	19.9 (11.9)	20.0 (12.1)	20.7 (12.9)
Median (range)	17.5 (1-51)	19.0 (1-65)	19.0 (0-58)
Preventive medication use during run-in period, n (%)			
Yes	62 (21)	58 (20)	62 (21)
No	232 (79)	233 (80)	228 (79)
Previous topiramate use for migraine, n (%)			
Yes	53 (18)	51 (18)	64 (22)
No	241 (82)	240 (82)	226 (78)
Number of headache days of at least moderate severity during run-in period			
N	293	291	288
Mean (SD)	6.9 (3.1)	7.2 (3.1)	6.8 (2.9)
Median (range)	7.0 (0-15)	7.0 (0-16)	6.5 (0-15)
Number of migraine days during run-in period			
N	293	291	288
Mean (SD)	9.1 (2.7)	9.3 (2.7)	8.9 (2.6)
Median (range)	9.0 (4-15)	9.0 (4-17)	9.0 (3-16)
Number of days of use of any acute headache medications during run-in period			
N	293	291	288
Mean (SD)	7.7 (3.6)	7.8 (3.7)	7.7 (3.4)
Median (range)	8.0 (0-15)	8.0 (0-16)	7.7 (0-15)
Number of days of use of migraine-specific acute headache medications during run-in period			
N	137	152	148
Mean (SD)	7.1 (3.0)	6.6 (3.1)	6.1 (3.1)
Median (range)	7.0 (1-14)	7.0 (1-14)	6.0 (1-14)

HALO EM Baseline characteristic	Placebo (n=294)	Fremanezumab quarterly (n=291)	Fremanezumab monthly (n=290)
Migraine Disability Assessment (MIDAS) total score			
N	290	287	287
Mean (SD)	37.3 (27.6)	41.7 (33.0)	38.0 (33.2)
Median (range)	32.5 (0-156)	33.0 (0-206)	33.0 (0-306)

Abbreviations: EM, episodic migraine; kg, kilogram; MIDAS, migraine disability assessment; SD, standard deviation.

ERG comment:

Overall, a limited number of population characteristics are reported for participants in HALO-EM at baseline. However, the ERG considered that these characteristics represented most of the key prognostic markers for this population.

According to their mean MIDAS score from the lead-in phase, overall participants experienced mild disability from their migraine. The data indicates some variation in the severity of migraine across the sample at baseline; participants reported a range of three to 17 migraine days in the lead-in phase, and a range of 0 to 16 headache days of at least moderate severity.

Generally population characteristics reported were consistent between arms, except for one outcome, which indicated that participants in the placebo arm were receiving more migraine-specific acute medications in the lead-in period than participants in both of the fremanezumab arms; though this difference was only statistically significant for patients in the monthly fremanezumab arm.

No baseline characteristics were reported for participants included in subgroups analysed in the trial. In particular, the ERG considered that baseline outcome data should have been reported for subgroups, to aid comparability of groups and interpretation of the data.

4.2.4.1.2 Clinical Outcomes

Clinical outcomes for the HALO-EM trial are reported in Table 14, Table 16, and Figure 2. All data reported is based on the full analysis set (FAS; see Table 10). At clarification, the company provided outcome data based on an ITT analysis; these data were consistent with the FAS set.

The data showed that participants in all three trial arms exhibit a reduction in mean monthly migraine days (MMDs) at 12 weeks. The reduction in MMDs was greater for participants receiving fremanezumab quarterly or monthly than for those receiving placebo. Both monthly and quarterly fremanezumab arms of the trial demonstrated a statistically significant

difference in mean monthly migraine days at 12 weeks compared to placebo; at a LSM difference of -1.5 (95% CI -2.01 to -0.93) for monthly fremanezumab and -1.3 (95% CI -1.79 to -0.72) for quarterly fremanezumab, both as compared to placebo.

The company reported that the MMRM sensitivity analysis also showed that fremanezumab was associated with a greater reduction in MMDs during the full 12 weeks. Data from this analysis is provided up to 4 weeks only in the CS, in Figure 2 and Table 15. Figure 2 displays reductions in MMDs across the three trial arms between baseline and four weeks, and shows that the difference in MMDs between the fremanezumab arms and placebo is statistically significant at one week from baseline, and remains statistically significant up until four weeks. Interestingly, while the reductions in MMDs seen in the fremanezumab arms remain relatively stable across the four weeks, MMDs continue to reduce for participants in the placebo arm. As this data was not provided it was not possible for the ERG to view the pattern of response to treatments between four and 12 weeks.

More participants receiving fremanezumab exhibited a ≥50% reduction in monthly migraine days at 12 weeks than those receiving placebo: 47.7% and 44.4% of those receiving monthly and quarterly fremanezumab, respectively, exhibited a ≥50% reduction compared to 27.9% of those receiving placebo. As seen in Table 16, the difference in the number of participants exhibiting a ≥50% reduction in migraine days between fremanezumab and placebo was statistically significant at one, two, and three months' follow-up. However, interestingly, while the proportion of participants with a ≥50% reduction in migraine days was consistently higher in the fremanezumab arm, a sizeable minority of participants in the placebo arm also exhibited a ≥50% reduction at all three timepoints; reaching a peak of 37.2% of participants at 3 months. The company further reported that the proportion of participants exhibiting a cumulative reduction of 75% of migraine days was also higher for participants receiving fremanezumab (25.8% of quarterly and 27.2" of monthly fremanezumab participants) than placebo (15.4%).

Participants in all three arms of the trial reported a reduction in mean monthly days in the use of acute headache medication at 12 weeks. This reduction was greater for participants receiving fremanezumab than those receiving placebo (a LSM difference of -1.3 and -1.4 days compared to placebo for participants in the quarterly and monthly arms, respectively).

The company reported incomplete data for the change in mean monthly headache days of at least moderate severity, and for the change in mean monthly hours of headache of at least moderate severity. The absolute change in each outcome across trial arms is not reported, but the company state that there was a statistically significant reduction in both fremanezumab arms as compared to placebo.

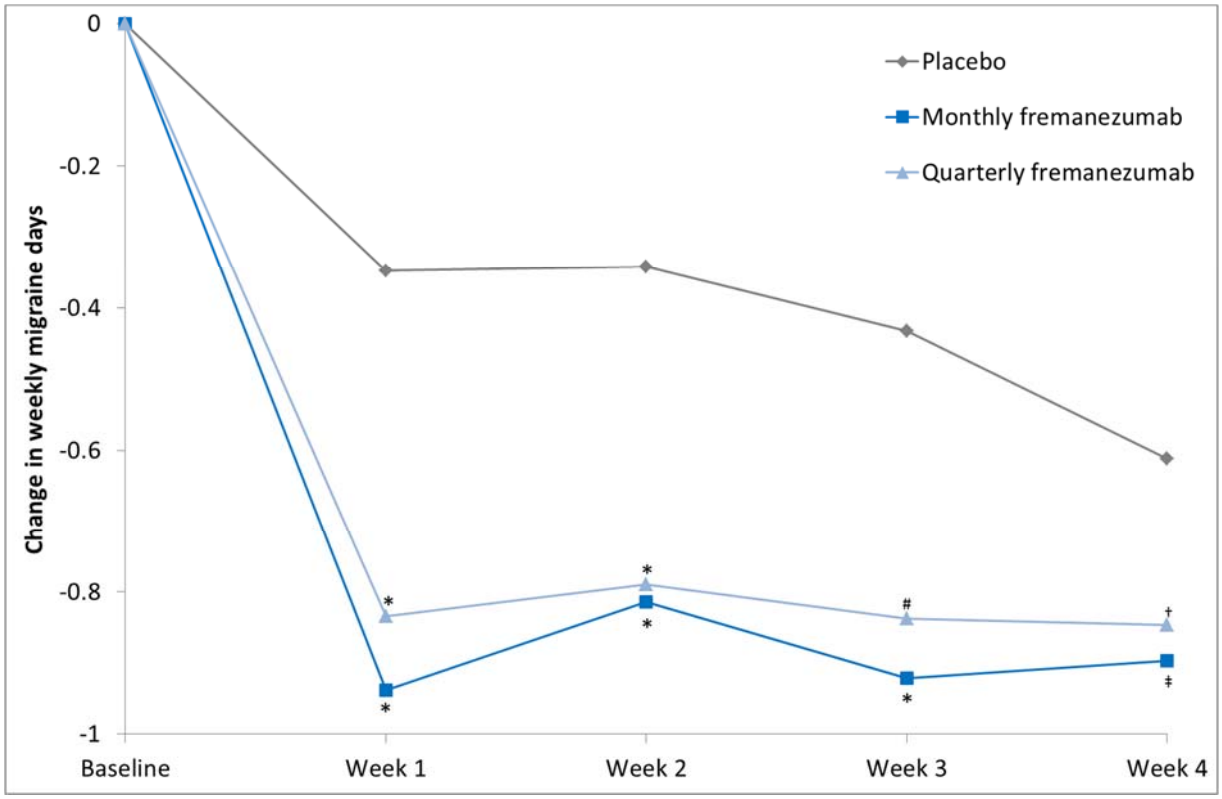
Finally, in terms of adherence, only a small minority of participants in the trial were reported to be non-compliant with treatment (1% of quarterly fremanezumab participants, and 2% of both placebo and fremanezumab monthly participants).

Table 14: HALO EM Main Efficacy Outcomes

	Placebo (n=290)	Fremanezumab quarterly (n=288)	Fremanezumab monthly (n=287)
MMDs			
Baseline (SD)	9.1 (2.7)	9.3 (2.7)	8.9 (2.6)
Median change (IQR)	2.7 (-4.7 to -0.5)	-4.0 (-6.4 to -1.9)	-4.2 (-6.2 to -2.0)
LSM change (95% CI)	-2.2 (-2.68 to -1.71)	-3.4 (-3.94 to -2.96)	-3.7 (-4.15 to -3.18)
Difference vs placebo (95% CI)		-1.3 (-1.79 to -0.72)	-1.5 (-2.01 to -0.93)
P-value vs placebo		<0.0001	<0.0001
Patients with at least 50% reduction in MMDs			
Number achieving endpoint (%)	81 (27.9%)	128 (44.4%)	137 (47.7%)
Difference vs placebo (%; 95% CI)		16.5 (8.9 to 24.1)	19.8 (12.0 to 27.6)
P-value vs placebo		<0.0001	<0.0001
Mean monthly days of use of any acute headache medication			
Baseline (SD)	7.7 (3.6)	7.8 (3.7)	7.7 (3.4)
Median (IQR)	-1.7 (-4.0 to 0.0)	-3.0 (-5.6 to -0.8)	-3.2 (-5.2 to -1.2)
LSM change (95% CI)	-1.6 (-2.04 to -1.20)	-2.9 (-3.34 to -2.48)	-3.0 (-3.41 to -2.56)
Difference vs placebo (95% CI)		-1.3 (-1.76 to -0.82)	-1.4 (-1.84 to -0.89)
P-value vs placebo		<0.0001	<0.0001
Mean change in monthly average number of headache days of at least moderate severity			
Baseline	6.9 (3.1)	7.2 (3.1)	6.8 (2.9)
LSM difference vs placebo (95% CI)	-	-1.5 (-1.96 to -1.04)	-1.5 (-1.92 to -0.99)
P-value vs placebo		<0.0001	<0.0001
Mean change in monthly average headache hours of any severity			
Baseline	NR	NR	NR
LSM difference vs placebo (95% CI)		-8.8 (-13.28 to -4.32)	-12.5 (-16.99 to -8.03)
P-value vs placebo		0.0001	<0.0001

Abbreviations: CI, confidence interval; EM, episodic migraine; IQR, interquartile range; LSM, least squares mean; MMDs, mean monthly migraine days; NR, not reported; SD, standard deviation; vs, versus.
Source: CS, Table 14, p. 50 – 51; p. 55.

Figure 2: HALO EM Change in weekly migraine days over time (MMRM analysis)



Abbreviations: EM, episodic migraine; MMRM, mixed-effects, repeated-measures.
Notes: * p<0.0001; #p=0.0003; †p=0.04; ‡p=0.01 vs placebo.
Source: CS, p. 53.

Table 15: HALO EM Change in weekly migraine days over time (MMRM analysis)

Visit	Category	Statistic	Placebo	Quarterly fremanezumab	Monthly fremanezumab
Week 1	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 2	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 3	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]
Week 4	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]	[redacted]
		95% CI		[redacted]	[redacted]
		p-Value		[redacted]	[redacted]

Abbreviations: CI: confidence interval; EM, episodic migraine; MMRM, mixed-effects, repeated-measures; SE: standard error; vs: versus.
Source: Clarification question A25.

Table 16: HALO EM Proportion of patients with 50% or greater reduction in MMDs

Time point statistic	Placebo N/n (%)	Fremanezumab quarterly N/n (%)	p-value quarterly *vs* placebo	Fremanezumab monthly N/n (%)	p-value monthly *vs* placebo
Month 1	73/290 (25.2)	127/288 (44.1)	<0.0001	135/287 (47.0)	<0.0001
Month 2	101/274 (34.8)	135/274 (46.9)	0.0032	139/274 (48.4)	0.0010
Month 3	108/268 (37.2)	141/269 (49.0)	0.0048	147/263 (51.2)	0.0003
Overall	81/290 (27.9)	128/288 (44.4)	<0.0001	137/287 (47.7)	<0.0001

Abbreviations: EM, episodic migraine; MMDs, mean monthly migraine days; vs: versus.
Source: CS, p.52

ERG comment:

Overall, the data indicated a consistent clinical benefit of fremanezumab across all reported outcomes as compared to placebo. The data showed that an additional 16.5% and 19.8% of participants receiving quarterly and monthly fremanezumab, respectively, experienced a ≥50% reduction in migraine days compared to placebo. Clinical advice to the ERG is that this difference is clinically meaningful. Moreover, participants receiving fremanezumab exhibited an absolute LSM reduction in MMDs of -3.4 (quarterly) and -3.7 (monthly) compared to -2.2 exhibited by participants receiving placebo. The reductions in the fremanezumab arms are greater than 30% of mean baseline MMDs, which clinical advice to the ERG suggests would be clinically meaningful, while the absolute reduction in the placebo arm is below this threshold. However, the relative difference in the reduction of MMDs between fremanezumab and placebo was reported to be 1.3 and 1.5 fewer days for participants receiving fremanezumab quarterly and monthly, respectively. This difference is smaller than the 30% threshold advised by expert clinical advice to the ERG, and therefore suggests that there was no clinically meaningful difference between fremanezumab and placebo. The ERG noted that there is some uncertainty in the size of all reported effects; it was noted that upper and lower 95% confidence intervals are all consistent with either a clinical benefit for fremanezumab or no clinical difference between fremanezumab and placebo (i.e. no clinical harm).

While the data demonstrated a consistent benefit for fremanezumab over placebo, and absolute improvements in the fremanezumab arms were considered to be clinically meaningful, the ERG were concerned by the improvements in all outcomes for participants in the placebo arm of the trial. These improvements in the placebo arm were all statistically significant changes from baseline, and clinical advice to the ERG is that these improvements were greater than natural variation in disease severity. The CS does not include discussion

of why the placebo arm in HALO-EM performed so well; for example if this may be due to the trial design or the care received by participants in the placebo arm. In addition, the ERG considered it possible that background care, for example the use of concomitant preventative therapies for migraine used by participants in all trial arms, may also have influenced the findings. While these effects would be likely to affect all trial arms similarly, and therefore would not undermine the relative effect data reported, these issues would impact on the absolute outcome data (for example the final mean MMDs in each arm). As such, the ERG considered that the absolute trial data should be interpreted with caution.

4.2.4.1.3 Subgroup Analyses

The results of pre-planned subgroup analyses for HALO-EM are reported in Table 17.

The data shows that reductions in mean monthly migraine days (MMDs) and mean headache days of at least moderate severity were exhibited by participants across all three arms and all subgroups. Reductions in MMDs ranged between -2.0 to -2.8 for placebo, and between -2.0 to -3.9 for fremanezumab. Reductions in monthly headache days of at least moderate severity ranged between -1.3 to -2.1 for placebo and -2.2 to -3.3 for fremanezumab.

As compared to placebo, fremanezumab quarterly and fremanezumab monthly were associated with larger numerical reductions in MMDs. Across all subgroups, the mean reduction ranged between -0.9 to -2.0 for MMDs and -0.9 to -1.7 for monthly headache days of at least moderate severity. These ranges do not include mean values reported for prior topiramate, which have been excluded due to the lack of variance data and the risk of reporting bias. Differences in MMDs and monthly headache days of at least moderate severity as compared to placebo were statistically significant for all subgroups, with the exception of analyses conducted in males and in non-Caucasian participants.

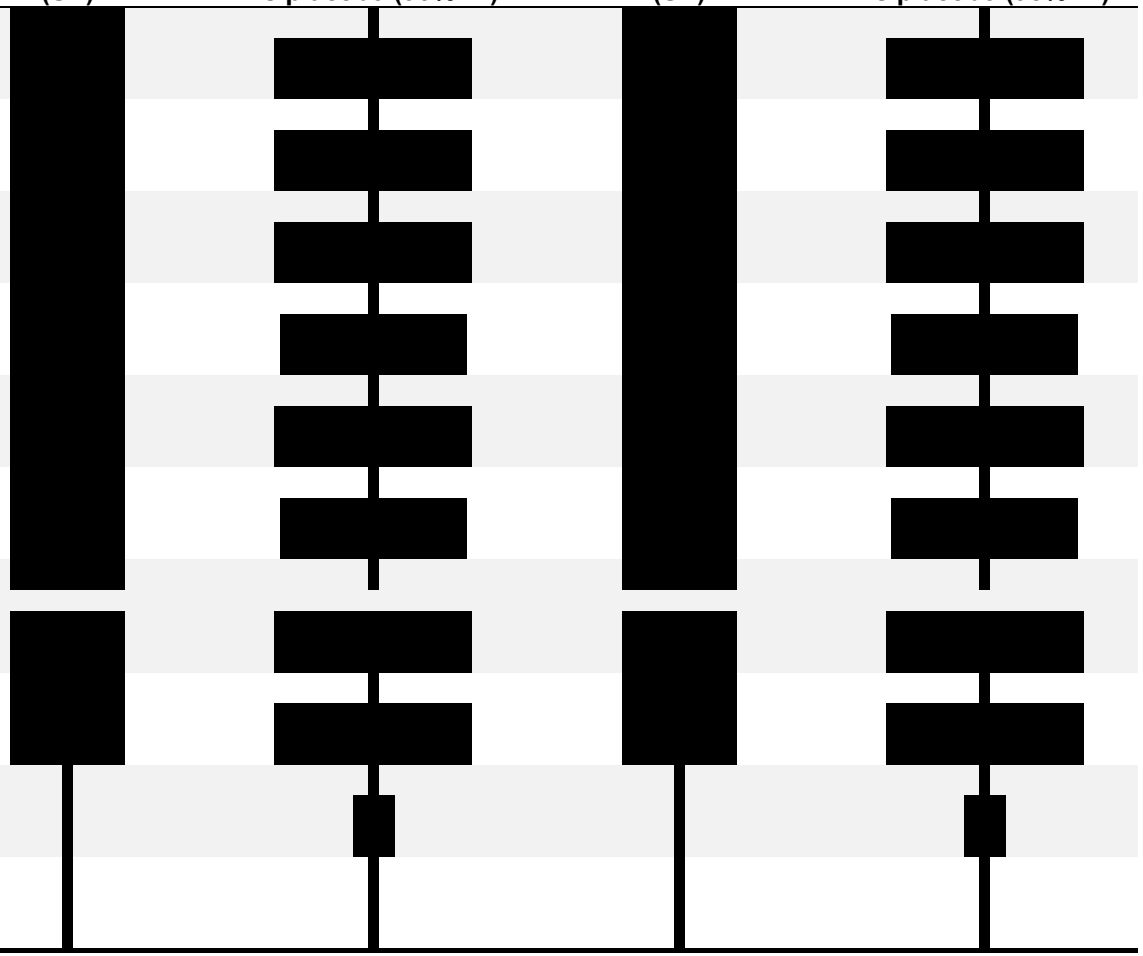
The CS does not report the outcomes of any statistical tests to evaluate whether the effect of fremanezumab varies between different subgroups. Based on the data reported, it was not possible for the ERG to conduct these analyses; however the numbers suggest that there may be a differential effect in adults over >45 years (compared to ≤45 years) and in participants receiving concomitant preventative therapies (compared to not). While the effect of fremanezumab is similar between monthly and quarterly administrations across all other subgroups, in adults over the age of 45 the effect is slightly larger for monthly fremanezumab for both outcomes. The data also suggests that the relative effect of fremanezumab for both outcomes may be smaller in participants who are not receiving concomitant preventative

therapy: a mean of -1.1 to -1.3 compared to -1.8 to -2.0, for those not receiving and receiving concomitant therapy, respectively.

Data were not reported in the CS for two of the planned subgroups: prior topiramate and prior OBA use. A footnote to the table explains that this was because the sample size for each was too small to perform the analysis; however, this explanation is inconsistent with the sample sizes reported for other reported subgroups. Further, as an adjusted (LSM) treatment difference without 95% confidence intervals for prior topiramate use was reported in the table, this suggests that this analysis was conducted and not reported. At clarification, the company provided a subgroup analysis that included participants who had previously used topiramate, OBA and/or another preventative treatment, for the outcome of the change from baseline in monthly average number of headache days of at least moderate severity. The results of this analysis are presented in Table 18, and appear to show a larger effect of fremanezumab on headache days than in the main trial population. As the company did not provide any further outcome data, it was not possible for the ERG to determine whether this was a trend across all outcomes.

Table 17: HALO EM Pre-planned Subgroup Analyses

			MMDs		Monthly headache days of at least moderate severity	
Subgroup	**Treatment group**	**n**	**Least squares mean (SE)**	**Treatment difference *vs* placebo (95% CI)**	**Least squares mean (SE)**	**Treatment difference *vs* placebo (95% CI)**
18 to 45 years	Placebo	181				
	Quarterly frem	175				
	Monthly frem	160				
>45 years	Placebo	109				
	Quarterly frem	113				
	Monthly frem	127				
Caucasian	Placebo	222				
	Quarterly frem	231				
	Monthly frem	240				
Non-Caucasian	Placebo	68				
	Quarterly frem	57				
	Monthly frem	47				
Female	Placebo	244				
	Quarterly frem	249				
	Monthly frem	242				
Male	Placebo	46				
	Quarterly frem	39				
	Monthly frem	45				
Concomitant preventive treatment	Placebo	60				
	Quarterly frem	58				
	Monthly frem	62				
No concomitant preventive treatment	Placebo	230				
	Quarterly frem	230				
	Monthly frem	225				
Prior topiramate*	Placebo	53				
	Quarterly frem	51				
	Monthly frem	64				
Prior OBA*	Placebo	8				
	Quarterly frem	15				
	Monthly frem	16				



Abbreviations: CI: confidence interval; EM, episodic migraine; frem: fremanezumab; MMDs, mean monthly migraine days; OBA, onabotulinum toxin A; SE: standard error.
Note: *The CS states that due to small patient numbers these analysis could not be conducted.
Source: CS, Appendix E; p. 4-5.

Table 18: HALO-EM Change from baseline in monthly average number of headache days of at least moderate severity in participants who have previously used topiramate, OBA, and/or another preventative therapy (ANCOVA)

Category	Statistic	Placebo (N=[redacted])	Quarterly fremanezumab (N=[redacted])	Monthly fremanezumab (N=[redacted])
Individual treatment group	Least squares means (SE)	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]
Difference (*vs.* Placebo)	Least squares means (SE)		[redacted]	[redacted]
	95% CI		[redacted]	[redacted]
	p-value		[redacted]	[redacted]

Abbreviations: CI: confidence interval; EM, episodic migraine; OBA, onabotulinum toxin A; SE: standard error.

ERG comment:

Subgroup analyses for HALO-EM demonstrated a consistent benefit of fremanezumab monthly and quarterly compared to placebo for both mean monthly migraine days and mean headache days of at least moderate severity. This difference was statistically significant across most subgroups. No statistical tests were reported in the CS to compare the effect of fremanezumab with placebo between subgroups; however the ERG noted that the effect of fremanezumab as compared to placebo appeared greater for participants receiving concomitant preventative therapy compared to those who were not. Further differences between subgroups noted were considered to likely be random, as clinical advice to the ERG is that there is no known clinical rationale for these differences. Across all subgroups, there was large variation in the effect of fremanezumab compared to placebo, with the difference in MMDs ranging between approximately 50% - 100%. Participants in the placebo arm across all subgroups also demonstrated improvements across both outcomes.

4.2.4.1.4 Quality of life and patient reported outcomes (PRO)

Quality of life and PRO are reported in Table 19. MSQoL was the company's chosen method for evaluating HRQoL in this population, however while it was evaluated in the HALO-EM trial, the data is not reported in the CS. Rather, the company reported a qualitative summary of the data (CS, p. 55) stating that 'differences' from placebo were demonstrated for fremanezumab across the three domains. The company go on to state that LSM differences for role function – restrictive were statistically significant (p<.01). LSM differences with placebo were reported (4.1 for quarterly and 7.0 for monthly), which are both above the recommended MID of 3.2[34]; however no accompanying variance data were reported. Mean values for the other domains were not reported and it's unclear whether the differences stated in these domains were above the scale MID or statistically significant.

MIDAS data was reported, which showed that participants in the placebo and fremanezumab arms all exhibited improvements, indicating reductions in the impact of migraines on their everyday functioning. All three trial arms also demonstrated improvements in EQ-5D VAS (data identified from the trial CSR), which indicates overall improvements in HRQoL. Fremanezumab was associated with a statistically significant greater improvement in MIDAS scores compared to placebo (a difference of -5.4 and -7.0 for fremanezumab quarterly and monthly, respectively). However, there was no statistically significant difference in EQ-5D VAS scores between placebo and either of the fremanezumab arms.

Table 19: HALO EM quality of life and PRO

	Placebo (n=290)	Fremanezumab quarterly (n=288)	Fremanezumab monthly (n=287)
Migraine Disability Assessment Score (MIDAS; possible scale 0-450; lower is better outcome)			
Baseline (SD)	37.3 (27.6)	41.7 (33.0)	38.0 (33.2)
LSM change (95% CI)	-17.5 (-20.62 to -14.47)	-23.0 (-26.10 to -19.82)	-24.6 (-27.68 to -21.45)
Difference vs placebo (95% CI)		-5.4 (-8.90 to -1.93)	-7.0 (-10.51 to -3.53)
P-value vs placebo		<0.0001	<0.0001
EQ-5D VAS (0-100; higher is better outcome)			
Baseline (SD)*	NR	NR	NR
LSM mean (95% CI)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]

Abbreviations: CI, confidence interval; EM, episodic migraine; LSM, least squares mean; MIDAS, migraine disability assessment; NR, not reported; PRO, patient reported outcomes; SD, standard deviation; VAS, visual analogue scale.
Notes: *Baseline EQ-5D scores were reported in an appendix to the trial CSR[38], which was not provided to the ERG.
Source: CS, p. 51; EQ-5D data was identified from the trial CSR.

ERG comment:

The ERG were concerned that data for HRQoL, as evaluated using the company's chosen method of assessment, was incompletely reported in the CS. The ERG considered that this may indicate reporting bias in the CS. Based on the data reported, participants receiving fremanezumab or placebo all experienced improvements in HRQoL at 12 weeks, as evaluated by the MSQoL and EQ-5D. It appears that fremanezumab may improve HRQoL and have a clinically meaningful benefit for the impact of migraines on daily functioning compared to placebo, as evaluated using the MIDAS. However there is some uncertainty about the size and statistical significance of differences evaluated using the MSQoL. Further, the ERG were not able to identify a MID for the MIDAS scale, and therefore it's unclear whether differences reported reflect a clinically meaningful change for participants.

4.2.4.2 HALO CM

4.2.4.2.1 Baseline characteristics

The baseline characteristics of participants included in the HALO-CM trial are reported in Table 20. Baseline characteristics were not reported for population subgroups.

Participants in the HALO-CM trial were aged between 18 and 71 years, with a mean age of between 40.6 – 42.0 years (SD 12.0 – 12.4). The majority of participants (87.7%, 991/1130)

were female, and had been diagnosed with migraines between one and 61 years prior to the trial (mean 19.7 – 20.1; SD 12.0 – 12.9). The line of treatment of participants in the trial was not reported in the CS, although at clarification the company submitted that 35.3% (399/1130) of participants in the trial had previously received between one and three preventative therapies, which may include OBA or topiramate. Topiramate was commonly used amongst these patients: the CS reports that (21.2%, 239/1130) of participants had previously received topiramate. The CS further reports that 31.1% (340/1130) of participants were receiving another preventative therapy for migraine in the run-up period to the trial. Evidence from the trial CSR[39] (p. 111) suggests that the majority of these participants continued their preventative therapy during the main trial ([redacted]).

Assessment of disease severity at baseline, as reported in the CS, was based on participant reports during the lead-in phase of the trial (28 days). Participants reported a mean of 16.0 – 16.7 migraine days (range 5 – 28; SD 4.9 – 5.2) and a mean of 12.8 – 13.3 moderately severe or severe headache days (range 0 – 28; SD 5.5 – 5.8). Participants reported using acute headache medication on 13.0 – 13.1 days (range 0 - 28; SD 6.8 – 7.2), and acute migraine-specific medications on 10.7 – 11.3 days (range 1 – 28; SD 6.0 – 6.3). Mean HIT-6 scores ranged between 64.1 – 64.6 (range 42 - 78; SD 4.4 – 4.8), indicating a mean score in the severe impact category for all trial arms.

Participant characteristics at baseline were similar across trial arms, with no significant differences between trial arms.

Table 20: Baseline Characteristics of Patients Included in HALO-CM

HALO CM Baseline characteristic	Placebo (n=375)	Fremanezumab quarterly (n=376)	Fremanezumab monthly (n=379)
Age, years			
Mean (SD)	41.4 (12.0)	42.0 (12.4)	40.6 (12.0)
Median (range)	41.0 (19-70)	43.0 (18-71)	40.0 (18-70)
Sex, n (%)			
Male	45 (12)	45 (12)	49 (13)
Female	330 (88)	331 (88)	330 (87)
Weight, kg			
Mean (SD)	72.6 (15.6)	72.4 (15.8)	72.5 (16.4)
Median (range)	71.2 (45-119)	70.5 (45-132)	69.8 (44-119)
Time since initial migraine diagnosis, years			
Mean (SD)	19.9 (12.9)	19.7 (12.8)	20.1 (12.0)
Median (range)	17.0 (1-57)	18.0 (1-61)	18.0 (1-55)
Preventive medication use during run-in period, n (%)			

HALO CM Baseline characteristic	Placebo (n=375)	Fremanezumab quarterly (n=376)	Fremanezumab monthly (n=379)
Yes	77 (21)	77 (20)	85 (22)
No	298 (79)	299 (80)	294 (78)
Previous topiramate use for migraine, n (%)			
Yes	117 (31)	106 (28)	117 (31)
No	258 (69)	270 (72)	262 (69)
Previous OBA use for migraine, n (%)			
Yes	49 (13)	66 (18)	50 (13)
No	326 (87)	310 (82)	329 (87)
Any acute headache medication use during run-in period, n (%)			
Yes	358 (95)	359 (95)	360 (95)
No	17 (5)	17 (5)	19 (5)
Total number of headache days of any duration and any severity during run-in period			
Mean (SD)	20.3 (4.2)	20.4 (3.9)	20.3 (4.3)
Median (range)	19.3 (11-28)	20.0 (13-28)	19.0 (8-28)
Number of headache days of at least moderate severity during run-in period			
Mean (SD)	13.3 (5.8)	13.2 (5.5)	12.8 (5.8)
Median (range)	12.6 (0-28)	13.0 (1-28)	12.0 (0-28)
Number of migraine days during run-in period			
Mean (SD)	16.4 (5.2)	16.2 (4.9)	16.0 (5.2)
Median (range)	15.5 (7-28)	15.9 (7-28)	15.4 (5-28)
Number of days of use of any acute headache medications during run-in period			
Mean (SD)	13.0 (6.9)	13.1 (6.8)	13.1 (7.2)
Median (range)	13.5 (0-28)	14.0 (0-28)	13.6 (0-28)
Number of days of use of migraine-specific acute headache medications during run-in period			
N	192	208	187
Mean (SD)	10.7 (6.3)	11.3 (6.2)	11.1 (6.0)
Median (range)	10.0 (1-28)	11.0 (1-28)	10.3 (1-27)
Headache Impact Test (HIT-6) Disability score			
N	373	370	377
Mean (SD)	64.1 (4.8)	64.3 (4.7)	64.6 (4.4)
Median (min, max)	64.0 (48-78)	65.0 (42-78)	64.0 (50-78)

Key: CM, chronic migraine; kg, kilogram; HIT-6, six-item headache impact test; OBA, onabotulinum toxin A; SD: standard deviation.
Source: CS p. 35-36

ERG comment:

Overall, a limited number of baseline characteristics are reported for participants in HALO-CM at baseline. However, the ERG considered that these characteristics represented most of the key prognostic markers for this population. The data indicated that participants varied

widely in the severity of migraine at baseline; participants reported a range of 5 to 28 migraine days in the lead-in phase, and a range of 0 to 28 headache days of at least moderate severity. Similarly, there was a wide range in the use of medications during the lead-in phase, which ranged between 0 and 28 days for acute medication, and 1 and 28 for migraine specific acute medications. According to their mean HIT-6 score from the lead-in phase, overall participants experienced severe disability from their migraine.

There were no significant differences between trial arms in population characteristics reported at baseline. No baseline characteristics were reported for participants included in subgroups analysed in the trial. In particular, the ERG considered that baseline outcome data should have been reported for subgroups, to aid comparability of groups and interpretation of the data.

4.2.4.2.2 Clinical Outcomes

Clinical outcomes for participants in the HALO-CM trial are reported in Table 21 and in Figure 3. All data reported are based on the full analysis set (FAS; see Table 10). At clarification, the company provided outcome data based on an ITT analysis; these data were consistent with the FAS set.

The data showed a reduction in mean monthly migraine days (MMDs) at 12 weeks in all three trial arms, although the reduction was greater for those participants receiving fremanezumab (LSM change: quarterly -4.9 days (95%CI -5.59 to -4.20); monthly -5.0 (95%CI -5.70 to -4.33)) than those receiving placebo (LSM change: -3.2 (95%CI -3.86 to -2.47)). The mean reduction in MMDs was statistically significantly greater for both monthly and quarterly fremanezumab arms as compared to placebo; LSM difference of -1.8 days (95% CI -2.61 to -1.09) for participants receiving monthly fremanezumab and -1.7 days (95% CI -2.48 to -0.97) for participants receiving quarterly fremanezumab.

As in HALO-EM, the company reported the results of a MMRM sensitivity analysis of MMDs at 12 weeks, although in this analysis they appear to have merged fremanezumab trial arms, and only report data to four weeks (Figure 3 and Table 22). It is unclear why this is the case. The data provided showed that the difference in MMDs between the fremanezumab arms and placebo is statistically significant at one week from baseline, and remains statistically significant up until four weeks. As with HALO-EM, the reduction in MMDs in the fremanezumab arms remained relatively stable across the four weeks, while MMDs appear to reduce for participants in the placebo arm, thus reducing the LSM difference between placebo and fremanezumab at four weeks.As these reductions are below the LSM differences in MMDs reported at 12-weeks, this suggests that MMDs in all three arms

continue to reduce after four weeks, but as this data was not provided it was not possible for the ERG to view the pattern of response to treatments between four and 12 weeks.,

More participants receiving fremanezumab also exhibited a ≥50% reduction in mean monthly migraine days at 12 weeks than placebo: 33.3% and 30.7% of those receiving monthly and quarterly fremanezumab, respectively, exhibited a ≥50% reduction compared to 19.9% of those receiving placebo. Unlike participants in the HALO-EM trial, the difference in the number of participants exhibiting a ≥50% reduction in migraine days between fremanezumab and placebo was not reported separately at one, two, and three months' follow-up. Similarly, the CS does not report the proportion of participants exhibiting a ≥75% reduction in migraine days.

Participants in all three arms of the trial also exhibited a reduction in mean monthly days of use of acute headache medication at 12 weeks, which was statistically significantly greater for participants receiving fremanezumab as compared to placebo (LSM difference of -1.8 and -2.3 days compared to placebo for participants in the quarterly and monthly arms, respectively).

All three trial arms also demonstrated a reduction in mean monthly headache days of at least moderate severity at 12 weeks: this was a difference of -4.3 days for fremanezumab quarterly, -4.6 days for fremanezumab monthly, and -2.5 days for placebo. The reduction was statistically significantly greater than placebo for both fremanezumab quarterly (LSM difference -1.8, 95%CI -2.46 to -1.15) and monthly (-2.1, 95%CI -2.76 to -1.45).

The CS also partially reported data for a reduction in the monthly average number of headache hours. The LSM difference in the number of headache hours of any severity was -13.7 headache hours (95% CI -21.10 to -6.31) for quarterly fremanezumab and 18.6 headache hours (95% CI -25.96 to -11.17) for monthly fremanezumab.

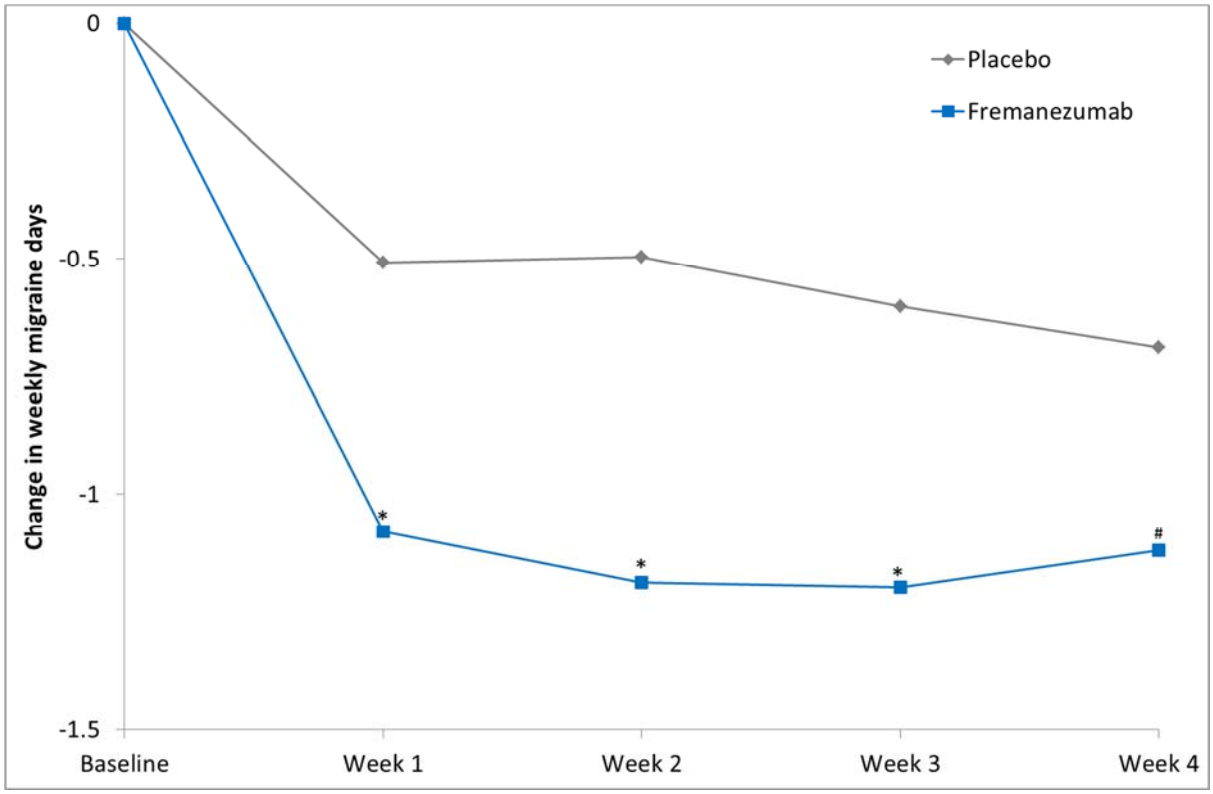
Finally, in terms of adherence, only a small minority of participants in the trial were reported to be non-compliant with treatment (0.5% of quarterly fremanezumab participants, 1.6% of monthly fremanezumab participants, and 2.1% of placebo participants).

Table 21: HALO CM Main Efficacy Outcomes

	Placebo (n=371)	Fremanezumab quarterly (n=375)	Fremanezumab monthly (n=375)
Mean monthly headache days of at least moderate severity			
Baseline (SD)	13.3 (5.8)	13.2 (5.5)	12.8 (5.8)
LSM change (95% CI)	-2.5 (-3.06 to -1.85)	-4.3 (-4.87 to -3.66)	-4.6 (-5.16 to -3.97)
Difference vs placebo (95% CI)		-1.8 (-2.46 to -1.15)	-2.1 (-2.76 to -1.45)
P-value vs placebo		<0.0001	<0.0001
MMDs			
Baseline (SD)	16.4 (5.2)	16.2 (4.9)	16.0 (5.2)
LSM change (95% CI)	-3.2 (-3.86 to -2.47)	-4.9 (-5.59 to -4.20)	-5.0 (-5.70 to -4.33)
Difference vs placebo (95% CI)		-1.7 (-2.48 to -0.97)	-1.8 (-2.61 to -1.09)
P-value vs placebo		<0.0001	<0.0001
Patients with at least 50% reduction in MMDs			
Number achieving endpoint (%)	74 (19.9%)	115 (30.7%)	125 (33.3%)
P-value vs placebo		0.0008	<0.0001
Mean monthly days of use of any acute headache medication			
Baseline (SD)	13.0 (6.9)	13.1 (6.8)	13.1 (7.2)
LSM change (95% CI)	-1.9 (-2.48 to -1.28)	-3.7 (-4.25 to -3.06)	-4.2 (-4.79 to -3.61)
Difference vs placebo (95% CI)		-1.8 (-2.43 to -1.12)	-2.3 (-2.97 to -1.67)
P-value vs placebo		<0.0001	<0.0001

Key: CI, confidence interval; CM, chronic migraine; LSM: least squares mean; MMDs, mean monthly migraine days; SD: standard deviation; vs; versus.
Source: CS. P. 56-57

Figure 3: HALO CM Change in weekly migraine days over time (MMRM analysis)



Key: CM, chronic migraine; MMRM, mixed-effects, repeated measures.
* p<0.0001; #p<0.0031 vs placebo.
Source: CS p. 60, with correction provided at clarification.

Table 22: HALO CM Change in weekly migraine days over time (MMRM analysis)

Visit	Category	Statistic	Placebo	Fremanezumab
Week 1	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]
		95% CI		[redacted]
		p-Value		[redacted]
Week 2	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]
		95% CI		[redacted]
		p-Value		[redacted]
Week 3	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]
		95% CI		[redacted]
		p-Value		[redacted]
Week 4	Individual treatment group	Least squares means (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
	Difference (vs. Placebo)	Least squares means (SE)		[redacted]
		95% CI		[redacted]
		p-Value		[redacted]

Key: CI: confidence interval; CM, chronic migraine; MMRM, mixed-effects repeated measures; SE: standard error; vs: versus.
Source: Clarification question A25.

4.2.4.2.3 Subgroup Analyses

The results of pre-planned subgroup analyses reported in the CS are reported in Table 23.

Reductions in mean monthly migraine days (MMDs) and mean headache days or at least moderate severity were exhibited by participants across all three arms and all subgroups. Reductions in MMDs ranged between -2.9 to -4.3 for placebo, and between -4.1 to -5.3 for fremanezumab. Reductions in monthly headache days of at least moderate severity ranged between -2.3 to -2.8 for placebo and -3.0 to -5.0 for fremanezumab.

Reductions in both outcomes were statistically significantly larger for participants receiving fremanezumab than those receiving placebo across all but two subgroups: non-Caucasian and male participants. This finding is consistent with data reported for HALO-EM. Across all

subgroups, mean improvements in outcomes ranged between -0.3 to -2.2 for monthly migraine days and -0.9 to -1.7 for monthly headache days of at least moderate severity. The latter does not include mean values reported for prior topiramate and OBA use, which have been excluded due to the lack of variance data and risk of reporting bias.

The CS does not report the outcomes of any statistical tests to evaluate whether the effect of fremanezumab varies between different subgroups. Based on the data reported, it was not possible for the ERG to conduct these analyses. However overall, there appeared to be a trend for the effect of fremanezumab to be greater relative to placebo in the following subgroups: participants aged between 18 and 45 years (compared to >45 years); Caucasians (compared to non-Caucasians); females (compared to males); and participants receiving concomitant preventative therapies (compared to not).

As for HALO-EM, data is not reported for two of the subgroups: prior topiramate and prior OBA use. A footnote to the table explains that this was because the sample size for each was too small to perform the analysis; however, this explanation is inconsistent with the sample sizes reported for other reported subgroups. Further, an adjusted (LSM) treatment difference without 95% confidence intervals was reported for prior topiramate use, suggesting that this analysis was conducted and not reported. At clarification, the company provided a subgroup analysis that included participants who had previously used topiramate, OBA and/or another preventative treatment, for the outcome of the change from baseline in monthly average number of headache days of at least moderate severity. The results of this analysis are presented in Table 23, and appear to show a larger effect of fremanezumab on headache days than in the main trial population. As the company did not provide any further outcome data, it was not possible for the ERG to determine whether this was a trend across all outcomes.

Table 23: HALO CM Pre-Planned Subgroup Analyses

			MMDs		Monthly headache days of at least moderate severity	
Subgroup	**Treatment group**	**n**	**Least squares mean (SE)**	**Treatment difference *vs* placebo (95% CI)**	**Least squares mean (SE)**	**Treatment difference *vs* placebo (95% CI)**
18 to 45 years	Placebo	226	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	217	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	244	[redacted]	[redacted]	[redacted]	[redacted]
>45 years	Placebo	145	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	158	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	131	[redacted]	[redacted]	[redacted]	[redacted]
Caucasian	Placebo	301	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	292	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	294	[redacted]	[redacted]	[redacted]	[redacted]
Non-Caucasian	Placebo	70	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	83	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	81	[redacted]	[redacted]	[redacted]	[redacted]
Female	Placebo	326	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	330	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	327	[redacted]	[redacted]	[redacted]	[redacted]
Male	Placebo	45	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	45	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	48	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant preventive treatment	Placebo	66	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	64	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	70	[redacted]	[redacted]	[redacted]	[redacted]
No concomitant preventive treatment	Placebo	294	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	298	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	290	[redacted]	[redacted]	[redacted]	[redacted]
Prior topiramate*	Placebo	117	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	106	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Treatment group	n	MMDs		Monthly headache days of at least moderate severity	
			Least squares mean (SE)	Treatment difference *vs* placebo (95% CI)	Least squares mean (SE)	Treatment difference *vs* placebo (95% CI)
Prior OBA*	Monthly frem	117	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	49	[redacted]	[redacted]	[redacted]	[redacted]
	Quarterly frem	66	[redacted]	[redacted]	[redacted]	[redacted]
	Monthly frem	50	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI: confidence interval; CM, chronic migraine; frem: fremanezumab; MMDs, mean monthly migraine days; OBA, onabotulinum toxin A; SE: standard error.
* The CS states that due to small patient numbers these analysis could not be conducted. ≠Minus values added by the ERG, as assumed to be a typo.
Source: CS, Appendix E; p. 6-7.

ERG comment:

Subgroup analyses for HALO-CM demonstrated a consistent benefit of fremanezumab monthly and quarterly compared to placebo for both mean monthly migraine days and mean headache days of at least moderate severity. This difference was statistically significant across most subgroups. No statistical tests were reported in the CS to compare the effect of fremanezumab with placebo between subgroups; however the ERG noted that the effect of fremanezumab as compared to placebo appeared greater for participants receiving concomitant preventative therapy. Further differences between subgroups noted were considered to likely be random, as clinical advice to the ERG is that there is no known clinical rationale for these differences. Participants in the placebo arm across all subgroups also demonstrated improvements across both outcomes.

4.2.4.2.4 Quality of life and patient reported outcomes (PRO)

Quality of life and PRO are reported in Table 24. MSQoL was the company's chosen methods for evaluating HRQoL in this population, however while it was evaluated in the HALO-EM trial, the data is not reported in the CS. Rather, the company reported a qualitative summary of the data (CS, p. 61) stating that 'differences' from placebo were demonstrated for fremanezumab across the three domains. The company went on to state that LSM differences for role function-restrictive were stated to be statistically significant (p<.0001). LSM differences with placebo were reported (6.1 for quarterly and 6.9 for monthly), which are both above the recommended MID of 3.2[34], although with no accompanying variance data. Mean values for the other domains were not reported and it is unclear whether the differences stated in these domains were above the scale MID or statistically significant.

With regards to the HIT-6 scale, improvements in the impact of migraines on everyday functioning above the recommended scale MID of 2.3[35] were exhibited across all three trial arms. Fremanezumab was associated with a greater improvement in HIT-6 scores than placebo (a difference of -1.9 and -2.4 for fremanezumab quarterly and monthly, respectively), which was statistically significant. All three treatment groups also demonstrated improvements in EQ-5D VAS, indicating improvements in HRQoL. Patients in the fremanezumab arms showed a statistically significant greater improvement in EQ-5D VAS scores than placebo.

Table 24: HALO CM Quality of Life and PRO at 4 weeks

	Placebo (n=371)	Fremanezumab quarterly (n=375)	Fremanezumab monthly (n=375)
Headache Impact Test Score (HIT-6)			
Baseline (SD)	64.1 (4.8)	64.3 (4.7)	64.6 (4.4)
LSM change (95% CI)	-4.5 (-5.38 to -3.60)	-6.4 (-7.31 to -5.52)	-6.8 (-7.71 to -5.97)
Difference vs placebo (95% CI)		-1.9 (-2.90 to -0.96)	-2.4 (-3.32 to -1.38)
P-value vs placebo		<0.0001	<0.0001
EQ-5D VAS (0-100; higher is better outcome)			
Baseline (SD)*	NR	NR	NR
LSM mean (95% CI)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]

Key: CI, confidence interval; CM, chronic migraine; EQ-5D, EuroQol-5 dimension; HIT-6: six-item headache impact test; LSM, least-squared mean; NR, not reported; PRO, patient-reported outcome; SD: standard deviation; VAS, visual analogue scale.
Notes: *Baseline EQ-5D scores were reported in an appendix to the trial CSR[39], which was not provided to the ERG.
Source: CS, p. 61; HALO CM CSR p. 116.

ERG comment:

Overall the data reported suggested that participants in all three trial arms experienced improvements in HRQoL at 12 weeks, as evaluated by the MSQoL and EQ-5D. It is unclear why data are not fully reported for the MSQoL, as this is the company's chosen outcome for evaluating HRQoL in this population. The ERG considered this may indicate reporting bias in the CS. Based on the data available, it appears that fremanezumab may improve HRQoL and have a clinically meaningful benefit for the impact of migraines on daily functioning, as evaluated using the HIT-6. However, there is some uncertainty about the size and statistically significance of differences as evaluated using the MSQoL.

The data also demonstrate an improvement for participants in the placebo arm of the trial, which is consistent with improvements in other clinical outcomes in these participants. Mean improvements in HIT-6 scores in the placebo arm more than double the recommended MID for the scale, indicating that participants in the placebo arm experienced a clinically meaningful improvement in the impact of their symptoms on everyday functioning at 12 weeks. The company did not include a discussion of these findings in the CS, and it is unclear why participants in the placebo arm are experiencing a benefit. While patients in the fremanezumab arms demonstrate statistically significantly greater improvement than those in the placebo arm, as evaluated using relative effect estimates, the positive performance of

the placebo arm may undermine the validity of the absolute data (including the absolute change relative to the scale MIDs).

4.2.4.3 HALO Extension

A total of [redacted]/2,005 ([redacted]) patients from the HALO trials (including [redacted]/875 [redacted] patients with EM and [redacted]/1,130 [redacted] patients with CM) elected to participate in the HALO extension phase. An additional [redacted] new patients ([redacted] with EM and [redacted] with CM) were also recruited. Based on information provided in Table 20 and 21 of the CS (p.72 and 74) the ERG estimates that [redacted]/581 ([redacted]%) of patients with EM and [redacted]/755 ([redacted]%) of patients with CM who were receiving fremanezumab in the main trial continued with the extension. A total of [redacted]/669 ([redacted]%) patients who received placebo in the main trial opted to join the extension.

4.2.4.3.1 Baseline Characteristics

The baseline characteristics of patients who were included in the HALO trials are reported in Table 25 and for participants with EM and Table 26 for participants with CM.

A total of 780 participants with episodic migraine participated in the HALO extension phase. Patients were aged between 18 and 71 years, with a mean age of between [redacted] years (SD [redacted]). The majority of participants ([redacted]780) were female, and had been diagnosed with migraines between 1 and 65 years prior to the trial (mean [redacted]; SD [redacted]). The line of treatment of participants in the trial was not reported, nor was the number of participants who were receiving another preventative therapy for migraine in the lead-in phase. It was reported that [redacted]/780) of participants had previously received topiramate.

Disease severity at baseline was based on participants' reports during the lead-in phase of the trial (28 days). Participants reported a mean of [redacted] migraine days (range [redacted]), and a mean of [redacted] moderately severe or severe headache days (range [redacted]; SD [redacted]). Participants reported using acute headache medication on [redacted] days (range [redacted]; SD [redacted]). The number of acute migraine-specific medications and mean migraine disability assessment scores were not reported at baseline.

No significant differences in population characteristics were reported between patients who received fremanezumab quarterly and monthly in the extension.

Table 25: Baseline characteristics of episodic patients in HALO extension trial

	Fremanezumab quarterly (n=[redacted])	Fremanezumab monthly (n=[redacted])
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Weight, kg		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Time since initial migraine diagnosis, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Previous topiramate use for migraine, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Number of MMDs		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Number of monthly headache days of at least moderate severity		
Baseline (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Number of monthly days of use of any acute headache medication		
Baseline (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

Abbreviations: kg, kilogram; MMDs, mean monthly migraine days; SD: standard deviation.

A total of 1,110 participants with chronic migraine participated in the HALO extension phase. Participants were aged between 18-71 years, with a mean age of between [redacted] (SD [redacted]). The majority of participants ([redacted]1,110) were female, and had been diagnosed with migraines between one and 61 years prior to the trial (mean [redacted]; SD [redacted]). The line of treatment of participants in the trial was not reported, nor was the number of participants who were receiving another preventative therapy for migraine in the lead-in phase. It was reported that [redacted]/1110) of participants had previously received topiramate.

Disease severity at baseline was based on participants' reports during the lead-in phase of the trial (28 days). Participants reported a mean of [redacted] migraine days (range [redacted]; SD [redacted]), and a mean of [redacted] moderate or severe headache days (range [redacted]; SD [redacted]). Participants reported using acute headache medication on [redacted] days (range [redacted]; SD [redacted]); the number of acute migraine-specific medications used in the run-up period and mean migraine disability assessment scores were not reported at baseline.

No significant differences in population characteristics were reported between participants who received fremanezumab quarterly and monthly in the extension.

Table 26: Baseline characteristics of chronic patients in HALO extension trial

	Fremanezumab quarterly (n=[redacted])	Fremanezumab monthly (n=[redacted])
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Weight, kg		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Time since initial migraine diagnosis, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Previous topiramate use for migraine, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Number of MMDs		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Number of monthly headache days of at least moderate severity		
Baseline (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Number of monthly days of use of any acute headache medication		
Baseline (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

Abbreviations: kg, kilogram; MMDs, mean monthly migraine days; SD: standard deviation.

ERG comment:

A limited number of baseline population characteristics were reported for participants in the HALO extension phase compared to the main trial phases. The HALO extension population was similar to the main trials on some characteristics, although the ERG noted that there was a trend for participants with both EM and CM included in the HALO extension to have a higher mean number of moderate or severe headaches during the run-in period, have a longer mean time since diagnosis, and be more likely to have used topiramate. Participants with CM in the extension also had a higher mean age. Not all differences were statistically significant, although the trend was consistent and suggests that there may a difference between patients who were included in the extension and the main trials. It is not clear why a smaller number of baseline population characteristics were reported in the CS for

participants in the extension than in the main trial; specifically, the number of headaches of any severity, previous use of OBA, baseline MIDAS/HIT-6 scores, and information on line of treatment were not reported for those entering the extension phase. It is possible that there are further differences between participants in the main trials and the extension on these characteristics that the ERG has been unable to review.

Population characteristics between participants receiving fremanezumab monthly and quarterly in the extension phase were similar, with no differences reported.

4.2.4.3.2 Clinical Outcomes – episodic migraine

Clinical outcome data for the extension phase of HALO EM is reported in **Error! Not a valid bookmark self-reference.**. Outcomes are reported separately for participants who continued to receive fremanezumab in the main trial ('active rollover' participants with 12 weeks of existing fremanezumab therapy) and those who were naïve to fremanezumab at the start of the trial (either because they received placebo in the main trial or they were newly recruited). It is unclear why outcome data for the combined population is not reported. A further limitation of the data reported is that there are no comparable time points between newly treated and active rollover participants reported in the CS to allow comparison. Those who rolled over into the extension received an additional three months of treatment (i.e. one-month follow-up is a total of four-months of treatment for those in the active rollover arm). A total of [redacted] of patients in the extension phase were included in final follow-up at 12 months (final sample size not stated in the CS, so this figure is based on the sample size reported for the proportion of patients exhibiting a 50% reduction in migraine days).

Overall the data (**Error! Not a valid bookmark self-reference.**) shows improvements in all outcomes from baseline for both groups at one, three, six, and 12 months (the ERG have assumed that baseline scores displayed in **Error! Not a valid bookmark self-reference.** for active rollover participants are at baseline of the main trial, and not of the extension). No statistical tests were reported; however, all 95% confidence intervals are consistent with statistically significant changes from baseline in all continuous outcomes. At 12 months, the data indicated that participants receiving fremanezumab exhibited a [redacted] to [redacted] day reduction in mean monthly migraine days compared to baseline, and between [redacted]- [redacted] of patients reported a 50% reduction in monthly migraine days ([redacted] of all patients in the extension phase). Reductions are similar in headache days of at least moderate severity, which reduced from [redacted] to [redacted] days at 12 months from baseline, and participants reported between [redacted] and [redacted] fewer days using acute headache medication.

No statistical tests were reported to compare outcomes between newly treated and active rollover participants. Overall, outcomes were relatively similar between active rollover and newly treated participants, although the data appears to indicate that outcome data in newly treated participants remained relatively stable between one and 12 months, while active rollover participants demonstrated a trend for a small but steady improvement between one and 12 months (i.e. four and 15 months). As no comparable time points are reported, it was not possible to determine whether this effect is statistically significant. Notably, active rollover participants receiving monthly fremanezumab exhibited a significant jump in response rates ([redacted] to [redacted]) between one and 12 months (i.e. four and 15 months).

Table 27: Clinical Efficacy Outcomes in HALO-EM Extension

	Fremanezumab quarterly		Fremanezumab monthly	
	Newly treated (n=[redacted])	Active rollover (n=[redacted])*	Newly treated (n=[redacted])	Active rollover (n=[redacted])*
Mean monthly migraine days				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean headache days of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least a 50% reduction in MMDs				
Number in month 1 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 3 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 6 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 12 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean monthly days of use of any acute headache medication				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Headache hours of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EM, episodic migraine; MMDs, mean monthly migraine days; SD: standard deviation.
Note: *The ERG have assumed that baseline scores for all outcomes in this table were measured at baseline of the original trial, rather than baseline of the extension.

ERG comment:

The data from the extension phase to HALO-EM suggests that reductions in improvements in clinical outcomes persist until final follow-up at 12 and 15 months for newly recruited and active rollover participants, respectively. Clinical advice to the ERG is that changes in outcomes between baseline and follow-up represent a clinically meaningful difference.

Generally, the ERG noted that the CS contains very limited discussion of the results from the extension phase of HALO, and provides no discussion of any trends in the data.

4.2.4.3.3 Clinical Outcomes – chronic migraine

Clinical outcome data for the extension phase of HALO EM is reported in Table 28. No statistical tests were reported to compare outcomes between newly treated and active rollover participants. Overall mean values appear similar between the two arms and are consistent with data from HALO-EM; the data appears to indicate that outcome data in newly treated participants remains relatively stable between one and 12 months, while active rollover participants show a trend for a small but steady improvement between one and 12 months (i.e. four and 15 months). As no comparable time points are reported, it was not possible to determine whether this effect is statistically significant. Notably, active rollover participants who received monthly fremanezumab exhibited a significant jump in response rates ([redacted] to [redacted]) between one and 12 months (i.e. four and 15 months), which is not replicated in other groups. It's unclear whether this is an anomaly or whether this represents a true differential effect of fremanezumab in this group.

As with HALO EM, outcomes are reported separately for participants who continued to receive fremanezumab in the main trial (active rollover participants) and those who were naïve to fremanezumab at the start of the trial (either because they received placebo in the main trial or they were newly recruited). Outcome data for the combined population are also not reported. A total of [redacted] of participants in the extension phase were included in final follow-up at 12 months (again, the final sample size was not reported in the CS and so this figure is based on numbers reported for the proportion of participants exhibiting a 50% reduction in migraine days).

Overall the data shows improvements in all outcomes from baseline for both groups at 1, 3, 6, and 12 months (the ERG have assumed that baseline scores displayed for active rollover participants are at baseline of the main trial, and not of the extension). No statistical tests were reported to compare outcomes between newly treated and active rollover participants. Overall mean values appear similar between the two arms, and are consistent with data from

HALO-EM; the data appears to show that improvements in outcomes in newly treated participants remains relatively stable between one and 12 months, while active rollover participants show a trend for a small but steady improvement between one and 12 months (i.e. four and 15 months). As no comparable time points are reported, it was not possible to determine whether this effect is statistically significant. Notably, active rollover participants who received monthly fremanezumab exhibited a significant jump in response rates ([redacted] to [redacted]) between one and 12 months (i.e. four and 15 months), which is not replicated in other groups. It is unclear whether this is an anomaly or whether this represents a true differential effect of fremanezumab in this group.

No statistical tests are reported, however upper and lower 95% confidence intervals are consistent with statistically significant changes from baseline in all continuous outcomes. At 12 months, the data indicates that participants receiving fremanezumab exhibit a 7.0- to 8.2-day reduction in mean monthly migraine days compared to baseline, and between [redacted] of participants reported a 50% reduction in monthly migraine days ([redacted] of all participants in the extension phase). Reductions are similar in headache days of at least moderate severity, which reduced from [redacted] to [redacted] days at 12 months from baseline, and participants used acute headache medication for between [redacted] and [redacted] fewer days.

Table 28: Clinical Efficacy Outcomes in HALO-CM Extension

	Fremanezumab quarterly		Fremanezumab monthly	
	Newly treated patients (n=[redacted])	Active rollover patients (n=[redacted])*	Newly treated patients (n=[redacted])	Active rollover patients (n=[redacted])*
Mean monthly migraine days				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean headache days of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least a 50% reduction in MMDs				
Number in month 1 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 3 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 6 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number in month 12 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean monthly days of use of any acute headache medication				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Headache hours of at least moderate severity				
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CM, chronic migraine; MMDs, mean monthly migraine days; SD: standard deviation.
Note: *The ERG assume that baseline scores for all outcomes in this table were measured at baseline of the original trial, rather than baseline of the extension.

ERG comment:

The data from the extension phase to HALO-EM suggest that improvements in clinical outcomes persist until final follow-up at 12 and 15 months, for newly recruited and active rollover participants, respectively. Clinical advice to the ERG is that changes in outcomes between baseline and follow-up all represent a clinically meaningful difference. The ERG noted that for all arms, there was a trend for improvements in outcomes to increase slightly over time.

4.2.4.4 FOCUS

The company stated in clarification that the data provided for FOCUS was the final cut for the double-blind part of the trial.

4.2.4.4.1 Baseline characteristics

In the overall population, the baseline characteristics of participants in the FOCUS trial were comparable between the three randomised groups of fremanezumab quarterly, fremanezumab monthly and the placebo groups (CS, p. 37).

For the EM population, the mean age of participants in the placebo group was similar to the mean age of the fremanezumab monthly group but appears higher than the mean age in the fremanezumb quarterly group, albeit [redacted] (CS, Appendix M, p. 5). The female population also showed a trend to be higher in the fremanezumab monthly group compared to the placebo group [redacted] The mean MIDAS scores for both fremanezumab groups [redacted] mean MIDAS score for the placebo group [redacted], for quarterly and monthly groups respectively). [redacted]. The differences and similarities [redacted] for the HFEM subgroup of the total EM population.

For the CM population, the male population [redacted] the two fremanezumab groups compared to placebo, also [redacted] for the quarterly and monthly regimen, respectively. [redacted]

The comparison of baseline characteristics for the EM population who have used three or more classes of migraine preventative therapies [redacted]. This was [redacted] for the HFEM population who have used three or more classes of migraine preventative therapies. For the CM population who have used three or more classes of migraine preventative treatment, [redacted]

[redacted] (Table 29).

Table 29: Baseline characteristics of EM patients and subgroup HFEM patients in FOCUS trial

	EM			HFEM		
Baseline characteristic	**Placebo (N=[redacted])**	**Fremanezumab quarterly (N=[redacted])**	**Fremanezumab monthly (N=[redacted])**	**Placebo (N=[redacted])**	**Fremanezumab quarterly (N=[redacted])**	**Fremanezumab monthly (N=[redacted])**
Age, years						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since initial migraine diagnosis, years						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of migraine days during run-in period						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of headache days of at least moderate severity during run-in period						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of days of use of any acute headache medications during run-in period						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MIDAS total score						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HIT-6 total score						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EM, episodic migraine; HFEM, high-frequency episodic migraine; HIT-6: six-item headache impact test; kg, kilogram; MIDAS, migraine disability assessment; SD: standard deviation

Table 30: Baseline characteristics of CM patients in FOCUS trial

FOCUS CM Baseline characteristic	Placebo (N=[redacted])	Fremanezumab quarterly (N=[redacted])	Fremanezumab monthly (N=[redacted])
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Weight, kg			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Time since initial migraine diagnosis, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Number of migraine days during run-in period			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Number of headache days of at least moderate severity during run-in period			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Number of days of use of any acute headache medications during run-in period			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
MIDAS total score			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
HIT-6 total score			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

Abbreviations: CM, chronic migraine; HIT-6, six-item headache impact test; kg, kilogram; MIDAS, migraine disability assessment; SD: standard deviation.
Source: CS, Appendix M. p. 10.

ERG comment:

Some baseline characteristics such as the age in the EM population, sex and MIDAS scores in both EM and CM showed a tendency to be different among treatment groups. This trend was not seen in the overall population when comparing the baseline characteristics between randomised treatment groups. The imbalance trend is likely due to the non-stratification of the randomisation by EM/CM migraine types and also by the population who have used three or more preventative therapies. Even though some of these differences might be

reasonably large, the underlying variability and the small sample sizes implied non-statistically significant differences.

4.2.4.4.2 Clinical outcomes – episodic migraine

The company presented clinical effectiveness data from the FOCUS trial. Here the company compared the treatment effects of the fremanezumab regimens with the placebo. The main efficacy outcomes from the FOCUS trial were based on a mixed population of EM and CM. The ERG focused on the clinical efficacy for the EM and CM populations as stated in the NICE scope and also in line with the migraine preventative treatment pathway.

Evidence for the main EM population is presented in Table 31, and evidence for participants who had previously used three or more preventative therapies is presented in Table 32. All data reported is based on the full analysis set (FAS; see Table 10). At clarification, the company provided outcome data based on an ITT analysis; these data were consistent with the FAS set.

For the EM population, a similar significantly different reduction in mean MMDs of -3.1 for both fremanezumab regimen compared to placebo was noted for the whole FOCUS EM population. This was [redacted] results from HFEM population but [redacted] for the population of EM and HFEM who have used three or more classes of preventive therapy, [redacted].

The odds of fremanezumab patients having a 50% reduction in MMDs was [redacted] in both fremanezumab treatment groups of the whole EM population and [redacted] in the HFEM subgroup as it was in the placebo group. The odds were [redacted] in the EM ([redacted] in fremanezumab quarterly group and [redacted] in fremanezumab monthly group) and the HFEM ([redacted] in fremanezumab quarterly group and [redacted] in fremanezumab monthly group) population who have used three or more preventative treatments, albeit with [redacted]

The findings for the reduction in the mean headache days of at least moderate severity in the EM whole population [redacted] what was demonstrated for the mean MMDs outcome (Table 31). This outcome was, however, [redacted]. Thus, the difference in the reduction in both fremanezumab groups compared to placebo was [redacted] in the EM whole population and in the EM/HFEM who have used three or more preventative treatments[redacted].

Additional outcomes were reported for the population relevant to the appraisal (Table 32). The differences in the reduction in mean monthly days of use of any acute headache medication versus the placebo group was [redacted] in both fremanezumab groups for both

EM and HFEM who have used three or more classes of preventative therapies. The differences in mean monthly headache hours of at least moderate severity was between [redacted] more in the fremanezumab groups, compared to the placebo group, for both EM and HFEM populations who have used three or more preventative therapies.

[redacted]

Table 31: Summary of main efficacy outcomes for patients with EM and HFEM in FOCUS clinical trial

	EM			HFEM		
	Placebo (n=111)	**Fremanezumab quarterly (n=107)**	**Fremanezumab monthly (n=110)**	**Placebo (n=[redacted])**	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Mean monthly migraine days						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	-0.7 (-1.50 to 0.19)	-3.7 (-4.59 to -2.84)	-3.8 (-4.66 to -2.90)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		-3.1 (-3.93 to -2.19)	-3.1 (-4.00 to -2.25)		[redacted]	[redacted]
P-value vs placebo		<0.0001	<0.0001baseli		[redacted]	[redacted]
Patients with at least 50% reduction in monthly average migraine days						
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio vs placebo (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]		[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]			

Abbreviations: CI: confidence interval; EM, episodic migraine; HFEM, high-frequency episodic migraine; LSM, least squares mean; SD, standard deviation.
Source: CS, p. 74-77.

Table 32: Summary of main efficacy outcomes for patients with EM who have used three or more classes of preventive therapies and the HFEM subgroup in FOCUS clinical trial

	EM			HFEM		
	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**	**Placebo (n=[redacted])**	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Mean monthly migraine days						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]	[redacted]
Patients with at least 50% reduction in monthly average migraine days						
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio vs placebo (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]	[redacted]
Mean headache days of at least moderate severity						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	EM			HFEM		
	Placebo (n=[redacted])	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**	**Placebo (n=[redacted])**	**Fremanezumab quarterly (n=[redacted])**	**Fremanezumab monthly (n=[redacted])**
Difference vs placebo (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]	[redacted]
Mean monthly days of use of any acute headache medication						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]	[redacted]
Mean monthly headache hours of at least moderate severity						
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P-value vs placebo		[redacted]	[redacted]		[redacted]	[redacted]

Abbreviations: CI, confidence interval; EM, episodic migraine; HFEM, high-frequency episodic migraine; LSM, least squares mean; SD, standard deviation.
Source: CS, p. 80-81, 85-86.

ERG comment:

Fremanezumab demonstrated significantly better treatment effects across all outcomes in the EM whole population as well as in the HFEM subgroup compared to the placebo group. The ERG expressed concerns about the cut-off definition of 8-14 headache days per month for the HFEM subgroup and requested in clarification for a sensitivity analysis using a more conventional cut-off of 10-14 headache days per month. The sensitivity analysis (company clarification response A39) showed very similar results to those originally reported.

The treatment effect reported in the fremanezumab groups who have used three or more preventative therapies appeared higher than in the overall EM population. This could be partly due to the lower precision in the former. The ERG noted that the sample size of the relevant group of people who have used three or more preventative therapies was low and could be underpowered especially for the ANCOVA and logistic regression analyses adopted by the company which could lead to model instability.

The ERG also noted that some baseline characteristics that demonstrated some imbalances between the treatment groups and the placebo were not adjusted for in the model. The impact of these unadjusted baseline differences in some covariates may be unpredictable.

4.2.4.4.3 Clinical outcomes – chronic migraine

Evidence for the main population is presented in Table 33, and evidence for participants who had previously used three or more preventative therapies is presented in Table 34. All data reported was based on the full analysis set (FAS; see Table 10). At clarification, the company provided outcome data based on an ITT analysis; these data were consistent with the FAS set.

For the CM whole population, the difference in the reduction of the mean MMDs between the fremanezumab groups and the placebo group was slightly higher in the monthly regimen (-3.8) compared to the quarterly regimen (-3.2). The effect [redacted] in the relevant CM population who have used three or more preventative therapies.

The odds of people on fremanezumab having a 30% reduction in MMDs was [redacted] in the fremanezumab quarterly and monthly groups respectively, as it was in the placebo group. This was [redacted] in the relevant population of people who have used three or more preventative therapies, albeit [redacted].

The difference in mean headache days of at least moderate severity in the fremanezumab quarterly and monthly groups showed [redacted] versus placebo of [redacted] and [redacted] respectively. The effect was [redacted] in the population who have used three or more preventative therapies.

Additional outcomes reported only for the relevant population of interest (used three or more preventative therapies) included the difference in the mean monthly days of use of any acute headache medication which showed [redacted] versus the placebo in both fremanezumab groups. Also, the difference in reduction in mean monthly headache hours of at least moderate severity was [redacted] more in the fremanezumab quarterly and [redacted] more in the fremanezumab monthly patient groups compared to placebo. The outcome was [redacted] than other outcomes assessed in the CM population.

Table 33: Summary of main efficacy outcomes for patients with CM in FOCUS clinical trial

	Placebo (n=167)	Fremanezumab quarterly (n=169)	Fremanezumab monthly (n=173)
Mean monthly migraine days			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	-0.7 (-1.64 to 0.20)	-3.9 (-4.79 to -2.99)	-4.5 (-5.39 to -3.61)
Difference vs placebo (95% CI)		-3.2 (-4.16 to -2.18)	-3.8 (-4.76 to -2.80)
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]

Abbreviations: CI, confidence interval; CM, chronic migraine; SD, standard deviation.
Source: CS, p. 78.

Table 34: Summary of main efficacy outcomes for patients with CM who have used three or more classes of preventive therapy 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]
Mean monthly headache hours 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]

Abbreviations: CI, confidence interval; CM, chronic migraine; LSM, least squares mean; SD, standard deviation.
Source: CS, p. 90.

ERG comment:

Both fremanezumab groups demonstrated [redacted] in the CM whole population as well as in people with CM who have used three or more preventative therapies, compared to placebo, with [redacted] compared to findings from the analysis of outcomes in the EM population. Thus, results from the analysis of outcomes for the CM population is [redacted] albeit still [redacted] The ANCOVA was also not adjusted for [redacted] which showed an imbalance trend.

4.2.4.4.4 Quality of life outcomes – FOCUS trial

HRQoL data presented in the CS is reported in Table 35 and Table 36. The CS presented HRQoL data for FOCUS whole population but not for the EM and CM subgroups of the whole population. In addition, HRQoL data for the relevant EM, HFEM and CM population of participants who had used three or more preventative therapies, were also presented. The data was captured at four weeks after final dose of treatment. For both EM and CM populations who have used three or more preventative therapies, the baseline mean scores for MIDAS, HIT-6 and MSQoL were [redacted] between fremanezumab groups and the placebo group, although the baseline mean MIDAS score for the fremanezumab monthly group of EM population who have used three or more preventative therapies, showed a [redacted] compared to the mean MIDAS score for the placebo group. The power to detect a statistically significant difference [redacted]

Quality of life in episodic migraine population who have used ≥3 previous preventative therapies

Posttreatment data for EM patients who have used three or more prior preventative therapies, showed a significant difference in the MIDAS score reduction in each of the fremanezumab groups versus placebo, by [redacted]. Similar findings were demonstrated also for the MIDAS score among the HFEM population who have used three or more preventative therapies Table 35. Also there was a significant difference in the HIT score reduction of about [redacted] for fremanezumab quarterly group and [redacted] for fremanezumab monthly group. This was slightly [redacted] for the HFEM subgroup who have used three or more preventative therapies. For the MSQoL domains, the differences in LSM [redacted] versus placebo were generally more than [redacted] for each of the fremanezumab groups in the EM population and also in the HFEM subgroup [redacted].

Table 35: Quality of life results for patients with EM and for patients with HFEM, who have used three or more classes of preventive therapy in FOCUS clinical trial

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

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

Abbreviations: CI, confidence interval; EM, episodic migraine; HFEM, high-frequency episodic migraine; LSM, least squares mean; SD, standard deviation.
Source: CS, p. 83 and 88.

Quality of life outcomes for chronic migraine population who have used three or more preventative therapies

The baseline quality of life measures for each of the fremanezumab group were comparable to those of the placebo group.

The MIDAS score showed a [redacted] for fremanezumab quarterly and monthly versus placebo by [redacted] and [redacted] respectively. There was also a [redacted] in HIT-6 score reduction for fremanezumab groups versus placebo [redacted]. For the MSQoL domains, the fremanezumab monthly showed a [redacted] versus placebo. The fremanezumab quarterly group showed a [redacted] only for role function – restrictive domain versus the placebo (Table 36).

ERG comment:

People with EM in both the fremanezumab quarterly and monthly groups who have used three or more preventative therapies reported a [redacted] in the quality of life measures based on the [redacted] in MIDAS and HIT-6 scores and [redacted] across all MSQoL dimension scores. Similar [redacted] was demonstrated among people with CM in both fremanezumab groups who have used three or more preventative therapies based on the [redacted] in MIDAS and HIT-6 scores. The ERG noted that the reported quality of life effects were [redacted] for the fremanezumab monthly group compared to the fremanezumab quarterly group especially with regards to the MSQoL scores where the fremanezumab monthly group reported [redacted] versus placebo across all three dimensions whereas the fremanezumab quarterly group reported [redacted] only for one of the three dimensions.

Table 36: Quality of life results for patients with CM who have used three or more classes of preventive therapy in FOCUS clinical trial

	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]
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]
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]
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]
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; CM, chronic migraine; LSM, least squares mean; SD, standard deviation.
Source: CS, p. 91.

4.2.4.5 Adverse events – HALO and FOCUS trials

In the HALO EM trial, the overall adverse event (AE) rate ($p = 0.05$) and proportion of participants with at least one treatment-related AE ($p < 0.02$) were significantly higher in both fremanezumab groups compared to placebo (Table 37). Few patients had serious adverse events (SAEs) in both fremanezumab groups (1.0%) and in the placebo group (2.4%). The most common individual AEs were injection site related and were comparable between fremanezumab groups and placebo except for duration which was significantly higher in the fremanezumab monthly group compared to the placebo group ($p = 0.006$) (CS, Section B 2.10.1, p. 101).

For the HALO CM trial, the fremanezumab groups also had a higher rate of overall AEs compared to placebo ($p = 0.059$ and 0.034 for the quarterly and monthly groups respectively) (Table 38). Treatment-related AEs were also higher in the fremanezumab groups than placebo ($p = 0.052$ and 0.016 for the quarterly and monthly groups respectively). Participants with SAEs and participants with at least one AE leading to study discontinuation were evenly distributed among treatment groups. One death, deemed unrelated to the study medication, was recorded in the CM fremanezumab quarterly group. All individual AEs were evenly distributed among the three groups. The most common individual AEs were also injection site related including pain, induration and erythema (CS, p. 104).

In the FOCUS trial, the data from the whole population show that participants with at least one AE, participants with at least one treatment-related AEs and participants with at least one SAE, were evenly distributed among treatment groups (Table 40). All individual AE rates were comparable between treatments. Most common individual AEs were also related to injection site including reaction, erythema and induration (CS, p. 105-106). For the relevant subgroup population who have used three or more classes of preventative therapies, [redacted] for participants who had at least one AE compared to the overall FOCUS population, [redacted] FOCUS EM and FOCUS CM population who had used three or more preventative therapies. Regarding the individual incidence of AEs,

[redacted]

[redacted]. Over the 12 months extension, participants with at least one AE [redacted] treatment-related AE (Table 39). The proportion

of participants with at least one SAE [redacted] There was however, [redacted]. Regarding individual AE incidence, [redacted] (CS, p. 111).

Table 37: Summary of adverse event numbers in HALO EM trial

	Placebo (n=293) N (%)	Fremanezumab quarterly (n=291) N (%)	Fremanezumab monthly (n=290) N (%)
Number of patients with at least one AE	171 (58.4)	193 (66.3)	192 (66.2)
Number of patients with at least one treatment-related AE	109 (37.2)	137 (47.1)	138 (47.6)
Number of patients with at least one SAE	7 (2.4)	3 (1.0)	3 (1.0)
Number of patients with at least one AE leading to study discontinuation	5 (1.7)	5 (1.7)	5 (1.7)
Number of patients with at least one protocol-defined AE of special interest*	1 (0.3)	1 (0.3)	3 (1.0)
Death	0 (0.0)	1 (0.3)	0 (0.0)

Abbreviations: AE, adverse event; ALT, Alanine transaminase; AST, Aspartate transaminase; EM, episodic migraine; INR, international normalised ratio; SAE, serious adverse event; ULN, upper limit of normal.
Note: * Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions.
Source: CS, p. 99.

Table 38: Summary of adverse event numbers in HALO CM trial

	Placebo (n=375) N (%)	Fremanezumab quarterly (n=376) N (%)	Fremanezumab monthly (n=379) N (%)
Number of patients with at least one AE	240 (64.0)	265 (70.5)	270 (71.2)
Number of patients with at least one treatment-related AE	159 (42.4)	186 (49.5)	194 (51.2)
Number of patients with at least one SAE	6 (1.6)	3 (0.8)	5 (1.3)
Number of patients with at least one AE leading to study discontinuation	8 (2.1)	5 (1.3)	7 (1.8)
Number of patients with at least one protocol-defined AE of special interest*	4 (1.1)	7 (1.9)	9 (2.4)
Death	0 (0.0)	1 (0.3)	0 (0.0)

Abbreviations: AE, adverse event; ALT, Alanine transaminase; AST, Aspartate transaminase; CM, chronic migraine; INR, international normalised ratio; SAE, serious adverse event; ULN, upper limit of normal.
Note: *Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions.
Source: CS, p. 102.

Table 39: Summary of adverse event numbers in HALO trial extension

	Fremanezumab quarterly (n=[redacted]) N (%)	Fremanezumab monthly (n=[redacted]) N (%)
Number of patients with at least one AE	[redacted]	[redacted]
Number of patients with at least one treatment-related AE	[redacted]	[redacted]
Number of patients with at least one SAE	[redacted]	[redacted]
Number of patients with at least one AE leading to study discontinuation	[redacted]	[redacted]
Number of patients with at least one protocol-defined AE of special interest*	[redacted]	[redacted]
Death	[redacted]	[redacted]

Abbreviations: AE, adverse event; SAE, serious adverse event.
Source: CS, p. 109

Table 40: Summary of adverse event numbers in FOCUS trial

	Placebo (n=277) N (%)	Fremanezumab quarterly (n=276) N (%)	Fremanezumab monthly (n=285) N (%)
Number of patients with at least one AE	134 (48.3)	151 (54.7)	129 (45.3)
Number of patients with at least one treatment-related AE	55 (19.9)	57 (20.6)	55 (19.3)
Number of patients with at least one SAE	4 (1.4)	2 (0.7)	4 (1.4)
Number of patients with at least one AE leading to study discontinuation	3 (1.1)	1 (0.4)	4 (1.4)
Number of patients with at least one protocol-defined AE of special interest*	[redacted]	[redacted]	[redacted]
Death	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; ALT, Alanine transaminase; AST, Aspartate transaminase; INR, international normalised ratio; SAE, serious adverse event; ULN, upper limit of normal.
Note: * Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions.
Source: CS, p. 104.

ERG comment:

The company stated that "The safety data collected for fremanezumab demonstrate that this treatment has an adverse-event profile that is generally comparable to placebo" (CS, p. 121) despite showing significant differences between fremanezumab groups and placebo in the number of patients with at least one AE, and in the number of patients with at least one treatment-related AE for both the HALO EM and the HALO CM trials especially for the fremanezumab monthly group. In the FOCUS trial however, the reported AEs were comparable between the fremanezumab groups and the placebo, although much lower than the proportions reported in the HALO trials. It is unclear why the safety profile of

fremanezumab in the FOCUS trial appeared better than that of the HALO EM and the HALO CM trials despite having the same duration of follow-up. The HALO extension lacked the placebo arm and comparison could not be made.

The most prominent individual AEs reported were related to the injection sites for example, injection site reaction, pain, induration, erythema, itching and haemorrhage. Other reported individual AEs (≥5%) included upper respiratory tract infection and nasopharyngitis.

The CS did not report the AE profile for any of the comparators, thus the ERG is unable to compare the AE profile between fremanezumab and comparators. Clinical advice suggested that OBA appeared highly tolerable and that side effects are typically cosmetic and short-lived and that cases of discontinuation due to AEs are few.

4.2.5 Applicability to clinical practice

The study population enrolled in the HALO trials may be partly comparable to populations within the first three lines in the NICE preventative pathway, although the clusters used to determine treatment line included drugs not used in UK practice including all of cluster B and several other drugs. The company has not provided any evidence comparing fremanezumab to the relevant comparators within the first three lines. The study population enrolled in the FOCUS trial is expected to be largely representative of patients seen in the UK regarding age, disease duration, frequency of headaches, and the number of prior therapies used, based on clinical advice to the ERG. However, depending on whether the care setting is primary, secondary or tertiary, a varying proportion of the population may be outside the age range of inclusion in the FOCUS trial. Clinical advice to the ERG suggested that adult neurology clinics do see patients from 16 years of age and that in headaches clinics in secondary care setting, patients aged 70 years and above are also seen. The ERG agreed that the patient population in the FOCUS trial is broadly similar to patients that would be seen in UK practice, even though the UK centres constituted only 5% of all centres. About 85% of the patient population in FOCUS were also from continental Europe while the rest were from the USA (CS, Appendix E, p. 8-9). Clinical advice to the ERG suggested that practices in north America are more likely to use opioids and barbiturates to treat acute migraine episodes and that these analgesics are not routinely used in the UK. Clinical advice to the ERG also suggested that this is not expected to influence appreciably the clinical effect of fremanezumab.

[redacted]. This may be partly due to [redacted]. There was no further subgroup analysis for the

FOCUS patients from the six UK centres [redacted]

The preventative therapies used in the FOCUS subgroup who have used three or more [redacted]. Thus, it appears that the overall proportion of the first three lines of preventative therapies used in the UK constituted [redacted] the prior therapies received by the FOCUS population. This may reflect some [redacted] in the other centres compared to the UK. It is unclear whether the types of therapy received by people with migraine may affect subsequent treatment efficacy, although clinical advice to the ERG suggested that there are various reasons for stopping preventative therapies (including both tolerability and contraindication issues), which influence how people progress to different lines in the pathway. The FOCUS [redacted] in the study sample. There is no evidence on how these factors may impact on treatment effects at later lines of therapy, and therefore this is a key uncertainty in the applicability of the FOCUS data to the UK target population.

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

The CS reports that "A network meta-analysis was conducted to compare relevant treatment within the population of interest for this appraisal (patients who have failed three or more classes of preventive therapies)" (CS, p. 94).

4.3.1 Search strategy

The company did not provide a separate search strategy for the ITC in the submission.

ERG comment:

- The ERG assumed that the ITC also used the SLR broad search strategy as all relevant comparators stated in the final scope were include in search C of the company's search strategy (CS, Appendix D, p. 7).
- The ERG also conducted a separate search for OBA trials (Appendix 2) but no additional trials were found

4.3.2 Feasibility assessment

The CS stated that feasibility was assessed for two outcomes (CS, Appendix D., p. 333):

- absolute change from baseline in monthly migraine
- response rates.

ERG comment:

It was unclear whether all outcomes were involved in the feasibility assessment, but the company appeared to have based choice of outcomes on the availability of sufficient information for analysis and also availability of common outcomes at comparable time points and connected network (CS, Appendix D, p. 333). The company also stated that the outcomes chosen were the best comparative evidence between treatments for which data existed. The ERG carried out a check on the feasibility of outcomes reported for fremanezumab and at least one of the comparators, and found that acute migraine-specific medication treatment days was also reported for erenumab in study 295 as well as frequency of acute headache pain medication intakes in the PREEMPT trials for OBA, though the outcome may not be in sufficiently similar forms. Other outcomes common to FOCUS and the PREEMPT trials included change from baseline in frequency of headache days at 24 weeks, frequency of moderate/severe headache days, and total cumulative hours of headache days. The CS did not report the HRQoL for PREEMPT trials.

4.3.3 Study inclusion criteria

The inclusion criteria for the ITC was not explicitly described but may be deduced from the CS. Only the CM subgroup who have used three or more classes of preventative therapies were included in the ITC. The company states that ITC was not conducted for the EM population because there were no relevant comparators with appropriate efficacy data.

ERG comment:

The ERG agreed that the SLR broad inclusion criteria would have captured all relevant studies for the ITC as all relevant comparators in the NICE final scope were considered in the search.

4.3.4 Included studies

The company included four studies in the NMA involving only a subgroup of the CM population who have used three or more classes of preventative therapies, and stated that "The relevant population for this study reflected the population considered for this appraisal, patients who had failed three or more prior preventive migraine therapies" (CS, Appendix D,

p. 328). The company stated that: “There were no active comparator studies identified and so all comparisons are made through the placebo arms” (CS, p. 94) and that “No appropriate clinical data was found to allow the inclusion of any other treatments within this NMA” (CS, p. 94).

The company stated that “The NMA for CM included three studies, FOCUS, Study 295 and PREEMPT” (CS, Appendix D, p. 328) which was contradicted in another statement (CS, p. 94) “…….This allowed the inclusion of four trials to inform the network, and therefore allowed the inclusion of fremanezumab, OBA and placebo as relevant treatments” (CS, p. 94). From the table, it does appear there were four trials included in the NMA (Table 41); FOCUS, Study 295, PREEMPT I and PREEMPT II.

Table 41: Clinical trials included in network meta-analysis for chronic migraine

	FOCUS (NCT03308968)	Study 295* (NCT02066415)	PREEMPT I and II (NCT00156910, NCT00168428)
Placebo	Yes	Yes	**Yes**
Fremanezumab monthly	Yes		
Fremanezumab quarterly	Yes		
Erenumab 70mg		Yes	
Erenumab 140mg		Yes	
OBA 155U-195U			**Yes**

Note: * Phase II study.
Source: CS, p. 95.

4.3.4.1 Included studies – Study 295

The company described Study 295 as: “Study 295 was a multicentre, randomised, double-blind, placebo-controlled, 12-week parallel-group study investigating the efficacy and tolerability of erenumab in patients with CM (≥15 headache days/month; ≥8 migraine days *per* month). Patients with medication overuse were allowed to participate in the study but patients were excluded if they had previously used more than three preventive therapies. Patients were randomised to erenumab, 70mg or 140mg, or placebo and stratified by region and medication overuse. Migraine symptoms were assessed using an electronic diary which was completed daily. The primary endpoint was the change in monthly migraine days. Key secondary outcomes included 50% and 75% responder rates and change in acute medication use” (CS, Appendix D, p. 328).

4.3.4.1.1 Comparison of baseline characteristics between Study 295 and FOCUS

In clarification, the company provided a comparison of the baseline characteristics between fremanezumab and erenumab in a CM population who have used ≥3 preventative therapies.

The company confirmed to have checked that important aspects of the trials such as treatment efficacy assessments, participant recruitment and baseline characteristics, were comparable (Table 42).

Table 42: Baseline characteristic comparison between fremanezumab and erenumab in the ≥3 treatment used population for CM

	Fremanezumab			Erenumab		
	FOCUS (NCT03308968)			Ashina, 2018 (NCT02066415)		
	Fremanezumab quarterly N=[redacted]	Fremanezumab monthly N=[redacted]	Placebo N=[redacted]	Erenumab 140 mg N=190	Erenumab 70 mg N=191	Placebo N=286
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	44.1 (11.3)	42.8 (11.5)	42.4 (11.5)
Female, n (%)	[redacted]	[redacted]	[redacted]	59 (90.8)	62 (89.9)	72 (73.5)
Mean disease duration, years (SD)	[redacted]	[redacted]	[redacted]	24.6 (11.9)	24.5 (13.3)	24.8 (13.2)
Mean monthly migraine days (SD)	[redacted]	[redacted]	[redacted]	19.0 (4.7)	18.9 (4.4)	18.6 (4.3)
Use of migraine-specific medication, n (%)	[redacted]	[redacted]	[redacted]	60 (92.3)	62 (89.9)	90 (91.8)
Mean monthly acute migraine-specific medication days (SD)	[redacted]	[redacted]	[redacted]	12.5 (6.1)	11.0 (7.6)	12.0 (7.1)
Medication overuse, n (%)	[redacted]	[redacted]	[redacted]	27 (41.5)	30 (43.5)	42 (42.9)

Abbreviations: CM, chronic migraine; MMD, monthly migraine days; mITT, modified intention to treat; SD, standard deviation.
Notes:
[1] Sample sizes, mean age, percent female, mean disease duration, migraine-specific medication use, mean monthly acute migraine-specific medication days, and medication overuse for FOCUS are based on the safety analysis population. Mean MMDs are based on the mITT population. [2] Data are mean (SD) or n (%).
Source:

ERG comment:

The ERG noted that the underlying population of the Study 295 compared with the FOCUS CM subgroup were importantly different. While the FOCUS evidence consisted of only a subpopulation of the trial, composed of people with chronic migraine who have used three or more preventive medications, the population in Study 295 included the whole trial population, which was composed of people who had CM and people who had medication overuse status. Only a third of this population (34.8%) included participants who have previously used ≥ 3 prior preventative therapies, and so may not directly be comparable to the FOCUS CM population, as described in Table 42 above.[27] Both trials included participants with medication overuse status, however the rate was 50% higher across the FOCUS population relative to the Study 295 values.

4.3.4.1.2 Clinical outcomes – Study 295

The company presented the following outcomes for erenumab in the submission as summarised in Table 43.

Table 43. Results of Study 295

Outcome after Month 3	Erenumab 140 mg (n=190)	Erenumab 70 mg (n=191)	Placebo (n=286)
Change from baseline in MMDs			
No failed therapies	-6.1	-7.9*	-5.7
≥1 failed therapy	-6.8**	-6.0**	-3.5
≥2 failed therapies	-7.0**	-5.4**	-2.5
≥50% responder rate (%)			
No failed therapies	41.9	50.0	38.1
≥1 failed therapy	40.8**	34.7**	17.3
≥2 failed therapies	41.3**	35.6**	14.2
≥75% responder rate (%)			
No failed therapies	22.6	23.4	14.3
≥1 failed therapy	20.0**	13.7*	5.1
≥2 failed therapies	21.7**	11.1*	3.5
Change from baseline in acute medication use (%)			
No failed therapies	-2.5	-2.5	-1.8
≥1 failed therapy	-4.9**	-3.8**	-1.5
≥2 failed therapies	-5.4**	-4.1**	-1.3

Abbreviations: MMDs, monthly migraine days.
Notes: *p<0.05 compared to placebo. **p<0.001 compared to placebo.
Source: CS, Appendix D, p. 239.

ERG comment:

Outcomes were presented for change from baseline in MMDs, proportions with ≥50% and ≥75% reduction in MMDs, and change from baseline in days of acute medication use. All outcomes showed a statistically significant improvement in population subgroups who have used at least one prior preventive treatment. Efficacy data for the subgroup who have used ≥3 preventative therapies were, however, not presented in the submission despite having been published.[27]

4.3.4.2 Included studies – PREEMPT trials

The company described the PREEMPT trials as: "The PREEMPT trials (PREEMPT 1 and PREEMPT 2) were double-blind, multicentre, randomised, placebo-controlled trials to confirm the efficacy, safety, and tolerability of OBA for prophylaxis of headaches in adults with CM. For analyses, PREEMPT 1 and 2 were pooled together. Each study had a 28-day screening phase, a 24-week double-blind phase and a 32-week, open-label phase. Eligible patients were aged between 18 and 65 years with a history of migraine, and ≥15 headache days plus ≥4 distinct headache episodes during the baseline phase. Patients were excluded if they had used preventive therapies or any OBA within four weeks prior to the baseline phase. Patients were randomised to OBA 155U, which could be increased up to 195U, or placebo, and stratified by medication overuse. The primary endpoint was the mean change from baseline in frequency of headache days. Secondary endpoints included frequency of migraine days, number of moderate/severe headache days, cumulative number of headache days, proportion of patients with severe disability (HIT-6), frequency of headache and migraine episodes and acute pain medication use" (CS, Appendix D, p. 329).

4.3.4.2.1 Comparison of baseline characteristics between PREEMPT and FOCUS

In clarification, the company provided a comparison of the baseline characteristics between fremanezumab and OBA. However, the baseline characteristics provided for OBA were for the pooled PREEMPT trial population and not for the CM subgroup who had used ≥3 preventative therapies. The baseline characteristics for this pooled trial population was broadly comparable to the FOCUS CM who have used ≥3 preventative therapies (Table 44).

Table 44: Baseline characteristic comparison between fremanezumab in the ≥3 treatment used population and OBA in the overall population for chronic migraine

	Fremanezumab FOCUS (NCT03308968)			OBA PREEMPT 1&2 (NCT00156910 & NCT00168428)	
	Fremanezumab quarterly N=[redacted]	Fremanezumab monthly N=[redacted]	Placebo N=[redacted]	OBA N = 688	Placebo N = 696
Mean age, years	[redacted]	[redacted]	[redacted]	41.1 (10.4)	41.5 (10.7)
Female, n (%)	[redacted]	[redacted]	[redacted]	(87.6)	(85.2)
Caucasian, n (%)	[redacted]	[redacted]	[redacted]	(89.7)	(90.5)
Mean frequency of headache days (SD)	[redacted]	[redacted]	[redacted]	19.9 (3.7)	19.8 (3.7)
Mean frequency of migraine days (SD)	[redacted]	[redacted]	[redacted]	19.1 (4.0)	18.9 (4.1)
Mean frequency of moderate/severe headache days (SD)	[redacted]	[redacted]	[redacted]	18.1 (4.1)	18.0 (4.3)
% Patients with severe (≥60) HIT-6 score, n (%)	[redacted]	[redacted]	[redacted]	(93.5)	(92.7)
Mean frequency of migraine episodes (SD)	[redacted]	[redacted]	[redacted]	11.4 (5.0)	12.2 (5.4)
% Patients overusing acute headache medication, n (%)	[redacted]	[redacted]	[redacted]	(64.8)	(66.1)
Mean frequency of acute headache medication days (SD)	[redacted]	[redacted]	[redacted]	14.6 (6.4)	14.9 (6.4)
Mean HIT-6 score (SD)	[redacted]	[redacted]	[redacted]	65.5 (4.1)	65.4 (4.3)
Role restrictive	[redacted]	[redacted]	[redacted]	38.5 (16.6)	38.7 (17.3)
Role preventive	[redacted]	[redacted]	[redacted]	56.0 (21.2)	56.1 (21.7)

	Fremanezumab FOCUS (NCT03308968)			OBA PREEMPT 1&2 (NCT00156910 & NCT00168428)	
	Fremanezumab quarterly N=[redacted]	Fremanezumab monthly N=[redacted]	Placebo N=[redacted]	OBA N = 688	Placebo N = 696
Emotional functioning	[redacted]	[redacted]	[redacted]	42.1 (24.1)	42.4 (25.0)

Abbreviations: HIT-6, six-item headache impact test; mITT, modified intention to treat; MMDs, monthly migraine days; MSQoL, migraine-specific quality of life questionnaire; SD, standard deviation.

Notes:

[1] Sample sizes, mean age, per cent female, per cent Caucasian, and mean disease duration for FOCUS are based on the safety analysis population. Mean MMDs, mean frequency of acute headache medication days, mean frequency of headache days, mean frequency of moderate/severe headache days, mean HIT-6 score and mean MSQoL scores are based on the mITT population.

[2] Data are mean (SD) or n (%).

4.3.4.2.2 Clinical outcomes – PREEMPT trials

The company also presented results for the combined PREEMPT trials but not for the relevant subgroup of people who have used three or more preventative therapies for migraine (Table 45)

Table 45: Results from the PREEMPT trials

Outcome after week 24	OBA (n=688)	Placebo (n=696)	p-value
Change from baseline in…			
Headache days	-8.4	-6.6	<0.001
Migraine days	-8.2	-6.2	<0.001
Cumulative headache hours on headache days	-119.7	-80.5	<0.001
Migraine episodes	-5.2	-4.9	0.004
Acute medication use	-10.1	-9.4	0.247
Severe (≥60) HIT-6 score	-4.8	-2.4	<0.001
Response rate			
50% responder rates	47.1%	35.1%	<0.001

Abbreviations: HIT-6, six-item headache impact test; OBA, onabotulinum toxin A.
Source: CS, Appendix D, p.330.

ERG comment:

OBA showed significantly better outcomes at 24 weeks compared to placebo in all outcomes except for the change from baseline in the acute medication use. The ERG could not confirm whether the findings reported for the pooled trial population was consistent also for the CM subgroup who have used ≥3 preventative therapies.

4.3.4.2.3 Adverse events – OBA

The CS did not report AE profile for any comparator. Clinical advice suggested that OBA is highly tolerable and that side effects are typically cosmetic and short-lived and that cases of discontinuation due to AEs are few. The ERG also obtained a summary of the AEs from the publication of the pooled PREEMPT trials.[42] This demonstrated that the discontinuation rate at 24 weeks due to AEs in the OBA group was 3.8% and in the placebo group was 1.2% (Table 46).

Table 46: Adverse event profile for OBA at 24 weeks in the pooled PREEMPT data[42]

	OBA (n = 687) n (%)	Placebo (n = 692) n (%)
All adverse events	429 (62.4)	358 (51.7)
Treatment-related adverse events	202 (29.4)	88 (12.7)
Serious adverse events	33 (4.8)	16 (2.3)
Treatment-related, serious adverse events	1 (0.1)	0 (0.0)
Discontinuations related to adverse events	26 (3.8)	8 (1.2)
Death	0 (0.0)	0 (0.0)

Abbreviations: OBA, onabotulinum toxin A.

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

Indirect treatment comparisons were undertaken for CM patients who had previously used ≥3 treatments, but not for EM patients who had used ≥3 treatments. Results were presented for fremanezumab as compared to OBA and as compared to placebo, but not for erenumab, as the company stated that erenumab was not part of the appraisal. While indirect comparisons used generally appropriate methods, the ERG required extensive clarification to determine this.

4.4.1 Methods used in the indirect comparison

Indirect comparisons were undertaken for three outcomes: reduction in monthly migraine days (MMD) in weeks 9-12, percentage of patients with at least 30% reduction in monthly average number of migraine days, and percentage of patients with at least 50% reduction in monthly average number of migraine days. Results were not presented for percentage of patients with at least 30% reduction in monthly average number of migraine days as the only active comparator in this network was erenumab. In the CS (CS Appendix D, p 333), the company made reference to calculating variance for an average reduction in MMD across several four-week time periods. On clarification (see responses A30 and A32), the company noted that these methods did not apply as only Weeks 9-12 were included in the ITC. The company also clarified that reference in this section to an ITC on percentage change from baseline in MMD was in error.

For each outcome, the company identified relevant data from included studies and constructed an evidence network. The company noted that erenumab was included to 'strengthen the network' even though results for this treatment were not presented (CS, p. 94). Each network included one contrast with placebo per active treatment, as the trials for OBA were pooled for analysis. The company noted in the CS (CS, Appendix D), that it assessed the 'feasibility' of each network; when asked in clarification to specifically establish

how transitivity, a key assumption of indirect treatment comparisons, was established between trials, it demonstrated that baseline characteristics of the relevant subgroup for trials in each network were broadly similar (see clarification response A28 and below).

As noted in the CS (CS, Appendix D, p. 333), continuous outcomes were estimated using an identity link and categorical outcomes were estimated using a logit link. Because the indirect treatment comparison was estimated in a Bayesian framework, prior distributions were required. In clarification response A34, the company described the vague prior distributions used (e.g. for treatment effects, a normal distribution with mean 0 and precision 0.0001). The company described in the CS (CS, Appendix D, p. 335) that it preferred fixed effects models to random effects models after having tested both, though CS p. 94 described that fixed effects models were preferred as 'no valid heterogeneity comparisons exist in these data'. The company clarified in response to questions A33 that only fixed effects models were used, meaning that text presented in the CS (CS, Appendix D, p. 334) on heterogeneity assessment was irrelevant to the ITCs presented.

ITCs were estimated using 50,000 burn-in iterations with an additional 50,000 iterations used to compute treatment effects. Convergence was assessed using Gelman-Rubin diagnostics, which were provided in response to clarification question A32. Trace and density plots for each outcome suggested that convergence was achieved for each presented indirect treatment comparison.

ERG comment:

The methods used by the company were broadly appropriate to the appraisal, once relevant aspects had been clarified. In the ERG's view, assessment of methods used to undertake the indirect treatment comparison was unnecessarily complicated by inclusion of ultimately irrelevant sections; for example, random effects models would have been inappropriate given the data available for each network.

A critical issue for which the company did not account was the justification of outcomes chosen for the indirect treatment comparison. While reduction in MMD and percentage attaining 50% reduction in MMD were both appropriate outcomes, other outcomes presented as key for the FOCUS trial (e.g. mean monthly days of use of any acute headache medication) did not appear to be considered for indirect treatment comparison. Of note is that in response to clarification questions A27 and A32, the company provided data inputs and convergence diagnostics for an indirect treatment comparison corresponding to the outcome percentage of patients with at least 75% reduction in MMD, but this was not mentioned in the main text of the appraisal.

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.

Finally, the ERG noted that the question of whether all relevant trials were included in the analysis is foundational to assessing the reliability and appropriateness of indirect treatment comparisons undertaken.

The searches used were the clinical effectiveness searches assessed in Section 4.1.1. The poor quality of these searches means that the ERG cannot be confident that all relevant records would have been picked up in the search results. Our concerns were such that we ran an additional search ourselves, for migraine and OBA only, in Medline, Medline-in-Process, Embase and Cochrane, with a recognised filter from the Cochrane Handbook[16] for RCTs and humans (see Appendix 2). However we did not identify any additional studies of interest.

4.4.2 Results of the indirect treatment comparisons

The results of the indirect treatment comparisons for the two outcomes presented are replicated in Table 47. Results suggest that there were no statistically significant advantages between either of the two fremanezumab dosing regimens and OBA, though both dosing regimens of fremanezumab were numerically superior to OBA in terms of percentage of patients with at least 50% reduction in monthly average number of migraine days [redacted]

Table 47; Monthly migraine days in chronic migraine (mean difference)

	Placebo	F monthly	F quarterly	O 155U-195U
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab monthly	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab quarterly	[redacted]	[redacted]	[redacted]	[redacted]
OBA 155U-195U	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients with ≥50% reduction in monthly migraine days (odds ratios)				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab monthly	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab quarterly	[redacted]	[redacted]	[redacted]	[redacted]
OBA 155U-195U	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: F, fremanezumab; OBA, onabotulinum toxin A.

ERG comment:

Findings presented for ITCs were verified mathematically by the ERG, using study-level data provided as part of clarification response A27. These suggested that the findings of the ITCs as presented were accurate. The ERG noted that point estimates presented as part of CS figure 7 (CS, p. 97) did not match point estimates in CS table 33 (CS, p. 98) for percentage of patients with at least a 50% reduction in MMDs, but consideration of confidence intervals and raw data presented suggested that the estimates contained in the table were accurate.

The sparseness of the networks used to estimate the indirect treatment comparisons are a major weakness of this model. While the ERG was satisfied that additional relevant trials to inform the network were not available, it agrees with the company that the use of subgroup analyses to provide data for the model and the incommensurate timing of measurements for OBA (24 weeks) and fremanezumab (12 weeks) weaken confidence in the estimates (CS, p. 98). Finally, it is important to note that transitivity, discussed above, is a key assumption underlying indirect treatment comparisons. While the ERG regarded that there was some—but not consistently clear—similarity between analysed subgroups in individual characteristics to minimise the risk of inappropriate estimates, the sparsity of networks made this assumption impossible to test.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Additional work on clinical effectiveness undertaken was reported in appropriate sections

4.6 Conclusions of the clinical effectiveness section

The population specified in the company's SLR was broader than was specified in the NICE final scope, but the evidence presented in the CS was for a narrower population. In all, four trials were presented: HALO EM, HALO CM, HALO extension and the FOCUS trials. The ERG identified two additional Phase II trials which were considered to meet the specified inclusion criteria; however, these were not included by the company. The final NICE scope specified "adults with chronic or episodic migraine" while the CS focused on a subgroup of people with EM and CM who have used three or more preventative treatments. Thus, the company considered only the FOCUS trial to be directly relevant to the population of interest. The FOCUS population appeared more representative of the UK population involving 85% of participants from Europe. Thus it's largely comparable to the UK population in respect of baseline demographic and clinical characteristics except for potential differences in the classes and types of drugs previously used.

Data from the HALO EM, HALO CM and FOCUS trials demonstrated better treatment effects in EM and CM for both fremanezumab quarterly and monthly regimens versus placebo across reported outcomes. The HALO extension trial also demonstrated significant improvement in all clinical outcomes compared to the baseline. Treatment effects appear consistent across EM and CM populations in the FOCUS as well as in the subgroup that have used three or more preventative therapies, albeit with reduced precision. The comparative effect versus placebo also appeared generally greater in the FOCUS population than in the HALO population. The ERG believed that the placebo in the FOCUS trial appeared more representative of best supportive care compared to the placebo group in the HALO trials because concomitant preventative therapies were allowed in 20% of the participants in HALO but not in FOCUS. No direct evidence comparing fremanezumab and comparators was found. The ITC containing a network of fremanezumab, erenumab and OBA and placebo, showed there was no statistically significant advantage between either of the two fremanezumab dosing regimens and OBA, though both dosing regimens of fremanezumab were numerically superior to OBA in terms of percentage of patients with at least 50% reduction in monthly average number of migraine days. The ITC estimates were confirmed by the ERG.

The HRQoL assessments broadly showed significant improvement compared to the placebo arms for both fremanezumab groups in both EM and CM populations and in the population, who have used three or more preventive therapies. The AE profile showed fremanezumab to be largely tolerable with treatment discontinuation rate due to AEs of 3% at 12 months. Overall, both fremanezumab regimens are likely to be beneficial in the EM and CM population who have used three or more therapies but the effect sizes may be unstable due to low sample sizes.

5 Cost-effectiveness

5.1 ERG comment on companies review of cost-effectiveness evidence

5.1.1 Objective

The company performed a literature review to identify cost-effectiveness evaluations of prophylactic interventions used to treat people with migraine.

5.1.1.1 Literature search strategy

5.1.1.1.1 Cost effectiveness search (Search D)

The company presented a literature search protocol to support its review of cost effectiveness. This protocol included systematic searches of key biomedical databases using a literature search strategy, and a search of grey literature sources. The literature searches were carried out for the period 2007- February 2018 and were updated in October 2018. It is not clear why this date range was used or why the searches have not been updated more recently.

The search strategy was applied in the following bibliographic databases: Medline and Embase (Elsevier at Embase.com) and Cochrane Library (Wiley). A range of grey literature sources were also searched.

The bibliographic database searching used a search strategy that took the following form:

- Controlled index and free text economics terms AND
- Controlled index and free text terms for migraine AND
- Controlled index and free text terms for either topiramate, botulinum toxin, amitriptyline, valproic acid, gabapentin, propranolol, atenolol, bisoprolol, metoprolol, flunarizine, fremanezumab, erenumab, eptinezumab, or galcanezumab AND
- Limit to Humans AND
- Free text terms for various European countries.

5.1.1.1.2 Health utilities search (Search B)

The company also presented a search for 'humanistic burden of disease' which was carried out for the period 2007 – February 2018 and updated in October 2018.

The bibliographic database searching used a search strategy that took the following form:

- Controlled index and free text terms for health utilities AND
- Controlled index and free text terms for migraine AND
- Limit to Humans AND
- Free text terms for various European countries.

5.1.1.1.3 Costs searches (Search C)

The searches for clinical effectiveness evidence also included searches for costs, see Section 4.1.1. Since these searches were limited to specific study types (mainly RCTs and observational studies) it is hard to see how any useful relevant information can have been obtained.

5.1.1.1.4 Summary

The literature search strategies for Searches D and B are poorly conducted and reported, to the extent that it is likely that relevant papers will have been missed. Some of the concerns are the same as for the clinical effectiveness searches, see section 4.1.1.

- The terms used for economics and for health utilities are not validated search filters, which is likely to result in missing relevant papers. It is unclear why the company did not use tested economics and health utilities filters such as those by SIGN [14] or CADTH [15].
- Numbers in the PRISMA diagrams do not tally with the results: grey literature searches yielded 977 results (Table 3) but the PRISMA for search B (Figure 1) reports 871 ‘records from other sources’ with no explanation of where these have come from. In clarification the company stated that these were grey literature search results but the figures are not consistent and the source of the additional records is unclear. An additional 5 results are listed as ‘Records manually added’ in the PRISMA but it is not clear what these records are, or how they were identified.
- No specific economics sources were searched (such as NHS EED or EconLit) for the database searches, which could result in missing relevant papers. While closed to new records in 2014, a search of NHS EED could still have resulted in relevant literature in the date range of these searches. However, some relevant economics sources were included in the grey literature searches.

ERG comment:

The structure of these searches is poor, which is likely to produce ill-defined search results. The searches are very poorly presented and it is hard to follow what has been done. Searches have been limited in ways that are not evidence-based, without the use of a recognised and validated economics or health utilities filter[14;15]. The decision to limit to some European countries (rather than e.g. countries with similar healthcare systems to the NHS), without justifying this or using MeSH terms for country names is questionable.

The poor quality of these searches means that the ERG cannot be at all confident that all relevant records would have been picked up in the search results.

5.1.2 Inclusion/exclusion criteria

Inclusion and exclusion criteria for cost effectiveness studies, utilities and costs and resource use studies are provided in Table 48.

Table 48: Eligibility criteria

PICOS	Inclusion criteria		
	Search D Economic evaluations	**Search B Utilities**	**Search C: costs**
Population	Adults (aged ≥18 years) with migraine or MOH	As for Search D (see left)	As for Search D (see left)
Intervention/ comparators	Prophylactic treatments: topiramate, OBA, amitriptyline, divalproex/valproate, gabapentin and propranolol, fremanezumab, erenumab, eptinezumab, galcanezumab	No relevant comparators	As for Search D (see left)
Outcomes	Economic evaluations[a]	Resource utilisation, treatment costs, productivity, HRQoL (including generic and migraine-specific instruments and functioning), utility	Resource utilisation, treatment costs, utility[b]
Study types	Economic evaluations (BIM of preventative treatments over short- and long-time periods, CEA of preventative treatments for migraine, cost-minimisations)	Reviews, original observational studies of resource utilisation, treatment costs, productivity loss, PROs, HRQoL, or utility	RCTs and observational trials – Phase III RCTs for all treatments and Phase II for anti-CGRPs only

PICOS	Inclusion criteria		
	Search D Economic evaluations	**Search B Utilities**	**Search C: costs**
Species	Humans	As for Search D (see left)	As for Search D (see left)
Language	English language	As for Search D (see left)	As for Search D (see left)
Geography	UK, France, Germany, Spain, Italy, The Netherlands, Poland, Denmark, Finland, Iceland, Norway and Sweden	As for Search D (see left)	No geographical limit

Abbreviations: BIM, budget impact model; CEA, cost-effectiveness analysis; CGRP, calcitonin gene-related peptide; HRQoL, health-related quality of life; LYGs, life years gained; MOH, medication overuse headache; OBA, onabotulinum toxin A; PICOS, population, intervention, comparators, outcomes and study design; PROs, patient reported outcomes; QALYs, quality-adjusted life years; RCTs, randomized controlled trials; SLR, systematic literature review;

Notes: a) No outcomes specified but by nature of the specification economic evaluations assume outcomes sought were QALYs, LYGs etc.);

b) Search C included clinical effectiveness outcomes as well but only the outcomes relevant to the SLR of costs and healthcare resource use are reported in the table.

Source: CS, Appendix G

ERG comment:

The ERG considered that the eligibility criteria reported were suitable to fulfil the company's objective to identify economic evaluations, utilities and healthcare resource use and costs. The population specified was broad: adults (aged 18 years-plus) with migraine or MOH; the included economic evaluations were conducted in the migraine population. For the review of economic evaluations and costs, the company restricted geographical area to European countries (Table 48). While the ERG acknowledges that these populations are relevant, no rationale was provided for the restriction.

The ERG noted that the company conducted a further round of screening at full text to identify studies that matched the scope of this appraisal. These additional criteria were not, however, explicitly reported (although it was assumed that they aligned with the PICOS criteria listed in the final scope for this appraisal). Studies excluded in the additional round of review (n=20) were reported by the company to either not match the scope of this appraisal or were conducted in countries other than England. Although the ERG accepts this as a pragmatic way to reduce the number of studies, the ERG cannot be certain that the company captured all potentially relevant data.

In the review of cost-effectiveness, the company specified outcomes as "economic evaluations". The ERG assumes that relevant outcomes considered eligible for inclusion were those typically assessed in the specified study designs (cost-effectiveness, cost-minimisation, and budget impact analyses); e.g. quality adjusted life years (QALYs), life

years gained (LYGs). For the reviews of healthcare resource use, costs and utilities, appropriate outcomes were specified and, in respect of utilities, generic and migraine-specific instruments and functioning were considered eligible for inclusion

5.1.3 Results

The initial SLR related to cost-effectiveness evidence identified publications which met the inclusion criteria, 1,009 titles/abstracts and 44 full texts were reviewed. A total of 23 studies were included. The company reported that a: "further round of review was carried out to identify studies that match the scope of this appraisal and this resulted in three relevant studies being identified. All other studies did not match the scope of this appraisal or were "focused on countries other than England." (CS, Appendix G, p.3). A summary of included studies is provided in Table 49.

Table 49: Summary of included studies

Study	Year	Summary of model	Patient population	QALYs	Costs	ICER
Brown et al.[43]	2006	Decision tree based on response level, 12-month time horizon, direct medical cost perspective	Migraine patients suitable for topiramate (average age not stated)	Not calculated, no preventive treatment had 6.0 MMD and treated had 4.19 MMD	Treatment average monthly cost £37.13, untreated average monthly cost £18.90	**Cost *per* migraine averted of £10.13, estimated ICER of £5,728**
Batty et al.[44]	2013	Markov model with 13 health states based on MHD bands, 2-year time horizon, negative stop after 24 weeks (at least 30% response), NHS perspective	• All CM patients (average age 42) • Patients who had previously received three or more oral migraine preventive treatments (average age 42)	All CM: treatment 1.34, placebo 1.24 3+: treatment 1.24, placebo 1.17	All CM: treatment £3,077, placebo £1,680 3+: treatment £3,070, placebo £1765	**All CM: £15,028** **3+: £17,212**
NICE TA260[2]	2012	Markov model with 13 health states based on MHD bands, 2-year time horizon, negative stop after 24 weeks (at least 30% response), NHS perspective	CM patients who had previously received three or more oral migraine preventive treatments (average age 42)	Not stated in FAD	Not stated in FAD	**£18,990**

Abbreviations: CM, chronic migraine; FAD, final appraisal determination; ICER, incremental cost-effectiveness ratio; MHD, monthly headache day; MMD, monthly migraine day; NHS, National Health Service; QALY, quality-adjusted life years.
Source: CS, Appendix G

The included cost-effectiveness studies were summarised (CS, Appendix G) and critically appraised using the Philips checklist (CS, Appendix G, Table 2).

A summary of the identification of cost and utilities was provided in Appendix H of the CS. The company reported that, after applying criteria to identify studies that matched the scope of this appraisal and requirements for the economic model (assumed to be aligned with NICE scope), no relevant studies reporting health-related quality of life data in sufficient detail were identified by the searches (see Section 5.2.7). A Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram is presented by the company in Appendix H of the CS (Figure 1).

A summary of the identification of cost and healthcare resource use was provided in Appendix I of the CS. The company reported that no relevant studies were identified in the population in England, and the most relevant study identified was the publication of the National Health and Wellness Survey[45]. Costs for the identified resource use categories were identified from NHS reference costs or PSSRU data (see Section 5.2.8).

ERG comment:

The CS and CS appendices provided an overview of the included cost-effectiveness, HRQL, and resource use and cost studies. None of the identified studies assessed the cost-effectiveness of fremanezumab. Identified economic evaluations assessed the cost-effectiveness of OBA (including one previous TA (TA260)[2] which was also published in a peer review journal). The economic assessments of OBA were used by the company to inform the development of the submitted model, and address some of the limitations identified with the OBA model (Section 5.2.2).

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

The company developed a *de novo* economic model to assess the cost effectiveness of fremanezumab in patients with migraine.

The following subsections describe the company's methods in more detail including the model structure, the data sources used and applicability of the analysis in comparison to the NICE reference case.[46]

5.2.1 NICE reference case checklist

The NICE reference case checklist is given in Table 50.

Table 50: NICE reference case checklist

Element of health technology assessment	Comments with reference to the scope	Issues arising	Section with detail
Defining the decision problem	The company presented results episodic and chronic populations, but not an all migraine population. The modelled population was narrower than the scope and product license, taking the company's expected position of product in the treatment pathway: for people who have used three or more previous preventative treatments.[1]	The cost-effectiveness of fremanezumab in people who have used fewer than three previous preventative treatments is not estimated.	5.2.3
Comparator(s)	The company did not compare the cost-effectiveness of fremanezumab against oral preventative treatments such as topiramide, propranolol, and amitriptyline. Erenumab is confirmed by NICE as excluded from this appraisal.	The cost-effectiveness of fremanezumab versus oral preventative treatments is not estimated.	5.2.4
Perspective on outcomes	Health effect in respect to migraine frequency, but not in respect to migraine intensity or the separate existence of headache. Although the aspects of health may have been captured in part and indirectly with HRQoL MSQoL questionnaire. The impact of adverse events on costs and benefits was not included in the model, they were judged as similarly infrequent and of low impact.	The absence of explicit consideration for headaches and migraine severity will introduce bias if treatment strategies differentially impact the severity of migraine. Exclusion of adverse events observed in the included short-term trials is reasonable. However, the long-term safety of fremanezumab is not known and not included, with potential to significantly favour fremanezumab in the cost-effectiveness calculation.	4.2.4.5
Perspective on costs	As per scope.	None.	5.2.5
Type of economic evaluation	As per scope.	None.	5.2.2
Time horizon	A ten-year time horizon is inherently problematic in respect of the prediction of long-term safety and effectiveness; but is a timeframe which should include most of the expected difference in costs and outcomes between strategies, so met the requirement of the scope.	Uncertainty within the model is very high. A range of alternative scenarios pertaining to time horizon and long-term effectiveness should be considered together.	5.2.5

Element of health technology assessment	Comments with reference to the scope	Issues arising	Sect-ion with detail
Synthesis of evidence on health effects	Estimates of response rates were the product of an indirect treatment comparison. Estimates of effect size were synthesised from a company analysis of responders and non-responders.	The ERG considered the quality of the ITC to be poor, with potential for bias in the rates carried through to the model. The validity of effect size estimates for responders and non-responders cannot be verified, only compared indirectly against the published trial outcomes. Simplistic methods were used to create an OBA comparison, the results of which should be considered unreliable.	4.3 5.2.6
Measuring and valuing health effects	Measured by response status and extent of migraine day reduction. Patients received a utility premium if and when on prophylaxis.		5.2.6
Source of data for measurement of health-related quality of life	HRQoL data were collected from the FOCUS trial population (MSQoL in preference to EQ-5D); the wider population of people who had used two or more previous prophylactic treatments. Participants were from the US and Europe, with only a small proportion from the UK.	Inconsistency in the population from which input parameters are estimated may introduce bias. HRQoL mapping is a deviation from the NICE reference case and incorporation of additional inaccuracy is likely.	5.2.7
Source of preference data for valuation of changes in health-related quality of life	It was unclear whether or not valuation used a representative sample of the UK public.	Unclear.	5.2.7
Equity considerations	Migraine is more common in women, in lower income earners, and people of a working age.[4]	Restricting access treatments for migraine may impact these groups most.	3.4
Evidence on resource use and costs	Unit costs were appropriately inclusive and unit costing used standard sources.	None.	5.2.8
Discounting	As per scope.	None.	5.2.5

Abbreviations: BSC, best supportive care; CM, Chronic migraine; CS, company submission; EM, episodic migraine; EQ-5D, EuroQol 5 dimension; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IPD, Individual patient data; MMD, monthly migraine days; MSQoL, Migraine specific quality of life; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OBA, onabotulinum toxin A; OLE, Open-label extension; RCT, Randomised controlled trial.

5.2.2 Model structure

The company developed a *de novo* cost-effectiveness model in Microsoft Excel to evaluate the cost-effectiveness of fremanezumab versus relevant comparators in two parallel analyses, separating episodic migraine from chronic migraine; each with a dedicated set of

input parameters. Final results were reported separately but could in theory be combined to represent an all migraine population. In each analysis a strategy of fremanezumab was compared to a strategy of best supportive care. In the chronic migraine analysis a further comparison was made versus a strategy of onabotulinum toxin A. A single model handed both analyses. It comprised an initial a decision-tree before a state transition model, although transitions were determined by a statistical distribution across the MSD health state range, rather than the employment of probability matrices. A schematic of the submitted model is presented in Figure 4. The decision tree allowed a division of migraineurs into responders and non-responders such that their costs and benefits were measured separately, and latterly combined according to weighted proportions. Response was determined after three model cycles (12 weeks) but dedicated change in migraine frequency was attributed from cycle one. The change in distribution of patients across the MMD health state range at each cycle was dictated by the mean MMDs estimate, which could change every cycle. The beta-binomial distribution was found to be the most representative based on a company analysis of individual patient data (IPD). Changes in mean MMDs over time for responders and non-responders are described in Section 0.

Figure 4: Model diagram

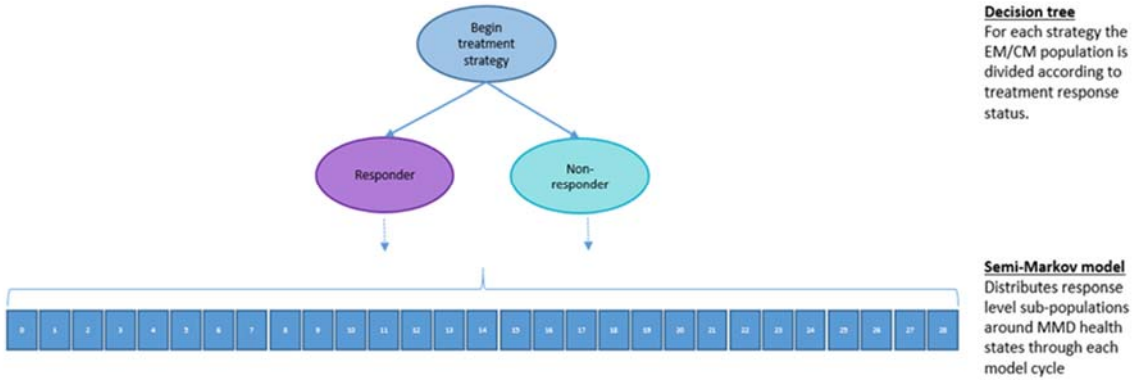


Figure partially redacted - CIC

Abbreviations: CM, chronic migraine; EM, episodic migraine; MMD, Monthly migraine days.
Note: Responders are defined as attaining at least 50% reduction in MMDs from baseline by week 12 in the EM analysis, and 30% reduction from baseline MMDs in the CM analysis.

The model used a cycle length of four weeks, compatible with the monthly administration of fremanezumab, and measured costs and QALYs over a 10-year time horizon (discussed further in Section 5.2.5). Account was made for background mortality throughout. Also,

patients on prophylaxis treatment were at constant risk of discontinuation every cycle (negative discontinuation), and consequent to an annual assessment for sustained effect off-treatment, a 20% of responders to prophylaxis were additionally modelled to discontinue (positive stop). People discontinuing due to loss of effect were returned to BSC monthly migraine day frequency, and people discontinuing having shown sustained effect were continued at full prophylactic effect indefinitely (whilst alive).

Cost and utilities were exclusive to each health state and were summed for responders and non-responders, separately, based on the proportion of patients in each MMD health state. In this way costs have been linked directly to effects.

ERG comment:

The ERG considered believed a cohort model to restrict the estimation of more sophisticated assumptions around long-term safety and effectiveness, as well as changes in the underlying condition with the progression of its natural history. However, the structure was consistent with previous models of migraine, insofar response rate and migraine frequency drove QALY accumulation. The company correctly noted the structural similarity to model used in the ongoing appraisal of erenumab (NICE ID1188), however, whilst the advancement from banded MMD health states has potential to add precision, the significant uncertainty arising from long-term predictions is a more relevant feature.

5.2.3 Population

Fremanezumab has an EMA marketing authorisation for the prophylaxis of migraine in adults who have at least four migraine days per month [1], a subgroup of the population of the scope issued by NICE, which is [all] adults with chronic or episodic migraine. The company explored the cost effectiveness of fremanezumab separately in chronic and episodic migraine. Episodic migraine was modelled as adults with ≥4 to <15 migraine days per month; and chronic migraine was modelled as adults with ≥15 migraine days per month. Adults experiencing <4 migraines per month were not included in this analysis. The company further restricted the modelled population to adults who had used three or more previous prophylactic treatments. In summary, the populations considered in the base case were:

- Adults with EM (≥4 to <15 MDs per month) with ≥3 prior prophylactic treatments used
- Adults with CM (≥15 MDs per month) with ≥3 prior prophylactic treatments used.

A company analysis of effect size according to response at initial assessment drew from FOCUS trial data. The company did not specify if the analysis used the ITT population of a

subset, but all participants must have experienced at least four migraine days, and between six and 14 headache days. This is aligned with the definition ≥4 to <15 MDs per month of the combined analysis population given that a migraine day also meets the criteria for a headache day. However, there were some inconsistencies in the extent of previous prophylactic use in populations from which key input estimates were drawn, and these are discussed in Section 5.2.6.

The modelled age range in was 41-51 years (a year older in the episodic analysis). No account for changes in the natural history of migraine were included.

The company presented a scenario analysis for high frequency episodic migraine, defined by the company as adults with between eight and 14 monthly headache days, so departing from the migraine based definition.

ERG comment:

The ERG note that the company have modelled a narrower migraine population than that laid out in the scope and is granted under their European market authorisation.[1]

The populations from which effectiveness parameters were estimated vary in respect to previous prophylactic use. Whilst imperfect information is expected, the ERG note that these inconsistencies may lead to bias in the model. Additionally, the model did not take account of changes in the natural history of the condition, such as the onset of the menopause, which may introduce further bias.

Not enough detail was provided by the company to be confident that the input parameters informing the HFEM subgroup analysis reflected a well described definition of HFEM.

5.2.4 Interventions and comparators

Fremanezumab was modelled as a self-administered subcutaneous injection using a pre-filled syringe, as either a single injection monthly (225mg) or three injections every three months (675mg). The model considered the two dosing schedules to be equivalent in cost. Fremanezumab were assumed to be self-administered on all occasions. Patients in all treatment strategies were assumed to use acute headache or migraine medication.

The EMA authorisation of fremanezumab recommends that treatment benefit should be assessed within three months after initiation of treatment, and evaluation of the need to continue treatment is recommended regularly thereafter. This initial assessment was the endpoint of the FOCUS trial and in the model marked the application of the pre-planned negative stopping rule (12 weeks for fremanezumab; 24 weeks for OBA). Discontinuation

was applied in the episodic migraine analysis for the proportion failing to reduce MMDs by ≥50% versus baseline; and ≥30% MMDs in the chronic migraine analysis.

A strategy of best supportive care was compared to fremanezumab in both analyses. The effectiveness of BSC was informed by the placebo control arm of FOCUS, which did not allow active prophylactic treatment but did allow acute headache and migraine specific medication. Like the prophylactic strategies, BSC was also modelled in terms of response and non-response. OBA was included as a second comparator to fremanezumab in the chronic migraine analysis, since it is recommended as an option for the prophylaxis of headaches in adults with CM that have not responded to at least three prior pharmacological prophylaxis therapies.[47] They must have headaches on at least 15 days per month, of which at least 8 days are with migraine, a definition consistent with fremanezumab. In the model, the negative stopping rule was applied should inadequate response be measured at initial assessment (24 weeks), defined as failing to reach ≥50% reduction in MMDs.

The company did not present a comparison versus other preventative treatments topiramate, propranolol, amitriptyline or gabapentin. This is in line with their recommendation as earlier options in the treatment pathway.

ERG comment:

That three-monthly fremanezumab administration would be no more resource intensive than monthly administration is a reasonable and potentially conservative assumption, but the plausibility of all patients self-administering fremanezumab is doubtful. The ERG presents a scenario analysis in which 10% of patients receive nursing support is presented in Section 5.3.3. ICERs are seen to reduce only marginally.

The stopping rule described in the OBA license refers to headache days not migraine days; and that discontinuation should follow a change in the condition to episodic frequency, defined as <15 headache days per month for three consecutive months. It is worth noting therefore that the stopping rule of the model is defined in terms of migraine days per month; and OBA is not discontinued when the intensity of the condition improves such that it is no longer defined as chronic. The ERG is concerned therefore that the evaluation fremanezumab versus OBA is inconsistent with its licence with implication at decision level.

5.2.5 Perspective, time horizon and discounting

The analyses assumed the perspective of the NHS and Personal Social Services (PSS), and future costs and benefits were discounted at 3.5% per annum. The time horizon of the base case analyses was ten years, which was varied up and down in scenario analyses (the

lifetime scenario models patients through 58 years). The premise for ten years being that >99% of patients are predicted to have discontinued treatment by this time. However, that this calculation is based on a tentative positive stop rate of 20% annually, and that the effect size of this group is effectively indefinite, weakens the company rationale. Changes in underlying migraine frequency stemming from progressing natural history were not considered by the model.

ERG comment:

The ERG considered that on balance a ten-year time horizon is reasonable given the competing requirements of capturing long-term treatment effect and avoiding increasing uncertainty as extrapolation lengthens. Importantly, the company state that the natural history of the condition is not considered in the simulation (due to a lack of informative evidence). This position becomes increasingly simplistic and uncertain with time horizons beyond ten-years, whilst shorter time-horizons may not be fully representative. By the end of the time horizon here patients exceed 50 years, at which age the onset of menopause in the female contingent becomes relevant. Since this is not accounted for the estimates of cost-effectiveness may be biased.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Baseline population settings

Age, gender and disease severity were baseline variables. Background mortality was age and gender specific and increased with every year in the model. Responder status was defined by adequacy of change in monthly migraine days versus baseline at 12 weeks.

Table 51: Baseline parameters in the model for target population (≥3 prior prophylactic therapies used)

	Episodic migraine	Chronic migraine	Source
[redacted]	[redacted]	[redacted]	FOCUS.
Proportion female	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	Company analysis

Abbreviations: CM, chronic migraine; CS, company submission; EM, episodic migraine; IPD, individual patient data; MMD, monthly migraine days.

Since baseline MMDs for the different arms of FOCUS were not equal these were adjusted in the model to a standardised baseline. The relevant data and method were not described. Baseline estimates are presented in Table 51.

5.2.6.2 Mortality

There was no difference in mortality modelled between strategies. Background mortality was included for all strategies equally, at the rate expected in the UK for age and gender baselines matched to participants of the FOCUS trial. Mortality rates were sourced from the most recent UK life tables[48].

5.2.6.3 Response assessment (pre-planned negative stopping)

Responders with episodic migraine must have reached 50% reduction in monthly migraine days versus baseline, whereas responders with chronic have reached ≥30% reduction versus baseline. Planned negative stopping was based on the initial assessment, which was at 12 weeks for fremanezumab and BSC strategies and 24 weeks for the OBA strategy. Response status dictated the rate and extent of treatment effectiveness in terms of reduction in migraine frequency, both before and after initial assessment.

Effect size parameters for fremanezumab were based on a company analysis of participants of FOCUS, whether the ITT population was used was not specified. Response rates were outcomes of the indirect treatment comparisons with BSC and OBA. In clarification, the company provided the data used to estimate the pooled placebo rates (see response B5). The ERG noted that the number of BSC responders provided for FOCUS in response to B5 ([redacted]) was at variance with the number provided in the company submission in Table 25 (CS, p 82-38; [redacted]). There was no clear reason for this discrepancy. Similarly, for CM, proportions used for 30% BSC responder rates from FOCUS were different between clarification response B5 ([redacted]) and Table 29 in the CS (p. 92; [redacted]). Subsequently, odds ratios from ITCs were applied to BSC response rates to generate response rates for fremanezumab. The estimation of the 30% responder rate for OBA in CM synthesised given that 30% responder estimates were not presented in the relevant trials. The company used the odds ratios generated from the indirect treatment comparison for a 50% responder rate to known estimates for 30% responder rates in placebo and fremanezumab to 'impute' an estimate for the number of people who would have been classified as responding at a 30% threshold. Response rates are presented in Table 52.

Table 52: Rates of response to treatment

	EM	CM
Fremanezumab (12 weeks)	[redacted]	[redacted]
OBA (24 weeks)	[redacted]	[redacted]
BSC (12 weeks)*	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CM, chronic migraine; EM, episodic migraine; OBA, onabotulinum toxin A.
Source: CS Table 50.

A second *per cycle* negative stopping was also applied, in which there was [redacted] per cycle attrition from the first cycle. This 4-week cycle rate was calculated from the annual treatment discontinuation rate for all causes in the HALO open label extension ([redacted]). People who discontinued for this reason were returned to the migraine frequency of BSC.

5.2.6.4 Reduction in migraine frequency

Reduction in migraine frequency was attributed in the model after the first treatment/model cycle, and in subsequent cycles until full effect was reached by 12 weeks for fremanezumab and BSC, and by 24 weeks for OBA. It was assumed that OBA reached the same frequency reduction as fremanezumab. Fremanezumab attained a superior effect versus OBA by virtue of a faster rate of reduction and higher proportion responding. In all strategies, responders maintained full treatment effect through the time horizon until death or discontinuation. Non-responders were returned to baseline mean MMDs, except BSC where patients are retained at baseline throughout. Table 53 presents the maximum reduction in migraine frequency (MMDs) for each treatment strategy.

Table 53: Mean change in MMDs from baseline by analysis and responder status

MMD reduction at response assessment	Episodic migraine (EM)		Chronic migraine (CM)	
	Non-responder	Responder	Non-responder	Responder
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]
OBA	n/a	n/a	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days; OBA, onabotulinum toxin A.
Source: model outputs.

The rate at which full effect was reached was linear in non-response, and exponential in response. The linear reduction in MMDs was an assumed rate, but the fast improvement for responders was based on observation of response in the FOCUS trial. The company found the exponential function to best fit individual patient data (analysis not supplied). That an evidenced based rate of improvement was not applied for non-response was not reasoned by the company, however, the impact on the ICERs of alternative rates of effect is small given the long extrapolation (97.7% of the time horizon), where QALY gain is dominated by strong assumptions around sustained treatment effect. For example, a linear increase for responders increased the fremanezumab versus BSC ICER by just <2% in the chronic analysis.

5.2.6.5 Extrapolation and positive stopping

Beyond response assessment at 12 weeks the estimation of treatment effect was not grounded on randomised controlled evidence. Observations from the one-year HALO open label extension supported key base case assumptions of an unchanging rate of prophylaxis discontinuation; and sustained full effect for patients on treatment as well as for positive stoppers. The mean MMDs experienced by positive stoppers in the first 64 weeks are presented in Figure 5 and

Figure 6 for the episodic and chronic analyses respectively. These illustrate the trend of sustained treatment effect beyond initial assessment that is carried through the lifetime of the model.

Figure 5: Mean MMDs in the first 64 weeks for people experiencing EM

Figure redacted - AIC

Abbreviations: BSC, best supportive care; EM, episodic migraine; frem, fremanezumab; MMD, monthly migraine days.

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Figure 6: Mean MMDs in the first 64 weeks for people experiencing CM

Figure redacted - AIC

Abbreviations: BSC, best supportive care; CM, chronic migraine; frem, fremanezumab; MMD, monthly migraine days, OBA, onabotulinum toxin A.

ERG comment:

The company's approach to the estimation of fremanezumab and BSC responder rates required clarification, however the ERG judged that the indirect treatment comparison was a reasonable approach though the lack of direct estimates between treatments represents a source of uncertainty. Further, the ERG notes some remaining uncertainty regarding the accurate number of placebo responders used in calculating model parameters. While the differences between clarification response and company submission tables are not large, these discrepancies introduce another area of possible bias. The division of the BSC strategy by response was an over complication given discontinuation was not applicable and concerning given that [redacted] was attributed to the very many non-responders. A [redacted] level of response would be expected. The company offered no explanation or justification for this apparent underestimation of BSC effect. This is part of a wider concern regarding the unavailability of information allowing the ERG to verify the responder/non-responder effect

size estimates provided in the submission without detail of their derivation, or publication of the analysis. Linked to this is the setup of the model without separate calculation sheets for responders and non-responders, hindering model checking and adaptation for further analysis.

The most plausible approach to simulating outcomes after 12 weeks, when no reliable evidence exists to populate the ten-year time horizon, is a point for clinical expert debate. Certainly, the modelling of costs and benefits during this period is very important to the evaluation. The selection of a long term horizon, contrary to the two-year horizon of OBA versus BSC in NICE TA260[2], brings into focus four assumptions which underlie the company's conclusion of cost-effectiveness: that the rate of prophylactic discontinuation observed in HALO was true for nine further years, there being no adjustment for long term safety; that 20% of patients had a positive stop; that positive stop patients received full and sustained treatment benefit; that changes in the natural history of the condition were not considered. The combined effect can't be estimated by the ERG, but the combined uncertainty is large and significant.

Singularly, the positive stopping rule of the company base case may be optimistic, in-particular the assumption of sustained full effect without treatment cost. [redacted] of fremanezumab patients were modelled to positively stop at 64 weeks, followed by batches of diminishing size annually after that. In a scenario analysis based on expert opinion contrary to that taken by the company, the ERG applied a linear waning of effect over 5 years for positive stoppers, coupled with treatment re-initiation after a loss of half the effect. See ERG additional analyses, Section 5.3.

The ERG were concerned about multiple weaknesses about the comparison of fremanezumab with OBA. Whilst the response rate estimates had an evidential basis (though not without criticism), the simplification of equating effect size and discontinuation rate to those of fremanezumab undermines the comparison with serious uncertainty about the incremental costs and benefits.

5.2.7 Health related quality of life

In their clarification response the company stated that the model drew from HRQoL data collected from the full FOCUS trial population (n=875) of people who had used ≥2 prior prophylactic therapies, not the ≥3 prior model population. Data collection points were at Week 0 (baseline), Week 4 and Week 12, and participants were surveyed using the disease specific MSQoL (Migraine-Specific Quality of life) questionnaire. Respondents were from the US and Europe and were aged between 18 and 70 years. HRQoL data collected in the

HALO trial was not considered due to the population including patients with no previous inadequate response to preventative migraine medications. The HALO extension did not collect long-term HRQoL data, and no HRQoL data beyond the 12 weeks post treatment initiation was presented by the company. Trial based estimates based on three data collection points supported the ten-year time horizon since it was assumed that MMD health state utilities remained constant and unsullied through time. This may be a simplification for long term sufferers of the condition, whose quality-of- life judgements may evolve.

Data from the disease-specific MSQoL questionnaire were preferred to EQ-5D data because it captured patient HRQoL over the previous four weeks rather than just the day of the clinic visit. The MSQoL is a 14-item HRQoL instrument that measures three dimensions of functional status specific to migraine: role prevention, role restriction, and emotional function. Items are scored on a six-point scale. A mapping technique (Model 1; [49]) was used to transform pooled EM and CM scores to utility values on the EQ-5D-3L scale. The company stated that adoption of the preferred 'model 2', which adjusts for patient characteristics between the source data and that which derives the algorithm (International Burden of Migraine Study[50]), was not possible owing to unavailable patient level outcomes (unspecified). Covariates found to be important to this mapping method were age, sex, race, employment status, headache medication use and comorbidities.

Two sets of utility estimates informed the model. An 'off-treatment' set using MSQoL data collected at baseline, and an 'on-treatment' set based on the Week 4 and Week 12 data collection points. Off-treatment estimates were applied to BSC with there being no use of prophylactic. The on-treatment utility set was used for the fremanezumab and OBA strategies, except following discontinuation. In their clarification response the company reasoned that people on prophylaxis benefit from a utility premium not captured by the MSQoL, and that this is supported by clinical trial data. However, the company did not cite supporting evidence. The company also state that premium was accepted by the appraisal committee of NICE TA260[2] (OBA). The ERG note, however, that the committee also stated that '*there was still considerable uncertainty around the degree to which differential utilities existed within each health state.'* In a scenario analysis the company effectively removed the differential by using the average values of the two sets; this increased the fremanezumab versus BSC ICER by [redacted] in the episodic analysis (to £16,142 per QALY gained), and [redacted] (to £12,860 per QALY gained) in the chronic analysis.

In order to estimate utilities for each of the 29 MMD health states individual patient data from the full FOCUS trial population were fitted to a beta regression model for on- and off-treatment utility sets. Table 54 shows the regression outputs, Figure 7 illustrates them, and

Table 55 details the point estimates for each MMD health state. Since the beta regression was fitted and defined by utility scores mapped from baseline some uncertainty is introduced in its application to on-treatment data. This was shown to be a minor issue since ICERs were not sensitive to minor changes intercept and slope parameters. Health state utilities were assumed constant through each four-week cycle and equal for every patient whenever they entered the health state.

Table 54: Parameters of the beta regression for utility MMD utility estimation

Intercept	Migraine day frequency		Fremanezumab
	Off treatment	On treatment	
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD, monthly migraine days.

Figure 7: Utility regression for MMD health states (≥2 prior prophylactic therapies)

Figure redacted - CIC

Abbreviations: MMD, monthly migraine days.

Table 55: Utility values for each MMD health state (≥2 prior prophylactic therapies)

MMDs	Utility values	
	Off treatment	On treatment
0	[redacted]	[redacted]
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
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24		
25		
26		
27		
28		

Abbreviations: MMD, monthly migraine day.

Table 56 illustrates the range of health state utilities for the on- and off- treatment sets (for reference, the UK population norm for people aged 35-44 years is 0.91; University of York, UK Population Norms for EQ-5D).[51] For comparison the table also shows the utility range used in the model of NICE TA260[2]. These were banded into to six monthly headache day health states, rather than 29 MMD health states here. However, a comparison shows disparity, particularly across at the high severity end of the range. The ERG note the concern of the NICE appraisal committee of TA260 that even their estimates may represent over-estimates.

Table 56: Summary of utility values as model inputs

	On-treatment*	Off-treatment*
Least severe (0 MMDs)	[redacted]	[redacted]
Most severe (28 MMDs)	[redacted]	[redacted]
Range	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; MMD, monthly migraine days. * Figures in parenthesis are those used for the modelling of OBA versus BSC in the NICE TA260, provided for comparison.

Table 57 and Table 58 provide detail of synthesised population level utilities extracted from the model. These represent the utility means accounting for the distribution of patients across the MMD health states and have been dissected by treatment status.

Table 57: Utility of modelled EM population

	Responders	Non-responders
Baseline MMD	[redacted] *(all strategies)*	[redacted] *(all strategies)*
Baseline utility	BSC = [redacted]	BSC = [redacted]
	Frem = [redacted]	Frem = [redacted]
Long-term utility		
	BSC = [redacted] (at 1 yr)	BSC = [redacted] (from 1 mth)
	Frem =	Frem = [redacted] (from 5 mths)
	1 yr = [redacted]	
	3 yrs = [redacted]	
	5 yrs = [redacted]	

Abbreviations: BSC, best supportive care; EM, episodic migraine; Frem, fremanezumab; MMD, monthly migraine days; mth, month; yr, year.

Table 58: Utility of modelled CM population

	Responders	Non-responders
Baseline MMD	[redacted] *(all strategies)*	[redacted] *(all strategies)*
Baseline utility	BSC = [redacted]	BSC = [redacted]
	Frem = [redacted]	Frem = [redacted]
Long-term utility		
	BSC = [redacted] (at 1 yr)	BSC = [redacted] (from 1 mth)
	Frem =	Frem = [redacted] (from 5 mths)
	1 yr = [redacted]	OBA = [redacted] (from 7 mths)
	3 yrs = [redacted]	
	5 yrs = [redacted]	
	OBA	
	1 yr = [redacted]	
	3 yrs = [redacted]	
	5 yrs = [redacted]	

Abbreviations: BSC, best supportive care; CM, chronic migraine; Frem, fremanezumab; MMD, monthly migraine days; mth, month; OBA, onabotulinum toxin A; yr, year.

In the episodic analysis the baseline utilities are similar across responder and non-responder groups ([redacted]), however the baseline mean of those on active treatments is higher versus those on BSC. Since this is pre-treatment, the use of the higher 'on-treatment' utility set is not appropriate. In the chronic analysis the baseline utilities are, as expected, lower across the board ([redacted]). Also, there is greater separation between responder and non-responder baseline scores, owing to the difference in migraine frequency between the two groups at baseline ([redacted]MMDs versus [redacted] MMDs, respectively). This phenomenon is not discussed by the company, but the ERG reasoned that the origin is related to the condition and arises

from the IPD analysis; i.e. the probability of ≥30% reduction in MMDs ('response') is lower in individuals with higher MMDs (more severe chronic migraine). In both EM and CM analyses, following the commencement of treatment and its discontinuation three months later, the utility of non-responders remains close to baseline values for BSC, and slightly above baseline for prophylactic strategies owing to a change from the higher utility set to the lower set after the negative stopping rule is applied. Again, in both analyses, the longer-term utility of responders is higher for prophylactic strategies than for the BSC given, as expected given their superior effectiveness. However, the placebo effect given to BSC, observed in the FOCUS trial, and implemented in the model, results in a mean utility difference of only [redacted] at one year (both analyses). This difference is eroded through the remainder of the time horizon as [redacted] of patients discontinue on treatment every three months and assume the MMD frequency of BSC.

ERG comment:

Utility estimates were based on survey findings from the wider FOCUS trial population of ≥2 used prior prophylactic treatments, so creating population inconsistency across utility and effectiveness estimates. What is gained from use of a larger sample size, and lost by drawing on a broader population is difficult to quantify, but the ERG considered that any inaccuracy introduced is likely to be inconsequential.

The company's preference for MSQoL derived data over directly gathered EQ-5D data was reasonable given the limitation so of the EQ-5D design, requiring mapping to the EQ-5D scale. However, the mapping method followed the model 1 algorithm of Gillard and colleagues,[49] and did not therefore account for differences in baseline characteristics the IBMS international trial and the FOCUS trial. Additionally, the source data was collected over a very short period and in a trial framework, and these values were carried through a ten-year horizon. These limitations make uncertain the degree of bias within the utility estimates. Taken as a whole, the ERG was concerned that health state utilities represent underestimates, especially in the chronic migraine range. A comparison with NICE TA260[2] supports this concern. Scenario analyses in which the utility sets are narrowed to a more conservative range indicate that ICERs are sensitive to inflation of potentially low utility estimates in the chronic range and the utility premium for prophylaxis. Each could bias QALY gain in favour of fremanezumab.

5.2.8 Resources and costs

5.2.8.1 Treatment

The cost of fremanezumab treatment comprised the acquisition cost and the cost of training self-administration, and a one-off at commencement. In respect to cost there was no difference between 28-day and 12-week dosing, in contrast to effectiveness for which the model used two levels corresponding to dosages. The OBA treatment cost comprised an acquisition cost and a regular administration cost based on a 12-week dosing schedule and clinic-based specialist administration. Monitoring costs were applied to both prophylactics as a small fixed cycle cost for people on treatment. Since BSC is in theory included as supportive treatment of the active prophylactic strategies, there were no additional treatment costs for BSC relative to the active treatments (the cost of medication for acute management of migraine was not included). Table 59 details drug, administration and monitoring costs, applied per model cycle.

Figure 8 and Figure 9 depict the proportion of patients remaining on prophylactic treatments through the lifetime of the model. In both analyses the proportion of patients on treatment can be seen to decline generally over time as patients discontinue through each cycle, but also discontinue in cohorts, and this is due to positive treatment discontinuation.

Table 59: Unit costs of the elements of prophylactic treatment

	Fremanezumab	OBA	Reference and justification
Drug acquisition	£415.38 *per* 28 days	£276.40 *per* 12 weeks	List price for fremanezumab. Cost of one 200 unit vial of OBA. All patients use one 200 unit vial *per* treatment (NICE TA260)
Therapy initiation cost	£37.00 (one off cost in first cycle)	Not applicable	One hour training session with Band 5 hospital based nurse
Administration cost	Not applicable	£85.50 *per* 12 weeks	Fremanezumab is self-administered and attracts no NHS resource for delivery. OBA assumed to require 30 minute neurologist visit (NICE TA260)
Monitoring cost	£4.50 *per* 28-days	£4.50 *per* 28-days	Active treatments assumed to require 15 minute with medical consultant every 6 months.

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OBA, onabotulinum toxin A; TA, technology appraisal.

Figure 8: Proportion remaining on active treatment for EM, Years 1 to 5

Figure redacted – AIC

Source: model output. Abbreviations: EM, episodic migraine.

Figure 9: Proportion remaining on active treatment for CM, Years 1 to 5

Figure redacted - AIC

Source: model output. Abbreviations: CM, chronic migraine; OBA, onabotulinum toxin A.

5.2.8.2 Disease management

Other included healthcare resources identified by the company as supportive of the condition were: GP visits, emergency department visits, hospitalisations, nurse practitioner consultations, neurologist consultations, and triptan consumption. Unit costs were obtained from the most recent NHS reference cost schedule and the PSSRU handbook. The rates of consumption of these resources were sourced from the National Health and Wellness

Survey [10;45], the same source used for the ongoing appraisal of erenumab (ID1188). Unit costs are presented in Table 60 and model cycle consumption rates are presented in Table 61, along with the total per cycle cost of disease management by MMD health state.

Table 60: Unit costs of general healthcare supportive of migraine

Resource	Unit costs	Source	Description
General practitioner visit	£37.00	PSSRU[52]	Cost *per* surgery consultation lasting 9.22 minutes, excluding travel
Nurse visit	£36.00	PSSRU[52]	Assumed be the cost of an hour of nurse time at a general practitioner practice
Neurologist visit	£171.00	NHS reference costs[53]	Consultant led neurology visit (service code 400) unit cost
Emergency department visit	£112.63	NHS reference costs[53]	HRG code VB09Z, as *per* OBA submission
Hospitalisation	£636.67	NHS reference costs[53]	Weighted average of HRG codes AA31C, AA31D and AA31E
Triptan use	£1.41	NHS prescription cost analysis[54]	Weighted cost of 1 triptan tablet

Abbreviations: HRG, Healthcare resource group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 61: Resource consumption calculated by frequency of migraine (contacts per person per 4 weeks)

Monthly migraine days	General practitioner visits	Emergency department visits	Hospitalisations	Nurse practitioner visits	Neurologist visits	Oral triptan usage	Weighted cost value *per* MMD health state
0	0.202	0.030	0.023	0.063	0.003	0.000	£28.55
1	0.288	0.067	0.042	0.102	0.015	0.295	£31.92
2	0.288	0.067	0.042	0.102	0.015	0.789	£31.92
3	0.288	0.067	0.042	0.102	0.015	1.283	£31.92
4	0.413	0.058	0.040	0.175	0.013	1.777	£34.28
5	0.413	0.058	0.040	0.175	0.013	2.271	£34.28
6	0.413	0.058	0.040	0.175	0.013	2.765	£34.28
7	0.413	0.058	0.040	0.175	0.013	3.259	£34.28
8	0.553	0.092	0.040	0.048	0.038	3.753	£33.99
9	0.553	0.092	0.052	0.048	0.038	4.247	£33.99
10	0.553	0.092	0.052	0.048	0.038	4.741	£33.99
11	0.553	0.092	0.052	0.048	0.038	5.235	£33.99
12	0.553	0.092	0.052	0.048	0.038	5.729	£33.99
13	0.553	0.092	0.052	0.048	0.038	6.223	£33.99
14	0.553	0.092	0.052	0.048	0.038	6.717	£33.99
15	0.585	0.117	0.052	0.127	0.073	7.211	£42.80
16	0.585	0.117	0.052	0.127	0.073	7.705	£42.80
17	0.585	0.117	0.052	0.127	0.073	8.199	£42.80
18	0.585	0.117	0.052	0.127	0.073	8.693	£42.80
19	0.585	0.117	0.052	0.127	0.073	9.187	£42.80
20	0.585	0.117	0.052	0.127	0.073	9.681	£42.80
21	0.585	0.117	0.052	0.127	0.073	10.175	£42.80
22	0.585	0.117	0.052	0.127	0.073	10.669	£42.80
23	0.585	0.117	0.052	0.127	0.073	11.163	£42.80
24	0.585	0.117	0.052	0.127	0.073	11.657	£42.80
25	0.585	0.117	0.052	0.127	0.073	12.151	£42.80
26	0.585	0.117	0.052	0.127	0.073	12.645	£42.80
27	0.585	0.117	0.052	0.127	0.073	13.139	£42.80
28	0.585	0.117	0.052	0.127	0.073	13.633	£42.80

Abbreviations: MMD, monthly migraine days.

Healthcare resource consumption estimates from the NHWS were based on headache days per month rather than migraine days per month, and patients were asked about their health system contacts in the previous six months.[45] The measurement of MHDs may lead to underestimation of resource use and thereby favour the least effective treatment strategies. The economic model implemented rates according to the reported MMD bandings 0, 1-3, 4-7, 8-14, and CM (15-28); and these were identical to the rates used in the ongoing appraisal of erenumab (ID1188).

5.2.8.3 Adverse events

Adverse events were not considered in the company's economic model.

ERG comment:

The unit costs of resources have been drawn from standard sources and generally appear reasonable if not accurate. The ERG believed that the assumption of 100% self-administration is unlikely but noted that when 10% of patients are assisted by a hospital nurse (Band 5) for half an hour, the ICERs increase only marginally (~0.5%).

The rates of resource consumption, revised mid-way through the ERG review, were aligned to the ongoing appraisal of erenumab, and are subject to several criticisms:

- Rates were based on a general migraine population, with no specification of previous prophylactic history, therefore it is not known if rates are representative of the ≥3 prior prophylactic treatment population.
- The MHD outcome is not equivalent to the MMD outcome, and therefore consumption rates may be underestimates and introduce conservative bias. The ERG noted that a rate inflation across service use of 20% reduces ICERs by up to 2.8% (EM: Frem vs. BSC).

HRQoL and costs associated with AEs are not reflected in the model (apart from causing treatment discontinuation). The ERG cannot rule out that the exclusion of AE-related resource use and costs, short and long-term, have introduced bias in the cost effectiveness results.

The social cost of migraine is calculated in the company scenario analysis based on missed days of work. In accordance with standard NICE methodology this was not included in the company base case.

5.2.9 Cost effectiveness results

Following clarification, the company submitted a revised model in which the rate of resource uptake across treatment strategies was revised. The results of the revised EM and CM analyses are presented below. Note that the company do not present a combined analysis for all migraine in which the outcomes of EM and CM are combined.

Error! Not a valid bookmark self-reference. details the total costs and QALYs of the fremanezumab and BSC strategies of the EM analysis. Over 10 years the average cost per person of employing a strategy of fremanezumab for prophylactic prevention of migraine was [redacted], some [redacted] more than the cost of acute treatments conforming BSC. This was [redacted] at one year ([redacted]); [redacted] at Year 2 ([redacted]); and [redacted] at year 5 ([redacted]). There was an increase in the mean per patient QALY accumulation over ten years with fremanezumab, leading to a total gain of [redacted] QALYs over BSC. This was [redacted] at 1 year ([redacted]); [redacted] at two years ([redacted]), and [redacted] at five years ([redacted]).

Table 62: Summary result of base case in EM (deterministic)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	**-**
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£13,954**

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

Error! Not a valid bookmark self-reference. details the total costs and QALYs of the fremanezumab, OBA, and best supportive care (BSC) strategies of the CM analysis. Over ten years the average cost per person of employing a strategy of fremanezumab for prophylactic prevention of migraine was [redacted], thereby predicted to be more costly in a CM population. This was and additional cost of [redacted] versus BSC and [redacted] versus OBA. Versus BSC the additional cost [redacted] at Year 1 ([redacted]); [redacted] at Year 2 ([redacted]); and [redacted] at Year 5 ([redacted]). Versus OBA the additional cost was [redacted] at one year ([redacted]); [redacted] at Year 2 ([redacted]); and [redacted] at Year 5 ([redacted]). An average patient using fremanezumab was predicted to accumulate [redacted] more QALYs than a strategy of BSC, and [redacted] QALYs more than a strategy of OBA. Versus BSC the QALY gain was [redacted] at one year ([redacted]); [redacted] at two years ([redacted]), and [redacted] at five years ([redacted]). Versus OBA the QALY gain was [redacted] at one year ([redacted]); [redacted] at two years ([redacted]), and [redacted] at five years ([redacted]).

Table 63: Summary result of base case in CM (deterministic)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs. BSC (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	**-**
OBA	[redacted]	[redacted]	[redacted]	[redacted]	£6,777	£6,777
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£11,825**	**£16,227**

Abbreviations: BSC, best supportive care; CM, chronic migraine; ICER, incremental cost-effectiveness ratio; OBA, onabotulinum toxin A; QALY, quality-adjusted life year.

Using the company base case assumptions and parameters, the model supports the conclusion that over 10 years fremanezumab is cost-effective versus BSC in EM, and versus BSC and OBA in CM. Behind this outcome it may be relevant to note that whilst additional costs associated with fremanezumab are gained early, additional QALYs are gained relatively late. This dynamic is largely consequent on the positive stopping rule by which every year 20% of responders maintain full prophylactic effect after discontinuation of active treatment; and serves to highlight the importance of this rule alongside the length of the chosen time horizon.

5.2.10 Sensitivity analyses

The company conducted limited tests of sensitivity of the ICER towards uncertainty arising from parameter point estimates and assumptions underlying model structure. It appears that the OWSA lacked tests of treatment effect (MMD reduction), though the company did undertake a OWSA on 'utility treatment effect', suggesting that the utilities accruing from treatment were varied +/- 20%. Further, the areas of greatest structural uncertainty, the assumptions pertaining to the positive stopping rule and length of the time horizon should have been subject to more extensive testing, specifically bi-variate tests in which both variables are changed simultaneously.

5.2.10.1 Uncertainty in parameters – PSA

The probabilistic sensitivity analysis (PSA) ran 1,000 iterations; no information was presented in respect to output stability at this level. Table 64 presents the mean result of the probabilistic sensitivity analysis of the EM analysis; Figure 10 is a plot of each iteration on the cost-effectiveness plane. Mean findings are consistent with the

deterministic EM analysis; the plot shows that QALY gain is highly sensitive to variation across the effectiveness variables relative to incremental costs.

Figure 11 illustrates the cost-effectiveness acceptability curve, this predicts a [redacted] probability of fremanezumab being the most cost-effective treatment in the EM analysis at the £20,000 per QALY gained willingness-to-pay threshold; and [redacted] probability at the £30,000 threshold.

Table 64: Summary result of base case in EM (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	**-**
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£13,843**

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

Figure 10: PSA result in EM plotted on the cost-effectiveness plane, fremanezumab vs. BSC

Figure redacted - CIC

Abbreviations: BSC, best supportive care; EM, episodic migraine; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 11: Cost-effectiveness acceptability curve for EM, fremanezumab vs. BSC

Figure redacted - CIC

Abbreviations: BSC, best supportive care; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; WTP, willingness to pay.

Table 65 presents the mean results of the PSA of the CM analysis, including the comparison with OBA;

Figure 12 and

Figure 13 show the plots of each iteration on the cost-effectiveness plane, for the comparison versus BSC and OBA, respectively. Mean findings are consistent with the deterministic CM analysis. Both plots show that QALY gain is highly sensitive to variation across the effectiveness variables relative to incremental costs, as was seen in the EM analysis.

Figure 14 and Figure 15 illustrate the cost-effectiveness acceptability curves versus BSC and OBA, respectively (and separately). Fremanezumab is predicted to be the most cost-effective option versus BSC in [redacted] of simulations when using a £20,000 per QALY gained WTP threshold; and [redacted] of simulations using the £30,000 threshold. Versus OBA the respective probabilities are [redacted] and [redacted].

Table 65: Summary result of base case in CM (probabilistic)

Technologies	Total costs (£) [SE]	Total QALYs [SE]	Incr. costs (£) [SE]	Incr. QALYs [SE]	ICER vs. BSC (£/QALY)	Incremental ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	**-**
OBA	[redacted]	[redacted]	[redacted]	[redacted]	£6,932	**£6,932**
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£12,102	**£16,654**

Abbreviations: BSC, best supportive care; CM, chronic migraine; ICER, incremental cost-effectiveness ratio; OBA, onabotulinum toxin A; QALY, quality-adjusted life year; SE, standard error.

Figure 12: PSA result in CM plotted on the cost-effectiveness plane, fremanezumab vs. BSC

Figure redacted - CIC

Abbreviations: BSC, best supportive care; CM, chronic migraine; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 13: PSA result in CM plotted on the cost-effectiveness plane, fremanezumab vs. OBA

Figure redacted - CIC

Abbreviations: BSC, best supportive care; CM, chronic migraine; OBA, onabotulinum toxin A; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WT0, willingness to pay.

Figure 14: Cost-effectiveness acceptability curve for CM, fremanezumab vs. BSC

Abbreviations: BSC, best supportive care; CM, chronic migraine; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; WTP, willingness to pay.

Figure 15: Cost-effectiveness acceptability curve for CM, fremanezumab vs. OBA

Figure redacted - CIC

Abbreviations: CM, chronic migraine; ICER, incremental cost-effectiveness ratio; OBA, onabotulinum toxin A; PSA, probabilistic sensitivity analysis; WTP, willingness to pay.

5.2.10.2 Uncertainty in parameters – Deterministic one-way sensitivity analysis

The company conducted a univariate sensitivity analysis of the EM and CM analyses, in each case presenting results across 13 altered variable (+/-20%). Results are illustrated in

Figure 16, Figure 17 and

Figure 18. Whilst a range of parameters are tested, a test of variation in effect size is absent, so the ERG conducted this additional test for inclusion in the set (Section 5.3). Results were presented as changes from mode net monetary benefit and used a cost-effectiveness threshold of £30,000 per QALY gained. The company interpret the one-way sensitivity analyses to conclude that the model was stable to changes in all inputs including those of greatest impact: fremanezumab cost, the time horizon, and utility treatment effect. However, the PSA plots (Section 5.2.9) suggest instability in the accumulation of QALYs, more specifically utility.

Figure 16: Tornado diagram of OWSA of selected parameters in EM, fremanezumab versus BSC

Figure redacted - CIC

Abbreviations: BSC, best supportive care; EM, episodic migraine; NMB, net monetary benefit; OBA, onabotulinum toxin A; OWSA, one-way sensitivity analysis, Tx, treatment.

Figure 17: Tornado diagram of OWSA of selected parameters in CM, fremanezumab versus BSC

Figure redacted - CIC

Abbreviations: BSC, best supportive care; CM, chronic migraine; NMB, net monetary benefit; OBA, onabotulinum toxin A; OWSA, one-way sensitivity analysis, Tx, treatment.

Figure 18: Tornado diagram of OWSA of selected parameters in CM, fremanezumab vs. OBA

Figure redacted – CIC

Abbreviations: CM, chronic migraine; NMB, net monetary benefit; OBA, onabotulinum toxin A; OWSA, one-way sensitivity analysis; Tx, treatment.

5.2.10.3 Uncertainty around structural assumptions

Table 66 presents the ICER result set of the company's scenario analyses for episodic migraine. Eleven alternative scenarios were tested. The ERG draw attention to the scenarios relating to the assumptions about which uncertainty is most profound. I.e. the time horizon (scenarios 1 and 2); the positive stopping rule and long-term treatment effect (scenarios 3, 4, 7 and 8).

The company have not provided adequate description of the methods for the implementation of less obvious. Of particular interest treatment waning. In this company scenario the difference in effect size (migraine frequency) between prophylactic strategies and BSC is waned linearly over ten years. The ERG believe this to be unlikely, since the treatment effect felt by responders in all strategies would more plausibly return to baseline. Moreover, when some or all effect is lost it can be expected that people would seek to re-start prophylaxis. The ERG explore this scenario in Section 5.3.3.

Table 66: Result of scenario analyses in the episodic migraine analysis

Scenario	ICER, Frem vs BSC
Base case	**£13,954**
(1) Time horizon reduced from 10 to 5 years	£22,598
(2) Time horizon increased from 10 years to lifetime (57.8 years)	£4,767
(3) Linear waning of active treatment effect to BSC level over 10 years post discontinuation.	£14,202*
(4) Lifetime horizon and 10-year waning of active treatment effect to BSC level	£4,835
(5) Treatment administration costs included for fremanezumab (monthly: £1.85 per cycle)	£14,054
(6) Treatment administration costs included for fremanezumab (quarterly: £0.62 per cycle)	£13,987
(7) Positive stopping rule affects only 10% of currently treated patients rather than 20% in the base case	£16,620
(8) No positive stopping applied at annual assessment due to sustained treatment effect	£20,214
(9) Impact of lost work days included in cost analysis	Dominates
(10) Use of quarterly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£13,976
(11) Use of monthly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£13,909

Abbreviations: BSC, best supportive care; Frem, fremanezumab; ICER, incremental cost-effectiveness ratio.
*The ERG advise caution with this result which appears to wane patients on prophylaxis as well as those those with positive discontinuation.

Table 67 presents the ICER result set of the company's scenario analyses for CM. Fourteen alternative scenarios within the CM analysis were tested; including three specific to OBA and the CM analysis (Scenarios 12-14). Again, the ERG draw attention to the scenarios relating to the base case assumptions about which uncertainty is most profound: time horizon (Scenarios 1 and 2); positive stopping rule / long-run treatment effect (Scenarios 3, 4, 7 and 8). These, and their variants are discussed in Section 5.3.

Table 67: Result of scenario analyses in the chronic migraine analysis

Scenario	ICER, Frem vs. BSC	ICER Frem vs. OBA
Base case	£11,825	£16,825
(1) Time horizon reduced from 10 to 5 years	£19,328	£27,517
(2) Time horizon increased from 10 years to lifetime (57.8 years)	£4,085	£5,555
(3) Linear waning of active treatment effect to BSC level over 10 years post discontinuation.	£12,017*	£16,382*
(4) Lifetime horizon and 10-year waning of active treatment effect to BSC level	£4,131	£5,589
(5) Treatment administration costs included for fremanezumab (monthly: £1.85 per cycle)	£11,907	£16,380
(6) Treatment administration costs included for fremanezumab (quarterly: £0.62 per cycle)	£11,853	£16,278
(7) Positive stopping rule affects only 10% of currently treated patients rather than 20% in the base case	£14,017	£19,634
(8) No positive stopping applied at annual assessment due to sustained treatment effect	£16,951	£24,756
(9) Impact of lost work days included in cost analysis	Dominates	Dominates
(10) Use of quarterly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£12,243	£17,325
(11) Use of monthly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£11,462	£15,326
(12) Proportion of patients responding to OBA increased to from [redacted] to [redacted]	£11,825	£22,411
(13) Proportion of patients responding to OBA decreased from [redacted] to [redacted]	£11,825	£12,742
(14) 50% reduction in MMDs used as response threshold in CM rather than 30%	£10,724	£17,155

Abbreviations: BSC, best supportive care; CM, chronic migraine; Frem, fremanezumab; ICER, incremental cost-effectiveness ratio; MMDs, monthly migraine days; OBA, onabotulinum toxin A.
*A modelling error was identified in the calculation of these estimates. Further, the ERG advise caution with this result which appears to wane patients on prophylaxis as well as those with positive discontinuation.

5.2.11 Subgroup analysis of high frequency episodic migraine (HFEM)

This analysis used efficacy data from the FOCUS clinical trial in patients with 8-14 monthly headache days. This patient group was assumed to have baseline characteristics of the overall EM population. Responders had baseline mean MMDs of [redacted] compared to [redacted] for non-responders. The fremanezumab treatment effect compared to BSC was [redacted] MMDs in

responders and [redacted] MMDs in non-responders. At least a 50% reduction in MMDs was seen in [redacted]% of fremanezumab patients and [redacted]% of BSC patients.

Table 68 presents the result of the subgroup analysis. The direct and size of incremental costs and QALYs are consistent with the main analyses of EM and CM, with the ICER for fremanezumab versus BSC lying marginally below that in the whole EM population.

Table 68: Summary result of HFEM subgroup analysis (deterministic), fremanezumab vs. BSC

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	**-**
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	**£12,275**

Abbreviations: BSC, best supportive care; HFEM, high-frequency episodic migraine; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The model result for HFEM was similar in costs, QALYs and incremental ratio to the analysis of EM. The outcomes of this subgroup analysis were subject to all the same sources of uncertainty as the outcomes of the main EM and CM analyses. Results here should be considered in that context. The company did not present sensitivity analyses specific to the subgroup.

5.2.12 Model validation and face validity check

Version 1 of the economic model was received by the ERG on 1 May 2019. This was replaced by Version 2 two days later. The initial check for functionality and presentation found that the model was in an unfit state for validation owing to a large quantity of redundant content and macros, a large number of unlabelled parameters, and implementation in VBA, which is non-standard software in NICE appraisals. Following an ERG request the company provided a revised version (Version 3, received 22 May 2019; Week 3). This was subsequently succeeded by Version 4 (17 June 2019; Week 7) following the company's identification of and correction of errors identified during the clarification process.

The company used clinical experts to review key inputs and assumptions and a health economist to review model execution. The company also refer to a form of internal calibration using trial evidence and methodology. This was unspecified so could not be reviewed by the ERG. Although methods and input estimates have been replicated from other NICE appraisals, no discussion was offered in respect to the validation of model outputs versus these appraisals.

Two ERG economic modellers undertook a systematic check of the company's economic model for execution error as well as development error versus intent as described in the CS. Sources and assumptions were then scrutinised against the presented evidence and expert clinical opinion of the ERG.

5.2.12.1 Issues in the company economic model identified by the ERG

Overall, notwithstanding redundant content, poor labelling, and sequential running of calculations, Version 4 of the company economic model was accurately executed, just two issues were identified by the ERG in the company base. These were corrected to form a revised ERG base case. No inputs or structural assumptions are replaced, but the ERG caution that due consideration be taken of alternative methods for estimating long-term benefit.

Calculation of mean cycle-level utility

The model code in column DJ <Tx1 Calculations (Ch)> incorrectly adjusted the impact of mortality in the mean utility calculation with the inclusion of the term '/(1-column E)'.

Treatment costs over annual assessment period

The report describes an annual 12-week treatment break to assess response to treatment. However, this was implemented as an eight-week break in the model, seemingly excluding the first off-treatment cycle. In the case of onabotulinum toxin A the two cycle assessment periods missed the treatment cycle such that treatment costs were not removed during assessment. The ERG has adapted the company economic model to create the intended 12-week period and adjusted the time between assessments downward from 52 weeks to a treatment year of 48 weeks. In this way the assessments are synchronised with treatment administration.

5.2.12.2 Responder level analysis

The company economic model required estimates of treatment effect size for responders and non-responders. The company conducted an analysis of patient level data from the FOCUS trial to inform the model of these inputs. This analysis was not provided to the ERG and is not available as published evidence. Therefore, the effect size estimators, central to the evaluation of the cost-effectiveness of fremanezumab, could not be reviewed and verified by the ERG.

5.2.12.3 Cost effectiveness of OBA versus BSC

NICE TA260[2] included a cost-effectiveness analysis of OBA versus BSC using a similar methodological framework, therefore it is informative to compare for consistency the

respective strategy level findings of the two appraisals, albeit that the comparison in this submission is simplified and reliant on OBA effectiveness equated to that of fremanezumab. The exception is that response at the 30% threshold level in CM was an outcome of the NMA and therefore drew on the findings of the OBA pivotal trials PREEMPT I and II. Table 69 compares the findings of the respective economic analyses and finds consistency across the ratio of costs and effects in each analysis. Since the time horizon of the TA260 cost-effectiveness analysis was just two years compared to ten, strategy cost and QALY totals are lower in the TA260 analysis, as would be expected in the context of the assumption around long-tern effectiveness of OBA in this analysis (sustained full effect of OBA prophylaxis and no positive discontinuation).

Table 69: Comparison of findings across appraisals, OBA vs. BSC

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	**-**
OBA	[redacted]	[redacted]	[redacted]	[redacted]	**£6,777****
BSC TA 260*	£1,895	1.20			
OBA TA260*	£2,438	1.09	£543	0.09	**£6,083**

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; OBA, onabotulinum toxin A; QALY, quality adjusted life year; TA, technology appraisal.
Notes: *For a population whose condition failed to respond to at least three prior preventive medications. ** Not presented in the company report but extracted from the CEM. Source: NICE TA260 FAD 3.16.

5.2.12.4 Model versus trial outcomes

Table 70 Effect size estimators versus FOCUS trial outcomeTable 70 presents the result of a simple comparison of effect estimators used in the model with respective outcomes from the FOCUS trial. The weighted estimators, using response rates used in the model, are higher than published figures for both fremanezumab and BSC/placebo strategies.

Table 70 Effect size estimators versus FOCUS trial outcome

MMD reduction at response assessment	Model						FOCUS trial**	
	Non-responder		Responder		Weighted*			
	EM	CM	EM	CM	EM	CM	EM	CM
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC/Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BSC, best supportive care; CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days; OBA, onabotulinum toxin A. *Weights were ITC responder rates: CM: Frem =54.25%; BSC = 21.69%; EM: Frem = 59.56%, BSC = 10.17%. ** CS B 2.6.2 Table 17.

ERG comment:

The inclusion of redundant content and code, unnecessarily complex formulation, and absent/poor labelling hindered model validation. This was compounded by the absence of clear and complete description in the report across numerous elements of the model. A second serious challenge to model verification, and adaptation, was the absence of separate calculation sheets for responders and non-responders. Instead a macro was used to run responder and non-responder analyses sequentially. This and the loss of instantaneous result calculation following changes to inputs increased model opacity.

Key trial evidence was synthesised for outcomes at response level, but detail of the analysis was not published or provided, therefore its method and accuracy could not be validated by the ERG. The company offered no external validation of model outputs, and the testing of uncertainty within model parameters failed to reasonable inclusion of key effectiveness inputs, leading to the company's optimistic conclusion of ICER stability.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 Expanded one-way sensitivity analysis

The ERG implemented a series of OWSAs to verify estimates provided in tornado diagrams. These OWSAs revealed that in CM as in EM, the model was sensitive to fremanezumab cost and to analysis timeframe. Varying fremanezumab cost by 20% yielded an ICER range of £10,376 in CM against BSC, and an ICER range of £12,481 in EM against BSC. Findings for CM are documented in Table 71 and Figure 19, whereas results for EM are documented in Table 72 and Figure 20. Inclusion of OWSAs for reducing in mean MMDs for fremanezumab did not generate large impacts on the ICERs.

Table 71 Univariate sensitivity analysis: impact of +/- 20% on selected parameters on the ICER vs BSC, CM

	-20%	+20%	Range
Company base case	£11,825		
Fremanezumab cost per 4 weeks	£7,075	£17,451	£10,376
Analysis timeframe (# of 4-week cycles)	£14,034	£10,237	£3,797
Fremanezumab discontinuation per treatment cycle	£12,707	£11,016	£1,691
Positive stopping rule percentage	£12,621	£11,120	£1,501
Utility treatment effect	£12,206	£11,473	£733
Reduction in mean MMD*	£11,974	£11,680	£294
Patient starting age	£11,799	£11,876	£78
Cost of monitoring per 4 weeks	£11,793	£11,857	£64
Proportion female	£11,829	£11,821	£8

	-20%	+20%	Range
OBA cost per 12 weeks	£11,825	£11,825	£0
OBA administration cost	£11,825	£11,825	£0
Fremanezumab administration cost	£11,825	£11,825	£0
Cost per missed work day	£11,825	£11,825	£0
OBA discontinuation per treatment cycle	£11,825	£11,825	£0

Abbreviations: MMD, monthly migraine days; OBA, onabotulinum toxin A; Tx, treatment.
*Additional parameter test conducted by the ERG

Figure 19: Univariate sensitivity analysis – fremanezumab vs. BSC, CM

Figure redacted – CIC

Abbreviations: BSC, best supportive care; CM, chronic migraine; MMD, monthly migraine days; OBA, onabotulinum toxin A; Tx, treatment.

Table 72 Univariate sensitivity analysis: impact of +/- 20% on selected parameters on the ICER, EM

	Decrease Result	Increase Result	Result Range
Company base case		£13,585	
Fremanezumab cost per 4 weeks	£8,151	£20,631	£12,481
Analysis timeframe (# of 4-Week Cycles)	£16,342	£12,017	£4,324
Fremanezumab discontinuation per Tx Cycle	£14,853	£12,927	£1,926
Positive stopping rule percentage	£14,319	£13,434	£885
Utility treatment effect	£13,809	£13,906	£97
Reduction in mean MMD*	£13,825	£13,921	£97
Patient starting age	£13,862	£13,853	£9
Cost of monitoring per 4 weeks	£13,858	£13,858	£0
Proportion female	£13,858	£13,858	£0
OBA cost per 12 weeks	£13,858	£13,858	£0
OBA administration cost	£13,858	£13,858	£0
Fremanezumab administration cost	£13,858	£13,858	£0
Cost per Missed Work Day	£13,858	£13,858	£0
OBA Discontinuation per Tx Cycle	£13,858	£13,858	£0

Abbreviations: EM, episodic migraine; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; OBA, onabotulinum toxin A; Tx treatment.
*Additional parameter test conducted by the ERG

Figure 20: Univariate sensitivity analysis – fremanezumab vs. BSC, EM

Figure redacted – CIC

Abbreviations: BSC, best supportive care; EM, episodic migraine; MMD, monthly migraine days; OBA, onabotulinum toxin A; Tx, treatment.

5.3.2 Bi-variate sensitivity analysis of time horizon and positive stopping

The model time horizon and the percentage of annual positive stop cases represent the most uncertain of the top five most sensitive parameters of the model. The former is determined by the latter, and has been both shorter and longer in other appraisals of prophylactic interventions for migraine. The latter represents a best guess estimate which has no evidential founding. It is therefore helpful to observe the impact on the EM and CM ICERs when both are changed in concert. Table 73 and Table 74 present findings and show that the ICER for the comparison of fremanezumab versus BSC is more sensitive to the length of the time horizon than the annual percentage of positive stoppers.

Table 73: Bi-variate analysis of time horizon and positive stopping rule percentage, EM. Showing resultant ICER.

	Annual positive stopping percentage				
Time Horizon	5%	10%	15%	20%	25%
2 years (104 weeks)	£36,739	£36,331	£35,922	£35,514	£35,106
10 years (520 weeks)	£18,303	£16,620	£15,183	£13,954*	£12,897
15 years (784 weeks)	£13,898	£12,353	£11,098	£10,066	£9,205

Abbreviations: EM, episodic migraine; ICER, incremental cost-effectiveness ratio.
Note: *Company base case.

Table 74: Bi-variate analysis of time horizon and positive stopping rule percentage, CM. Showing resultant ICER

	Annual positive stopping percentage				
Time Horizon	5%	10%	15%	20%	25%
2 years (104 weeks)	£32,031	£31,686	£31,340	£30,994	£30,649
10 years (520 weeks)	£15,402	£14,017	£12,836	£11,825*	£10,956
15 years (784 weeks)	£11,654	£10,395	£9,373	£8,531	£7,830

Abbreviations: CM, chronic migraine; ICER, incremental cost-effectiveness ratio.
Note: *Company base case

5.3.3 Waning and re-starting of prophylactic treatment effect

The ERG considered that it is plausible, in the absence of evidence, to apply waning of prophylactic treatment rather than model a sustained full effect for people who discontinue prophylaxis due to positive assessment. The balance of ERG expert opinion is a preference of the waning of prophylactic following positive discontinuation such that full effect is diminished to baseline by five-years. However, this should be coupled with the re-start of prophylaxis after a period of decline in benefit equal to half of the full treatment benefit. The ERG believes the inclusion of this additional analysis, albeit necessarily simplified, will better reflect clinical reality and the cost-effectiveness of fremanezumab. This additional analysis has been incorporated into the CEM and taken-up as an ERG preference, contributing to a revised ERG base case.

5.3.4 Additional ERG scenario analyses

Table 75 presents results of additional deterministic scenario analyses based on the company base case settings.

Table 75: Additional scenarios conducted by the ERG

Scenario	EM ICER, Frem vs BSC	CM ICER, Frem vs BSC	CM ICER, Frem vs OBA
Base case	**£13,954**	**£11,825**	**£16,227**
a) 5-year linear wane of fremanezumab effect to baseline for positive stoppers, and 5-year linear wane of BSC effect in responders	*	£9,719	*
b) 5-year linear wane of fremanezumab effect to baseline for positive stoppers, and 5-year linear wane of BSC effect in responders, plus re-start at 50% loss of full effect	*	£13,835	*
c) 10% of fremanezumab patients require 30mins of nurse support for monthly drug administration	£14,022	£11,881	£16,332
d) Rate of consumption of disease management resources increased by 10%	£9,088	£7,205	£11,328
e) Upper and lower bounds of utility range matched to TA260	£21,992	£19,808	£28,510
f) Utility premium for prophylaxis removed	£16,435	£13,363	£20,681
g) e + f	£29,364	£24,520	£45,779

Abbreviations: BSC, best supportive care; CM, chronic migraine; Frem, fremanezumab; ICER, incremental cost-effectiveness ratio.
Note: *analysis not conducted for this comparison

5.4 Conclusions of the cost-effectiveness section

The company's presented SLR for economic evidence included searches of poor quality. The methods presented for the SLR led the ERG to conclude that it was likely key studies would have been missed. In addition, the company's model was presented in non-standard

software and was presented several times to the ERG with progressive updates. This complicated model checking substantially.

The ERG considered an individual patient simulation would have provided a model framework better suited handling alternative long-term outcomes, but the model structure was adequate and has a precedence in the evaluation of cost-effectiveness in migraine. Central to the estimation of benefits were responder rates and treatment driven changes in migraine frequency, other trial outcomes were not included but this followed the pattern of NICE TA260 for OBA an the ongoing appraisal of erenumab. MSQoL data was mapped to the EQ-5D scale using a method also seen before, but resultant MMD health state utility estimates appear low compared with historic values in migraine appraisal. This and assumptions around the prediction of long-term effect introduces significant uncertainty to the model outcomes.

ICERs for fremanezumab as compared to BSC in the company's base case were £13,585 for EM and £11,825 for CM. In CM, the ICER for fremanezumab as compared to OBA was £16,227. Presented PSAs suggested a high likelihood of acceptability at thresholds of £20,000 and £30,000; however, the company's testing of uncertainty was limited and the conclusion of model stability questionable. At variance with the company, the ERG regarded that one-way sensitivity analyses and scenario analyses in fact indicated uncertainty with respect to key parameters and structural assumptions, notably utility estimators and the length of the time horizon. The ERG identified errors in the model relating to the estimation of mean utility, and treatment costs over the annual assessment period. Regarding the positive stopping rule, alternative assumptions relating to waning of treatment effect and restarting of treatment may be a more plausible starting position. In sum, the ERG regards that there remains substantial uncertainty in the model stemming from the combination of clinical opinion, short-term trial evidence, impact of structural assumptions, and unverifiable parameters.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG identified two areas for correction following a review of the company model for coding and implementation error (See Section 5.2.12.1):

i. Correction of coding for averaging of cycle level utility.

ii. Correction of assessment period length and alignment with 24-week treatment cycles to produce a 48 week treatment year.

Table 76, Table 77 and Table 78 present the impact on the ICERs of the two corrections, which are not large and do not increase deterministic ICERs above the £20,000 per QALY threshold.

Table 76 Impact of ERG changes on EM ICER, fremanezumab versus BSC

Change	Section in ERG report	+/- ICER £/QALY	Cumulative ICER £/QALY	Cumulative +/- ICER (%)
Company base-case	5.2.9	£13,954	-	-
Correction of utility estimation	5.2.12	£13,703	£13,703	-4.6%
Correction of length of positive stop assessment (2 to 3 cycles)	5.2.12	£13,093	£12,486	-10.5%

Abbreviations: BSC, best supportive care; EM, episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 77 Impact of ERG changes on CM ICER, fremanezumab versus BSC

Change	Section in ERG report	+/- ICER £/QALY	Cumulative ICER £/QALY	Cumulative +/- ICER (%)
Company base-case	5.2.9	£11,825	-	-
Correction of utility estimation	5.2.12	£11,903	£11,903	0.7%
Correction of length of positive stop assessment (2 to 3 cycles)	5.2.12	£11,412	£11,487	-2.9%

Abbreviations: BSC, best supportive care; EM, episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 78 Impact of ERG changes on CM ICER, fremanezumab versus OBA

Change	Section in ERG report	+/- ICER £/QALY	Cumulative ICER £/QALY	Cumulative +/- ICER (%)
Company base-case	5.2.9	£16,227	-	-
Correction of utility estimation	5.2.12	£16,339	£16,339	0.7%
Correction of length of positive stop assessment (2 to 3 cycles)	5.2.12	£16,265	£16,378	0.9%

Abbreviations: BSC, best supportive care; EM, episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

7 End of life

Migraine is not a life shortening condition and no evidence was submitted to demonstrate survival benefit from fremanezumab, therefore the criteria for end of life are not met.

8 Overall conclusions

The ERG reviewed the clinical and cost-effectiveness evidence for fremanezumab in adults with chronic or episodic migraine. The company has provided evidence focused on a narrower population of people who have used three or more prior preventative therapies, using subgroup data mainly from the FOCUS trial. The evidence showed potentially substantial benefit for both fremanezumab monthly and quarterly regimens compared to placebo across all clinical outcomes. Fremanezumab also appeared to be highly tolerable with low discontinuation rates due to adverse events. The ERG is concerned about the differences in the types of drugs previously used by the FOCUS trial population which created some doubts about the positioning of fremanezumab as a fourth line therapy in the migraine preventative treatment pathway.

No direct evidence comparing fremanezumab and comparators was found. The ITC showed that fremanezumab demonstrated numerically superior clinical benefits compared to OBA in terms of the percentage of CM people who had a reduction of 50% or more in average MMD although, this was not statistically significant. However, the ITC conducted was restricted to monthly migraine days; other important clinical outcomes, for example, number of headache hours and acute medication use, were not considered.

As a consequence, only monthly migraine days provided clinical effectiveness inputs into the cost-effectiveness model. The company's base case assumptions and parameters support the conclusion that fremanezumab is cost effective versus best supportive care (BSC) in episodic migraine and versus BSC and OBA in chronic migraine. The ERG found that uncertainty is most profound in the base case assumptions relating to the positive stopping rule and response to BSC. For people experiencing chronic migraine the ERG conducted a substantial scenario analysis which incorporated a five year wane to baseline of fremanezumab effect for people who positively discontinued fremanezumab treatment. This was coupled with treatment re-initiation at the point when half of treatment effect is lost relative to baseline. Within the same scenario, the treatment effect of BSC was linearly waned to baseline for all responders. Combined, this had an impact on the company base chronic migraine ICER of [redacted]% (£13,836 per QALY gained) for the comparison of fremanezumab versus BSC ([redacted]% including the ERG fixes), which provides some reassurance. The comparison of fremanezumab with OBA is deemed weak in the absence of reliable estimates of relative effectiveness. Assuming equivalent effect size and a lower probability of response to OBA, the approximated ICER is indicative of cost-effectiveness but the ERG have not tested this under the assumption of bilateral waning and re-commencement. In the analysis of fremanezumab for episodic migraine, the ERG's ICER

versus BSC estimate varied little from the company's, although no change was made to the positive stopping assumption or prolonged placebo effect supporting responders to BSC.

8.1 Implications for research

While the potential benefit of fremanezumab appears substantial, a well-powered RCT for the proposed population of people with episodic and chronic migraine who have used three or more preventative therapies would demonstrate more precise estimates for the clinical outcomes. The evidence presented for the clinical benefit of the fremanezumab monthly regimen with a loading dose of 675 mg among people with CM may differ from the expected benefit of the 225 mg starting dose approved in the marketing authorisation. More evidence is needed on the effectiveness of the approved starting dose of 225mg among people with CM who have used three or more preventative therapies. Only a short-term fremanezumab AE profile evidence of 12 weeks duration was provided in the submission for the FOCUS population. The ongoing extension of the FOCUS trial would give a more adequate medium-term evidence for the AE profile among the population of interest who have used three or more preventative therapies. Also, medium term data on HRQoL is needed.

Acknowledgements

We are thankful for the excellent and committed administrative support provided by Sue Whiffin and Jenny Lowe of PenTAG, University of Exeter.

References

1. Teva. Ajovy: summary of product characteristics. 2019.

2. National Institute for Health and Care Excellence. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine; Technology appraisal guidance 260. 2012.

3. Borsook D, Dodick DW. Taking the headache out of migraine. Neurology Clinical practice. 2015;5(4):317-25.

4. Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The Prevalence and Disability Burden of Adult Migraine in England and their Relationships to Age, Gender and Ethnicity. Cephalalgia : an international journal of headache. 2003;23(7):519-27.

5. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia : an international journal of headache. 2018;38(1):1-211.

6. BASH. Guidelines for all healthcare professionals in the diagnosis and management of migraine. . 2010.

7. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-9.

8. Bigal ME, Lipton RB. Clinical course in migraine: conceptualizing migraine transformation. Neurology. 2008;71(11):848-55.

9. Lipton RB. Tracing transformation: chronic migraine classification, progression, and epidemiology. Neurology. 2009;72(5 Suppl):S3-7.

10. Silberstein SD, Lee L, Gandhi K, Fitzgerald T, Bell J, Cohen JM. Health care Resource Utilization and Migraine Disability Along the Migraine Continuum Among Patients Treated for Migraine. Headache. 2018;58(10):1579-92.

11. Torres-Ferrus M, Quintana M, Fernandez-Morales J, Alvarez-Sabin J, Pozo-Rosich P. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. Cephalalgia : an international journal of headache. 2017;37(2):104-13.

12. NICE. Headaches: Evidence update october 2014. 2014.

13. Administration FaD. Letter of approval. In: FDA, editor. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/761089Orig1s000ltr.pdf2018.

14. Scottish Intercollegiate Guidelines Network. Search filters: Healthcare Improvement Scotland; [cited 2019 12/06/2019]. Available from: https://www.sign.ac.uk/search-filters.html.

15. Canadian Agency for Drugs and Technologies in Health. Strings Attached: CADTH's Database Search Filters: CADTH; [cited 2019 12/06/2019]. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#eco.

16. Lefebvre C, Manheimer E, Glanville J. In: Higgins JPT GSe, editor. Cochrane Handbook for Systematic Reviews of Interventions Version 510 [updated March 2011] The Cochrane Collaboration; 2011.

17. Bigal M, Lipton RB, Burstein R, Dodick DW, Newman L, Ma M, et al. A multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group, multi dose study comparing subcutaneous TEV-48125 to placebo for the preventive treatment of high frequency episodic migraine. Headache. 2015;5):251-2.

18. Bigal ME, Dodick DW, Krymchantowski AV, VanderPluym JH, Tepper SJ, Aycardi E, et al. TEV-48125 for the preventive treatment of chronic migraine: Efficacy at early time points. Neurology. 2016;87(1):41-8.

19. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurology. 2015;14(11):1081-90.

20. Cohen JM, Dodick DW, Yang R, Newman LC, Li T, Aycardi E, et al. Fremanezumab as Add-On Treatment for Patients Treated With Other Migraine Preventive Medicines. Headache. 2017;57(9):1375-84.

21. Halker Singh RB, Aycardi E, Bigal ME, Loupe PS, McDonald M, Dodick DW. Sustained reductions in migraine days, moderate-to-severe headache days and days with acute medication use for HFEM and CM patients taking fremanezumab: Post-hoc analyses from phase 2 trials. Cephalalgia : an international journal of headache. 2019;39(1):52-60.

22. Silberstein SD, Rapoport AM, Loupe PS, Aycardi E, McDonald M, Yang R, et al. The Effect of Beginning Treatment With Fremanezumab on Headache and Associated Symptoms in the Randomized Phase 2 Study of High Frequency Episodic Migraine: post-Hoc Analyses on the First 3 Weeks of Treatment. Headache. 2018;(no pagination).

23. VanderPluym J, Dodick DW, Lipton RB, Ma Y, Loupe PS, Bigal ME. Fremanezumab for preventive treatment of migraine: Functional status on headache-free days. Neurology. 2018;91(12):e1152-e65.

24. Yeung P, Aycardi E, Bigal M, Blankenbiller T, Grozinski-Wolff M, Yang R, et al. Early onset of action with fremanezumab versus placebo for the preventive treatment of episodic migraine. Journal of Headache and Pain Conference: 11th European Headache Federation Congress Jointly with 31st Congress of the Italian Society for the Study of Headaches Italy. 2017;18(1 Supplement 1).

25. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-Controlled Phases of the PREEMPT Clinical Program. Headache: The Journal of Head and Face Pain. 2010;50(6):921-36.

26. Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia : an international journal of headache. 2010;30(7):793-803.

27. Ashina M, Tepper S, Brandes JL, Reuter U, Boudreau G, Dolezil D, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment

failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia : an international journal of headache. 2018;38(10):1611-21.

28. Spierings EL, Yeung P, Blankenbiller T, Ning X, Yang R, Ma Y, et al. Efficacy of fremanezumab in patients with chronic migraine who had prior use of topiramate or onabotulinumtoxinA. Headache2018.

29. Yeung P, Spierings EL, Blankenbiller T, Ning X, Yang R, Ma Y, et al. Efficacy of fremanezumab in patients with chronic migraine who had prior use of topiramate or onabotulinumtoxina. Neurology Conference: 70th Annual Meeting of the American Academy of Neurology; LA, USA2018.

30. Yeung P, Spierings EL, Ning X, Yang R, Ma Y, Aycardi E, et al. Efficacy of fremanezumab in patients with chronic migraine who had prior use of topiramate or onabotulinumtoxina. Postgraduate Medicine2018.

31. Kudrow D, Sakai F, Yeung P, Blankenbiller T, Ning X, Yang R, et al. Efficacy of fremanezumab in patients with episodic migraine who had prior use of topiramate or onabotulinumtoxina. Headache2018.

32. Kudrow D, Sakai F, Yeung P, Blankenbiller T, Ning X, Yang R, et al. Efficacy of fremanezumab in patients with episodic migraine who had prior use of topiramate or onabotulinumtoxina. Neurology Conference: 70th Annual Meeting of the American Academy of Neurology, AAN; LA, USA2018.

33. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. : The Cochrane Collaboration; 2011. Available from: http://handbook.cochrane.org.

34. Cole JC, Lin P, Rupnow MF. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version. Cephalalgia : an international journal of headache. 2009;29(11):1180-7.

35. Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. Journal of clinical epidemiology. 2006;59(4):374-80.

36. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. Jama. 2018;319(19):1999-2008.

37. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. The New England journal of medicine. 2017;377(22):2113-22.

38. Teva I. Clinical Study Report. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of Fremanezumab (TEV-48125) Versus Placebo for the Preventive Treatment of Episodic Migraine. 2017.

39. Teva I. Clinical Study Report. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of Fremanezumab (TEV-48125) Versus Placebo for the Preventative Treatment of Chronic Migraine. 2017.

40. Teva I. FOCUS clinical study report. 2019.

41. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain. 2000;88(1):41-52.

42. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia : an international journal of headache. 2010;30(7):804-14.

43. Brown JS, Papadopoulos G, Neumann PJ, Price M, Friedman M, Menzin J. Cost-effectiveness of migraine prevention: the case of topiramate in the UK. Cephalalgia : an international journal of headache. 2006;26(12):1473-82.

44. Batty AJ, Hansen RN, Bloudek LM, Varon SF, Hayward EJ, Pennington BW, et al. The cost-effectiveness of onabotulinumtoxinA for the prophylaxis of headache in adults with chronic migraine in the UK. Journal of medical economics. 2013;16(7):877-87.

45. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. The journal of headache and pain. 2018;19(1):82.

46. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. London: NICE, 2013.

47. Allergan. BOTOX Summary of product characteristics. 2019(12 June 2019).

48. Office for National Statistics, National life tables: England and Wales. Available at httpswwwonsgovukpeoplepopulationandcommunitybirthsdeathsandmarriageslifeexpectancie sdatasetsnationallifetablesunitedkingdomreferencetables Accessed April PSSRU Unit costs of health social care Available at httpswwwpssruacukprojectpagesunitcostsunitcosts Accessed April NHS trust and NHS foundation trusts National schedule of reference costs 18. 2017.

49. Gillard PJ, Devine B, Varon SF, Liu L, Sullivan SD. Mapping from disease-specific measures to health-state utility values in individuals with migraine. Value Health. 2012;15(3):485-94.

50. Bloudek LM, Stokes M, Buse DC, Wilcox TK, Lipton RB, Goadsby PJ, et al. Cost of healthcare for patients with migraine in five European countries: results from the International Burden of Migraine Study (IBMS). The journal of headache and pain. 2012;13(5):361-78.

51. Paul Kind GH, Susan Macran. UK Population Norms for EQ-5D. Centre for Health Economics. 1999.

52. Curtis L. PSSRU Unit Costs of Health and Social Care 2018. 2018.

53. costs NIR. National Schedule of Reference Costs. 2017/2018.

54. Digital N. Prescription Cost Analysis - England, 2018 [PAS]. 2018.

Appendix 1. Evidence Review Group Medline search strategy for fremanezumab

1	exp Migraine Disorders/
2	migrain*.ti,ab,kw.
3	1 or 2
4	fremanezumab.ti,ab,kw.
5	(tev-48125 or tev 48125 or tev48125).ti,ab,kw.
6	ajovy.ti,ab,kw.
7	(LBR-101 or RN-307).ti,ab,kw.
8	1655501-53-3.ti,ab,kw.
9	or 5 or 6 or 7 or 8
10	3 and 9

Appendix 2. Evidence Review Groups Medline search strategy for OBA

1	exp Migraine Disorders/
2	migrain*.ti,ab,kw.
3	1 or 2
4	exp Botulinum Toxins, Type A/
5	(onabotulinumtoxinA or (onabolutinum toxin* adj2 A) or (onabotulinumtoxin* adj2 A) or onabotulinum toxinA).ti,ab,kw.
6	(botulinumtoxinA or botulinum toxinA or (botulinumtoxin* adj2 A) or (botulinum toxin* adj2 A)).ti,ab,kw.
7	(botox or xeomin or lantox or prosigne or neuronox or bocouture or azzalure or dysport).ti,ab,kw.
8	((botulin adj2 A) or botulinA).ti,ab,kw.
9	(BTX-A or BTX A or BTXA).ti,ab,kw.
10	(93384-43-1 or M03AX01 or MO3AXO1).ti,ab,kw.
11	(bont a or bont serotype a).ti,ab,kw.
12	clostridium botulinum.ti,ab,kw.
13	(botulinium adj3 a).ti,ab,kw.
14	or/4-13
15	3 and 14
16	randomized controlled trial.pt.
17	controlled clinical trial.pt.
18	randomized.ab.
19	placebo.ab.
20	drug therapy.fs.
21	randomly.ab.
22	trial.ab.
23	groups.ab.
24	or/16-23
25	exp animals/ not humans.sh.
26	24 not 25
27	15 and 26
28	limit 27 to yr="2011 -Current"

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

ERG report – factual accuracy check

Fremanezumab for preventing migraine [ID1368]

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

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 25 July 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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

Issue 1 Loading dose in chronic migraine (CM)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response	Action required
The loading dose within the trials for CM appears to have caused some confusion. p32, para 4 "*It appears that none of the CM population on the fremanezumab monthly regimen was commenced on the 225 mg dose.*"	Clarification around the use of a loading dose in CM.	Teva wishes to clarify that none of the clinical trials conducted on fremanezumab to date have commenced CM patients on a 225mg dose. The loading dose of 625mg was originally included to allow a steady-state in blood plasma to be reached more quickly. Once a patient is established on treatment, the presence or absence of the loading dose has no impact on the efficacy of a treatment. The removal of the loading dose simplifies the dosing of fremanezumab for both patients and clinicians, whilst decreasing the risk of incorrect dosing. Evidence was presented to the EMA (which was reproduced in the company submission, p12) to demonstrate that the loading dose led to no meaningful differences in efficacy, and allow for the simplified licence to be approved by the EMA. Teva feels that this should be acknowledged by the ERG.	The evidence referenced does not appear relevant given the differences between the HALO and the FOCUS population	None

p33, para 1 "*It is unclear whether the licensed starting dose of 225 mg would have a similar clinical effect compared to the evidence provided for the loading dose of 675 mg in the trials.*"	"***The available evidence demonstrates that it is highly likely*** *the licensed starting dose of 225 mg would have a similar clinical effect compared to the evidence provided for the loading dose of 675 mg in the trials of* ***CM patients, and this was accepted by the EMA within the EPAR for fremanezumab. The EMA therefore accepted a 225 mg starting dose for all patients as the registered dosing schedule for fremanezumab.***"	Evidence was presented to the EMA (which was reproduced in the company submission, p12) to demonstrate that the loading dose led to no meaningful differences in efficacy. These analyses compared efficacy between patients with EM who had ≥12 headache days per month (considered as a good surrogate for patients with CM) receiving monthly dosing (with no loading dose) and patients with CM receiving quarterly dosing. Analysis of the primary endpoint of mean monthly migraine days in comparison to placebo showed a similar effect size between these two groups, with no clinically meaningful difference in effect size (least square mean difference versus placebo of -1.6 for monthly fremanezumab in patients with EM and -1.7 for quarterly fremanezumab in patients with CM). Furthermore, comparisons between all treatment groups in these patient populations (patients with EM with ≥12 headache days per month and patients with CM) showed no	This remains an area of uncertainty	None

		meaningful differences. A further analysis was conducted using exposure-response models, which were developed to characterise the relationship between plasma fremanezumab concentration and efficacy outcomes. This model was able to predict responses consistent with clinical results, and predicted a treatment effect of a comparable size in patients with CM receiving quarterly fremanezumab and monthly fremanezumab (with no loading dose). Furthermore, it was found that a single dose of 225mg or 675mg fremanezumab had very similar median times to maximum concentration (t_{max}) of 5 to 7 days. These analyses therefore provide strong evidence of a similarity in clinical effect when no loading dose is used in CM, and were sufficient for the EMA to accept a 225mg starting dose for all patients as the registered dosing schedule for fremanezumab. The EPAR for fremanezumab concluded when considering the dosing regimens, "*Based on these phase 3 data the*		

		225 mg monthly regimen appears to be equally effective in the CM population compared to the 225 mg monthly regimen with a 675 mg starting dose."		
p58, para 5 "*Participants with EM received a dose of 900 mg of fremanezumab; either in one quarterly administration, or in a dose of 675 mg at baseline, followed by two monthly administrations of 225 mg.*"	"*Participants with **CM** received a dose of **675 mg of fremanezumab as one quarterly administration, or a dose of 675 mg at baseline, followed by two monthly administrations of 225 mg**.*"	Typographical error between EM and CM, and a misstating of the dosing administered in CM patients.	We agree and have replaced with suggested revision.	p. 58, para 5: Replace "Participants with EM received a dose of 900 mg of fremanezumab; either in one quarterly administration, or in a dose of 675 mg at baseline, followed by two monthly administrations of 225 mg." With "Participants with CM received a dose of 675 mg of fremanezumab as one quarterly administration, or a dose of 675 mg at baseline, followed by two monthly administrations of 225 mg."
The MMRM analysis and the impact of the loading dose on this have been misinterpreted p99, para 5 "…*although in this analysis they appear to have merged fremanezumab trial arms, and only report*	"…*although in this analysis the **fremanezumab trial arms have been merged in this report of** data to four weeks (Figure 3 and Table 22). **This was due to the loading dose in the HALO CM trial, which means that all patients received an initial dose of***	Clarification of the impact of the loading dose on the analysis of the four-week efficacy data, as this had been misinterpreted.	This is not a factual inaccuracy. The rationale for merging the trial arms was not explicit in the company's submission.	None

data to four weeks (Figure 3 and Table 22). It is unclear why this is the case."	***675mg fremanezumab for this initial four week period***."			

Issue 2 Medication overuse headache

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
There is confusion around the inclusion of medication overuse headache (MOH) within the evidence submitted. p14, para 2 "*The company presented a systematic literature review (SLR) involving a broad population of adults ≥18 years with migraine or medication overuse headache*."	"*The company presented a systematic literature review (SLR) involving a broad population of adults ≥18 years* ***with migraine***."	MOH was included within the initial search terms of the literature searches, but was not included in the evidence presented.	This is not a factual inaccuracy. The search strategy implemented was broad and involved MOH.	None
There is confusion around the inclusion of MOH within the evidence submitted, and the prevalence of MOH within the UK. p44, para 2 Paragraph commencing "*The SLR specified that participants with medication overuse*	Replace paragraph with "*People with MOH are* ***commonly encountered*** *in UK practice,* ***despite the*** *reduced use of opioid therapy in the UK compared with other countries.* ***The search strategies for the SLR included participants with medication overuse headache (MOH); at clarification the company stated that no studies included in the***	The ERG report was inaccurate around the inclusion of patients with medication overuse within the FOCUS trial. Due to the high prevalence of medication overuse in migraine, some patients that fit the criteria for medication overuse status were included within the FOCUS trial (as is found in all major clinical trials of migraine). Medication overuse status at entry into FOCUS was determined through the recorded usage of acute	The lack of clarity in the inclusion of patients with MOH in the included evidence is due to a lack of clarity in the CS, and the conflicting information provided by the company during clarification and in this fact check.	Delete sentence stating that MOH is rarer in the UK: p. 44, line 15-16, and p. 55 lines 5-6.

headache (MOH) were eligible for inclusion…"	***SLR recruited people with a primary diagnosis of MOH as these were excluded during the filtering stages. Due to the high prevalence of MOH in migraine, some patients with 'medication overuse status' were included within the FOCUS trial (191/293, 65.2%).***"	migraine medications during the run-in period that met ICHD-3 criteria for medication overuse. Patients enrolled in FOCUS had to have a primary diagnosis of migraine and were excluded if they used opioid medications on more than four days during the run-in period (thereby excluding patients with excessive opioid usage). Also, as stated in the company submission, the FOCUS trial fulfilled the recommendations of the International Headache Society in the Guidelines for controlled trials of preventive treatment of chronic migraine in adults recommendations (Tassorelli C *et al*. *Cephalalgia* 2018; 38: 815–832.), including around the inclusion of patients with medication overuse. It should be noted that the efficacy outcomes of the FOCUS trial show that acute medication usage was reduced with fremanezumab, which would reduce the reported rate of medication overuse within the trial population. Additionally, the expert advice received by Teva indicates that MOH is a common problem within UK practice, but one that may be underreported to physicians. The response from BASH to the NICE erenumab appraisal includes the statement "…*in real life nearly two third of patients with chronic migraine have co-existing medication overuse*." Similar sentiments are expressed by expert opinion on the Migraine Trust	The suggested wording by the company is also factually incorrect. At clarification the company stated in response to question A26: "*the final included studies (as per the updated PRISMA in question A6)* ***had no patients*** *that were defined as having medicine overuse headache as opposed to migraine*" Based on this, the ERG assumed that no patients in the included studies were characterised as having MOH, and therefore reported a lack of clarity over the high rates of MOH in the FOCUS trial (discussed p. 44, line 18-19). The company's query in this fact check appears to suggest that high numbers of patients with MOH	

		website around MOH (https://www.migrainetrust.org/about-migraine/types-of-migraine/other-headache-disorders/medication-overuse-headache/). Based on this evidence the statement that MOH is rarely seen in UK practice can be seen to be inaccurate.	during the trial run-in period were included. Regarding the prevalence of MOH in the UK, the ERG will accept that rates may be under-reported and therefore the true rates of MOH may be unknown. Therefore we have amended two sentences in the report referring to MOH as rarer in the UK.	
There is confusion around the inclusion of MOH within the evidence submitted and makes an erroneous reference to the company submission. p54, para 5 Paragraph commencing "*As noted in Section 4.1.2, participants with 'other migraine disorder', described elsewhere in the CS as 'medication overuse headache' (MOH) were also eligible for inclusion in the trials (CS p.48)...*"	Delete paragraph	The ERG report was inaccurate around the inclusion of patients with medication overuse within the FOCUS trial. Due to the high prevalence of medication overuse in migraine, some patients that fit the criteria for medication overuse status were included within the FOCUS trial (as is found in all major clinical trials of migraine). Medication overuse status at entry into FOCUS was determined through the recorded usage of acute migraine medications during the run-in period that met ICHD-3 criteria for medication overuse. Patients enrolled in FOCUS had to have a diagnosis of migraine and were excluded if they used opioid medications on more than four days during the run-in period (thereby	Due to errors the company provided multiple copies of the CS to the ERG. This reference refers to p. 48 of the original version of the CS that was provided to the ERG. We have now replaced the reference to match the final version of the CS provided. The company's inconsistent use of 'medication overuse	p. 54 para 5: Replace CS reference "CS p. 48" With "CS p. 47"

		excluding patients with excessive opioid usage). Also, as stated in the company submission, the FOCUS trial fulfilled the recommendations of the International Headache Society in the Guidelines for controlled trials of preventive treatment of chronic migraine in adults recommendations (Tassorelli C *et al*. *Cephalalgia* 2018; 38: 815–832.), including around the inclusion of patients with medication overuse. It should be noted that the efficacy outcomes of the FOCUS trial show that acute medication usage was reduced with fremanezumab, which would reduce the reported rate of medication overuse within the trial population. The reference to page 48 of the company submission does also not match to any reference to patients with "*other migraine disorder*" or MOH in that and so Teva has been unable to interpret what the ERG0020 was specifically referring to.	headache', 'medication overuse' or 'medication overuse status' appears confusing. Clinical advice to the ERG suggested that the terms all refer to MOH. We have now replace the CS reference.	
p58, para 3 "*It is unclear from the CS whether a significant number of participants in the FOCUS trial developed MOH during the trial. If true, this could affect the generalisability of the treatment effect to the UK population, although the ERG were unable to*	Delete sentences	Some patients that fit the criteria for medication overuse status were included within the FOCUS trial (as is found in all major clinical trials of migraine). MOH was not reported as an adverse event experienced by more than 2% of trial participants in the FOCUS trial.	This is not a factual error. It remains unclear whether 65.2% of participants classified as 'medication overuse status' developed MOH during the trial or were	None

determine from the information provided in the CS and at clarification if this was the case."			known MOH at trial entry.	
There is confusion around the inclusion of MOH within the evidence submitted. p158, para 1 "*The population specified was broad: adults (aged 18 years-plus) with migraine or MOH; the included economic evaluations were…*"	"*The population specified was broad: adults (aged 18 years-plus) with **migraine;** the included economic evaluations were…*"	MOH was included within the initial search terms of the literature searches, but was not included in the evidence presented.	This is not a factual inaccuracy. The search strategy implemented was broad and involved MOH.	None

Issue 3 References to statistical significance in relation to Bayesian network meta-analysis (NMA)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
Throughout the ERG report, the NMA results are described in terms of statistical significance. Including in the following locations: p15, para 3 "…no statistically significant advantages…" p151, para 4 "there were no statistically significant advantages between either of the two fremanezumab	The complexities of statistical interpretation of a Bayesian analysis need to be more clearly stated to ensure that there is no potential misinterpretation of this analysis where statistical significance is challenging to demonstrate.	Bayesian analysis does not lend itself to a frequentist (classical) interpretation of statistical significance and the implication of statistical significance in a Bayesian analysis is complex. As the NMA for this appraisal has been conducted under Bayesian principles, the results must be analysed and interpreted within this setting and Teva feels that this should	While we appreciate there are a number of differences between frequentist and Bayesian approaches to estimation, and interpretation of inference tests, we believe it is clear to the reader that in this case we mean 'not statistically significant' to indicate that the relevant credible interval	None

dosing regimens and OBA…" p153, para 2 "…showed there was no statistically significant advantage between either…" p207, para 2 "…although, this was not statistically significant."		be made clearer in the ERG report to prevent potential misinterpretation of this analysis by readers less acquainted with Bayesian analyses.	embraces the point of no effect.	

Issue 4 Dosing regimen of fremanezumab misstated

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
p20, para 2 The dosing schedule of fremanezumab is misstated "*The 28-day and 12-week dosing schedules…*"	*"The **monthly** and **quarterly** dosing schedules…*"	Monthly and quarterly dosing are the frequency of administration specified in the SmPC. This schedule means that twelve injections are required over one year of treatment, compared to thirteen that would be required if a four-weekly schedule is used.	This is not a factual inaccuracy.	None

Issue 5 Misinterpretation of the economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
There has been a misinterpretation of the	Acknowledge that the effect of best supportive care (BSC) was fully	The modelling of BSC was based on the results of the	This is not a factual inaccuracy. We arrived at	None

response modelling within the economic model. p22, para 1 "*The division of the BSC strategy by response was unnecessary and concerning given that* [redacted] *was attributed to non-responders of BSC but not non-responders to prophylaxis, in contrast to expectation from the FOCUS trial.*" p171, para 1 "*The division of the BSC strategy by response was an over complication given discontinuation was not applicable and concerning given that* [redacted] *was attributed to the very many non-responders. A* [redacted] *level of response would be expected.*"	modelled on the data from the FOCUS trial.	FOCUS clinical trial. In a number of cases the mean monthly migraine day (MMD) change seen for BSC was [redacted].	our interpretation based on the information provided within the CS. Indeed, within the company's response there appears to be a contradiction; either the effect of BSC 'was fully modelled on the data from the FOCUS trial' or the estimates were [redacted]'.	
p195, para 4 There is a potential misinterpretation of the 12-week treatment break implemented as part of the positive stopping rule.	Acknowledge that a two cycle break would equate to a twelve-week gap between fremanezumab administrations.	The ERG state that the treatment break was implemented as an eight-week break (two cycles) and not a twelve week break (three cycles). However, as fremanezumab is administered once *per* cycle (for monthly dosing), a two cycle break combined with the	Treatment cost should not be allocated to the treatment break week. Hence, this is not this is not a factual inaccuracy.	None.

		period within a cycle where patients do not receive treatment, would mean that a two cycle treatment break would equate to a twelve-week gap between administrations of fremanezumab.		

Issue 6 Blinding in HALO extension

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
The blinding in the HALO extension trial has been misinterpreted. p50, para 4 "*Treatment with fremanezumab was delivered open label in the extension, although participants were blinded to the dose (monthly or quarterly administration) that they were receiving for the first three-months.*"	"*Treatment with fremanezumab was delivered open label in the extension, although participants were blinded to the dose (monthly or quarterly administration) that they were receiving* ***throughout the trial***."	The patients in the HALO extension trial remained blinded to the dose of fremanezumab that they received throughout the open-label extension, with identical placebo injections administered to maintain the blinding despite the differences in injection schedule.	We agree and have incorporated revision.	p. 50, para 4: Replace "…..for the first three-months" With "……..throughout the trial"

Issue 7 Reporting of health-related quality of life (HRQoL) measures within trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
The HRQoL measures within the FOCUS trial have been incorrectly listed. p63, para 3 "*In participants with EM, HALO EM and FOCUS also evaluated the Migraine Disability Assessment (MIDAS), while in participants with CM, HALO CM and FOCUS evaluated the six-item Headache Impact Test (HIT -6).*"	"*In participants with EM, HALO **EM also** evaluated the Migraine Disability Assessment (MIDAS), while in participants with CM, HALO **CM evaluated** the six-item Headache Impact Test (HIT-6). **FOCUS evaluated HIT-6 and MIDAS in both EM and CM patients***"	Correction to clarify which HRQoL measures were utilised in the FOCUS trial and in what patient group.	We agree and have incorporated revision.	p. 63 para 4: Replace "In participants with EM, HALO EM and FOCUS also evaluated the Migraine Disability Assessment (MIDAS), while in participants with CM, HALO CM and FOCUS evaluated the six-item Headache Impact Test (HIT -6)." With "In participants with EM, HALO EM also evaluated the Migraine Disability Assessment (MIDAS), while in participants with CM, HALO CM evaluated the six-item Headache Impact Test (HIT-6). FOCUS evaluated HIT-6 and MIDAS in both EM and CM patients"

Issue 8 Headache and migraine definitions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
The measurement of clinical headache outcomes was incorrectly stated and the definitions used were not stated.	"*The distinction between headache and migraine used in the trials is **specified within Table 3 on p31 of the CS**. **Standard definitions of migraine and headache in line with***	To correctly detail the definitions of headache and migraine used in the clinical trials (as described in the company submission), and to	We agree and have incorporated the suggested revision.	p. 63 para 2: Delete: "The distinction between…….vomiting, photophobia, or phonophobia."

p64, para 2 "*The distinction between headache and migraine used in the trials is not specified, and it's unclear if this was based on participants' judgement (i.e. in their diaries) and/or whether established criteria were used to guide this.*"	***ICHD-3 criteria were used, and were calculated based on the headache information (time, severity, duration, presence of migraine symptoms etc.) recorded within participants headache diaries***."	clarify how the data from the headache diaries were interpreted.		Replace with: "Standard definitions of migraine and headache in line with ICHD-3 criteria were used, and were calculated based on the headache information (time, severity, duration, presence of migraine symptoms etc.) recorded within participants headache diaries."

Issue 9 Adverse event (AE) reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
p67, Table 9 footnote "*The CS reports that data for AEs experienced by ≥5% of any treatment group was also assessed (p.101), but the data was not reported in the CS.*"	Delete footnote as it is incorrect.	Data for AEs experienced by ≥5% of any treatment group is reported within the CS in the following locations: HALO EM – Table 36, p101 HALO CM – Table 39, p104 FOCUS – Table 42, p106-107 FOCUS 3+ subgroup – Table 43, p108-109 HALO extension – Table 45, p111-112	We agree and have incorporated revision.	p. 67, Table 9 footnote: Delete footnote: "The CS reports that data for AEs experienced by ≥5% of any treatment group was also assessed (p.101), but the data was not reported in the CS."

Issue 10 FOCUS CSR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
The report refers to the FOCUS CSR not being supplied to NICE. p68, para 3 "…*were not provided to the ERG, nor was the full CSR for FOCUS*…" and "… *were unable to confirm this for FOCUS as the CSR was not provided to the ERG*."	Clarify that the CSR of the FOCUS trial has not yet been completed and will be supplied to NICE at the earliest opportunity. "… *were unable to confirm this for FOCUS as the CSR **has not yet been** provided to the ERG*."	Due to the timescales from the completion of the FOCUS trial to the submission of evidence to NICE, the CSR for the FOCUS trial has not yet been completed. Teva intends to supply this to NICE at the earliest opportunity and this should be made clear within the ERG report.	This is not a factual inaccuracy. The FOCUS CSR was not provided to the ERG.	None
p72, para 2 "…*although the ERG have no access to the FOCUS CSR to determine this*."	"…*although the ERG have **not yet had** access to the FOCUS CSR to determine this*."	Due to the timescales from the completion of the FOCUS trial to the submission of evidence to NICE, the CSR for the FOCUS trial has not yet been completed. Teva intends to supply this to NICE at the earliest opportunity and this should be made clear within the ERG report.	The statement is not inaccurate.	None.

Issue 11 Previous treatments in FOCUS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
p139, para 2 Previous treatments used prior to the	"[redacted]	Correct the description of drugs used before the	We agree with the first suggestion and have	p. 139, para 2:

FOCUS trial are misidentified “[redacted]”	[redacted]”	FOCUS trial to match the trial eligibility criteria (as shown on page 54 of the ERG report) and correction of the spelling of propranolol.	incorporated appropriate change. The calcium channel blockers are not recommended for use in the NHS England.	Replace ““[redacted] With ““[redacted]”

Issue 12 Typographical errors in data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
p21, para 1 typographical error in data values “*The PSA of the EM analysis found that in [redacted] of simulations fell below £20,000 per QALY gained, and [redacted] below £30,000 per QALY gained. The respective predictions for CM were [redacted] and [redacted] versus BSC, and [redacted] and [redacted] versus OBA*.”	“*The PSA of the EM analysis found that in [redacted] of simulations fell below £20,000 per QALY gained, and [redacted] below £30,000 per QALY gained. The respective predictions for CM were [redacted] and [redacted] versus BSC, and [redacted] and [redacted] versus OBA*.”	Typographical error of data that does not match the company submission.	Thank you for your comment. We have actioned the proposed change.	P21, para 1; Replace: “*The PSA of the EM analysis found that in [redacted] of simulations fell below £20,000 per QALY gained, and [redacted] below £30,000 per QALY gained. The respective predictions for CM were [redacted] and [redacted] versus BSC, and*

				[redacted] *and* [redacted] *versus OBA*." With: "*The PSA of the EM analysis found that in* [redacted] *of simulations fell below £20,000 per QALY gained, and* [redacted] *below £30,000 per QALY gained. The respective predictions for CM were* [redacted] *and* [redacted] *versus BSC, and* [redacted] *and* [redacted] *versus OBA*."
p23, para 2 decreased used rather than increased, "*Slightly fewer QALYs are gained in the CM analysis, at similar cost, so the predicted probability of fremanezumab being the more cost effective than BSC decreased…*"	"*Slightly **more** QALYs are gained in the CM analysis, at similar cost, so the predicted probability of fremanezumab being the more cost effective than BSC **increased**…*"	Typographical error when comparing results of the PSA provides an inverted interpretation of the results.	Thank you for your comment. We have actioned the proposed change.	P23, para 2; Replace: "Slightly fewer QALYs are gained in the CM analysis, at similar cost, so the predicted probability of fremanezumab being the more cost effective than BSC decreased" With: "*Slightly **more** QALYs are gained in the CM analysis, at similar cost, so the predicted probability of fremanezumab*

				being the more cost effective than BSC ***increased***".
p44, para 3 "*The ERG also noted that the evidence for fremanezumab in the fourth-line population is derived from a subgroup of the FOCUS trial, and therefore does not retain randomisation.*"	"*The ERG also noted that the evidence for fremanezumab in the fourth-line population is derived from a subgroup of the FOCUS trial, and therefore does not retain* ***stratification of*** *randomisation.*"	Typographical error that alters the reporting of the FOCUS trial.	This is not inaccurate	None
p54, para 3 "*The CS states that ineligibility in the FOCUS trial was determined by having previously used two to four classes of preventative therapies, defined as…*"	"*The CS states that* ***eligibility for*** *the FOCUS trial was determined by having previously used two to four classes of preventative therapies, defined as…*"	Typographical error that described the previous treatment eligibility criteria of FOUCS as ineligibility.	Thank you for your comment. We have corrected the text.	p. 54, para 3: Replace "….ineligibility in…" With "…eligibility for.."
p87, Table 14 result for median MMD change in placebo stated to be "*2.7*"	Correct to "***-2.7***"	Typographical error where by minus sign had been missed from result.	Thank you for your comment. We have corrected the text.	p. 87, Table 14, Add minus to median MMD change for placebo.
p97, para 1 "*The CS further reports that 31.1% (340/1130) of participants were receiving another preventative therapy for migraine in the run-up period to the trial*."	"*The CS further reports that* ***30.1%*** *(340/1130) of participants were receiving another preventative therapy for migraine in the run-up period to the trial*."	Typographical error in number	Thank you for your comment. We have corrected the text.	p. 97, para 1: Replace 31.1% with 30.1%.

p104, para 1 "…*mean improvements in outcomes ranged between -0.3 to -2.2 for monthly migraine days and -0.9 to -1.7 for monthly headache days of at least moderate severity*."	"…*mean improvements in outcomes ranged between -0.3 to -2.2 for monthly migraine days and **-0.2 to -2.7** for monthly headache days of at least moderate severity*."	To correct the data included within the text.	Thank you for your comment. We have corrected the text.	p. 104, para 1: Replace "-0.9 to -1.7" with "-0.2 to -2.7".
p107, para 2 "…*while it was evaluated in the HALO-EM trial*…"	"…*while it was evaluated in the HALO-**CM** trial*…"	Typographical error between HALO EM and HALO CM.	Thank you for your comment. We have corrected the text.	p. 107, para 2: Replace "…..while it was evaluated in the HALO-EM trial…" With "….while it was evaluated in the HALO-CM trial……"
p109, para 5 "*Participants reported a mean of 9.1 – 9.2 migraine days (range 3 – 21; SD 9.0), and a mean of 7.3 – 7.4 moderately severe or severe headache days (range 0 – 15; SD 3.0 – 3.2). Participants reported using acute headache medication on 8.0 – 8.3 days (range 0 – 22; SD 3.4 – 3.7)*."	"*Participants reported a mean of 9.1 – 9.2 migraine days (range 3 – 21; SD **2.6 – 2.7**), and a mean of 7.3 – 7.4 moderately severe or severe headache days (range 0 – **21**; SD 3.0 – 3.2). Participants reported using acute headache medication on 8.0 – **8.1** days (range 0 – 22; SD **3.5 – 3.6**)*."	To correct the data included within the text.	Thank you for your comment. We have corrected the text.	P. 109, lines 24-27, edited as suggested by the company.
p112, para 4 "…*and between [redacted] - [redacted] of patients reported a 50% reduction in monthly migraine days*…"	"…*and between [redacted] - [redacted] of patients reported a 50% reduction in monthly migraine days*…"	Typographical error missing out value after decimal point.	Thank you for your comment. We have corrected the text.	p. 112, para 4: with Replace [redacted] with [redacted]

p117, Table 28, mean headache days of at least moderate severity at 12 months for newly treated quarterly fremanezumab patients stated to be "[redacted]"	"[redacted]"	Typographical error where by minus sign had been missed from result.	Thank you for your comment. This was stated in the CS.	None
p115, para 3 "*Clinical outcome data for the extension phase of HALO EM is reported in Table 28. No statistical tests were reported to compare outcomes between newly treated and active rollover participants. Overall mean values appear similar between the two arms and are consistent with data from HALO-EM…*"	"*Clinical outcome data for the extension phase of HALO **CM** is reported in Table 28. No statistical tests were reported to compare outcomes between newly treated and active rollover participants. Overall mean values appear similar between the two arms and are consistent with data from HALO **CM**…*"	Typographical errors between HALO EM and HALO CM.	Thank you for your comment. We have corrected the text..	p. 115, para 3: Replace both HALO-EM in the paragraph with HALO-CM
p115, para 3 "*Notably, active rollover participants who received monthly fremanezumab exhibited a significant jump in response rates ([redacted] to [redacted]) between one and 12 months (i.e. four and 15 months), which is not replicated in other groups. It's unclear whether this is an anomaly or whether this represents a true differential*	Delete sentences	Data from HALO EM are included in the text and do not match the characteristics of the results for HALO CM.	Apologies, this data has been mistakenly associated with HALO CM in the ERG report, whereas it is relevant for HALO-EM. We agree that this sentence should be deleted. The same data is discussed with relevance to HALO-EM on p.113 (line 7).	ERG report p. 115, delete relevant sentence (para 3; lines 16-20)

effect of fremanezumab in this group."				
p116, para 1 "…*and are consistent with data from HALO-EM*…"	"…*and are consistent with data from HALO **CM***…"	Typographical error between HALO EM and HALO CM.	This is not a typographical error. The report stated that data from the HALO-CM trial discussed in this paragraph is consistent with the data reported for HALO-EM.	No change needed.
p116, para 1 "*Notably, active rollover participants who received monthly fremanezumab exhibited a significant jump in response rates ([redacted] to [redacted]) between one and 12 months (i.e. four and 15 months), which is not replicated in other groups. It's unclear whether this is an anomaly or whether this represents a true differential effect of fremanezumab in this group.*"	Delete sentences	Data from HALO EM are included in the text and do not match the characteristics of the results for HALO CM.	This section is included within a paragraph that has been mistakenly duplicated in the ERG report. The paragraph beginning on page 11, line 33 and ending page 116, line 9 has been deleted.	Delete text p. 115, line 33 – page 116, line 9.
p118, para 1 "*The data from the extension phase to HALO-EM suggest that*…"	"*The data from the extension phase to HALO **CM** suggest that*…"	Typographical error between HALO EM and HALO CM.	We agree and have incorporated revision.	p. 118, para 1: Replace HALO-EM with HALO-CM
p135, para 1 "…*which was significantly higher in the fremanezumab monthly group compared to the*	"…*which was significantly higher in the fremanezumab monthly group*	Typographical error in round of p-value from 0.0066 as	We agree and have incorporated revision.	p. 135, para 1: replace "p = 0.006" with "p = 0.007"

placebo group (p = 0.006) (CS, Section B 2.10.1, p. 101)."	*compared to the placebo group (**p = 0.007**) (CS, Section B 2.10.1, p. 101).*"	reported in company submission.		
p143, Table 42 Mean monthly acute migraine-specific medication days in FOCUS for placebo stated to be "[redacted]"	"[redacted]"	Typographical error where by minus sign had been included.	This was what was presented in the clarification response Table A.28.1	None
p166, para 4 "*ICERs are seen to reduce only marginally.*"	"ICERs are seen to **increase** only marginally."	Typographical error between increase and decrease.	Thank you for your comment. We have corrected the text.	P166, papa4; the Replace the word "**reduce**" in the sentence with **increase**.
p181, Table 61, weighted cost *per* MMD health state data are incorrect (compared to Table 54 (p146) of the company submission)	Correct the data within this table	Typographical error of data within table that does not match the company submission.	This is not a factual inaccuracy. Resource use by MMD (and as a result Table 54) later revised in company response to clarification questions.	None.
p186, para 1, typographical error in data values "*Fremanezumab is predicted to be the most cost-effective option versus BSC in [redacted] of simulations when using a £20,000 per QALY gained WTP threshold; and [redacted] of simulations using the £30,000 threshold. Versus*	"*Fremanezumab is predicted to be the most cost-effective option versus BSC in [redacted] of simulations when using a £20,000 per QALY gained WTP threshold; and [redacted] of simulations using the £30,000 threshold. Versus OBA the respective probabilities are [redacted] and [redacted].*"	Typographical error of data that does not match the company submission.	Thank you for your comment. We have corrected the text.	P186, para 1; the mentioned sentence should change to "*Fremanezumab is predicted to be the most cost-effective option versus BSC in [redacted] of simulations when using a £20,000 per QALY gained WTP threshold; and*

OBA the respective probabilities are [redacted] and [redacted]."				[redacted] *of simulations using the £30,000 threshold. Versus OBA the respective probabilities are [redacted] and [redacted].*"
p197, Table 69 footnote "** *Not presented in the company report but extracted from the CEM.*"	Remove footnote	The ICER for OBA versus BSC was reported in the company submission (Table 59, p155) and this table was reproduced by the ERG in their report (Table 63, p184). It is assumed that this footnote has been included in error.	Thank you for your comment. We have corrected the text.	P197, Table 69; Remove the part of the footnote stating "*Not presented in the company report but extracted from the CEM*".

Issue 13 Missing confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
p153, para 2 "…showed there was no statistically significant advantage between either…"	Include AIC confidential marking as below: "…showed there was no statistically significant advantage between either…"	Confidential information as marked in company submission has not been marked as confidential in ERG report	Confidential markings changed multiple times during the appraisal. Suggested revisions now incorporated.	p. 153, para 2: Mark "..no statistically significant advantage.." as AIC
p194, Table 30 "*(12) Proportion of patients responding to OBA increased to from* [redacted]"	"*(12) Proportion of patients responding to OBA increased* ~~*to*~~ *from* [redacted] ***to*** [redacted]"	Confidential information as marked in company submission has not been marked as confidential in ERG report and	As above	p. 194, Table 67: (12) Mark [redacted] as AIC

		typographical error relating to position of word "to"		
p194, Table 30 "*(13) Proportion of patients responding to OBA* decreased *from* [redacted] *to* [redacted]"	"*(13) Proportion of patients responding to OBA* decreased *from* [redacted] *to* [redacted]"	Confidential information as marked in company submission has not been marked as confidential in ERG report.	As above	p. 194, Table 67: (13) Mark [redacted] as AIC
p207, para 2 "…*although, this was* [redacted]."	Include AIC confidential marking as below: "…"…*although, this was* [redacted]."	Confidential information as marked in company submission has not been marked as confidential in ERG report	As above	p. 207, para 2: Mark "….. [redacted]." As AIC

Issue 14 Ambiguous wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
The overall costs within the economic analysis were reported in an ambiguous manner that could easily be interpreted as the treatment cost for fremanezumab. p20, para 3 "*The company base case for EM found that over 10 years the average cost per person of fremanezumab was…*"	"*The company base case for EM found that over 10 years the average cost per person* ***using a*** *fremanezumab* ***treatment strategy*** *was…*"	Clarification in wording to prevent misinterpretation.	Issue 14 does not contain factual inaccuracy.	None
The overall costs within the economic analysis were	"*The company base case for CM found that over 10 years the average*	Clarification in wording to prevent misinterpretation.		

reported in an ambiguous manner that could easily be interpreted as the treatment cost for fremanezumab. p21, para 1 "*The company base case for CM found that over 10 years the average cost per person of fremanezumab was…*"	*cost per person* ***using a*** *fremanezumab* ***treatment strategy*** *was…*"			
Ambiguous and confusing wording around evidence sources. p28, para 2 "*The CS states that "In the UK, the annual direct costs per person with migraine have been estimated to be £736.58 for EM and £3,160.67 for CM in 2010" (CS, p. 18) and also presented evidence for the disparity in the resource use between EM and CM. The evidence presented was from the US setting and may not be applicable to the UK…*"	"*The CS states that "In the UK, the annual direct costs per person with migraine have been estimated to be £736.58 for EM and £3,160.67 for CM in 2010" (CS, p. 18) and also presented evidence for the disparity in the resource use between EM and CM. The evidence on* ***disparity in resource use*** *presented was from the US setting and may not be applicable to the UK…*"	Clarification in wording to prevent misinterpretation. Teva assumes that the evidence being referred to as being from the US is that around disparity in resource use, as the other study referred to in the previous sentence was a European study that included the UK; however, the wording the ERG report does not make this clear.		
The ERG report does not make clear the FOCUS baseline characteristics reported are for the subgroup of patients who have failed three or more classes of migraine	Clarify that the baseline characteristics reported are for the subgroup of patients who have failed three or more classes of migraine preventive treatment.	The data presented is not accurately described.		

preventive treatment, p120 Table 29.				
The ERG report does not make clear the FOCUS baseline characteristics reported are for the subgroup of patients who have failed three or more classes of migraine preventive treatment, p121 Table 30.	Clarify that the baseline characteristics reported are for the subgroup of patients who have failed three or more classes of migraine preventive treatment.	The data presented is not accurately described.		
The impact of the negative stopping rule on discontinuation is not clearly described for Figures 8 and 9 (p179).	Clarify that Figures 8 and 9 show the proportion of patients remaining on treatment, without consideration of the negative stopping of non-responder patients.	The discontinuation as modelled within the model is not accurately described.		

In addition to the factual errors identified above, Teva also identified the following minor typographical errors and inconsistencies within the ERG report. These are reported here to allow for the most accurate and clear report to be produced by NICE.

Issue 15 Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
p14, para 4 "…*EM subgroup who have used three or more preventative therapies. EM patients who have used three or fewer more drugs and*…"	"…*EM subgroup who have used three or more preventative therapies. EM patients who have used three* ***or more*** *drugs and*…"	Typographical error between more and fewer	Issue 15 does not contain factual inaccuracy.	None
p17, para 3 "*The company also presented an SLR of utilities and healthcare resource utilisation and costs No relevant*…"	"*The company also presented an SLR of utilities and healthcare resource utilisation and* ***costs. No*** *relevant*…"	Typographical error whereby full stop missing		
p17, para 4 "*The model handled responders and on-responders*…"	"*The model handled responders and* ***non-responders***…"	Typographical error whereby non-responders incorrectly spelt		
p18, para 2 "*This is a narrower population that the EMA license for fremanezumab (prophylaxis of migraine in adults who have at least four migraine days per month [1])*"	"*This is a narrower population that the EMA license for fremanezumab (prophylaxis of migraine in adults who have at least four migraine days per* ***month[1])***"	Typographical error whereby extra space before reference		
p20, para 2 "*Fremanezumab costs £415.38 per 28-day treatment cycle, also one model*	"*Fremanezumab costs £415.38 per 28-day treatment cycle, also one model*	Typographical error whereby any spelt incorrectly		

cycle, and did not attract an administration costs…"	*cycle, and did not attract* ***any*** *administration costs…*"			
p20, para 2 "*A small monitoring cost was applied for equal for both prophylactic strategies*."	"*A small monitoring cost was* ***applied for both*** *prophylactic strategies*."	Typographical error with inclusion of for equal		
p20, para 2 "*Healthcare resource consumption estimates drew from the National Health and Wellbeing Survey 2017 and were based…*"	"*Healthcare resource consumption estimates* ***were drawn*** *from the National Health and Wellbeing Survey 2017 and were based…*"	Typographical error of drew		
p21, para 2 "*There were poorly presented, hard to follow, were limited in ways that are not evidence-based…*"	"***They*** *were poorly presented, hard to follow, were limited in ways that are not evidence-based…*"	Typographical error whereby there used instead of they		
p26, para 2 "*The CS also states that "Migraine prevalence has been shown to rise through early adult life with a peak at 30 to 40 years" (CS, p. 16) and that "Furthermore,…"*	"*The CS also states that "Migraine prevalence has been shown to rise through early adult life with a peak at 30 to 40 years" (CS, p. 16) and* ***that "Furthermore****,…"*	Typographical error whereby extra space included between that and furthermore		
p27, para 3 "*The CS reports that "UK results…*"	"*The CS reports* ***that "UK*** *results…*"	Typographical error whereby extra space included between that and UK		
p31, para 1 "*The marketing authorization indication was for preventing migraine in adults with*	"*The marketing* ***authorisation*** *indication was for preventing migraine in adults with at least four migraine days per month*."	Typographical error whereby American spelling used		

at least four migraine days per month."				
p31, para 1 "*…(defined as a lack of a clinically meaningful improvement after at least three months of therapy, intolerance to the treatment or contraindication/unsuitability for a treatment)" (CS, p. 29)..*"	"*…(defined as a lack of a clinically meaningful improvement after at least three months of therapy, intolerance to the treatment or contraindication/unsuitability for a treatment)" (CS,* ***p. 29).***"	Erroneous full stop included		
p32, para 4 "*In the HALO CM trial and the FOCUS CM subgroup, a loading dose of 675 mg fremanezumab for the monthly regimen was administered which is not in line with the marketing authorization*."	"*In the HALO CM trial and the FOCUS CM subgroup, a loading dose of 675 mg fremanezumab for the monthly regimen was administered which is not in line with the marketing* ***authorisation***."	Typographical error whereby American spelling used		
p37, bullet 4 "*The Cochrane Library searches do not include any MESH terms at all which is very poor practice*."	"*The Cochrane Library searches do not include any* ***MeSH*** *terms at all which is very poor practice*."	Typographical error whereby incorrect abbreviation used		
p38, bullet 4 "*In clarification, the company stated that their searches of Embase.com would have picked up in-Process papers*."	"*In clarification, the company stated that their searches of Embase.com would have picked up* ***in-process*** *papers*."	Erroneous capitalisation		
p39, para 4 "Both trials are placebo-controlled RCTs[17-24]."	"Both trials are placebo-controlled **RCTs.[17-24]"**	Erroneous citation placement		

p45, para 3 "*The ERG judged that the screening process described by in the CS is of limited quality.*"	"*The ERG judged that the screening process **described in the** CS is of limited quality.*"	Erroneous inclusion of by		
p46, para 3 "*these reported quality appraisal as conducted using the JADAD scale (reported in Appendix D, p. 325)…"*	"***These** reported quality appraisal as conducted using the JADAD scale (reported in Appendix D, p. 325)…"*	Typographical error whereby these not capitalised		
p62, Table 8 "*Merge with HALO EM*"	It is assumed that an instruction to merge these cells has been left in place rather than the cells being merged. If this is the case, then these cells should be merged as this text deleted.	Typographical error where extraneous text has been included in the Table.		
p62, Table 8 "*Merge with FOCUS EM*"	It is assumed that an instruction to merge these cells has been left in place rather than the cells being merged. If this is the case, then these cells should be merged as this text deleted.	Typographical error where extraneous text has been included in the Table.		
p74, Table 11 "*N: the ERG agreeds with the company assessment*"	"*N: the ERG **agreed** with the company assessment*"	Typographical error whereby agreed spelt incorrectly		
p80, Table 12 " *Yes, but were blinded to treatment schedule (monthly or quarterly administration)*"	"***Yes,** but were blinded to treatment schedule (monthly or quarterly administration)*"	Typographical error whereby extra space before yes		
p86, para 3 "*As seen in Table 16, the difference in the number of participants exhibiting a ≥50% reduction in migraine days between fremanezumab and*	"*As seen in Table 16, the difference in the number of participants exhibiting a ≥50% reduction in migraine days between fremanezumab and placebo was*	Typographical error		

placebo was statistically significant at one, two, and three months' follow-up."	*statistically significant at one, two, and three* ***months*** *follow-up*."			
p86, para 3 "*The company further reported that the proportion of participants exhibiting a cumulative reduction of 75% of migraine days was also higher for participants receiving fremanezumab (25.8% of quarterly and 27.2" of monthly fremanezumab participants) than placebo (15.4%)."*	"*The company further reported that the proportion of participants exhibiting a cumulative reduction of 75% of migraine days was also higher for participants receiving fremanezumab (25.8% of quarterly and* ***27.2%*** *of monthly fremanezumab participants) than placebo (15.4%)."*	Typographical error		
p87, Table 14 result for Mean change in monthly average number of headache days of at least moderate severity change, LSM difference vs placebo in placebo stated to be "-"	Delete	Erroneous "-" included in what should be a blank cell.		
p97, Table 20 "Age, years"	"**Age, years**"	Typographical error whereby table subtitle not in bold		
p99, para 3 "…*thus reducing the LSM difference between placebo and fremanezumab at four weeks.As these reductions are below*…"	"…*thus reducing the LSM difference between placebo and fremanezumab at four* ***weeks. As*** *these reductions are below*…"	Typographical error whereby space missing before as		
p100, para 1 "*…but as this data was not provided it was not possible for the ERG to view the*	"*…but as this data was not provided it was not possible for the ERG to view the*	Erroneous comma included		

pattern of response to treatments between four and 12 weeks.,"	*pattern of response to treatments between four and 12* ***weeks.***"			
p100, para 2 "*Unlike participants in the HALO-EM trial, the difference in the number of participants exhibiting a ≥50% reduction in migraine days between fremanezumab and placebo was not reported separately at one, two, and three months' follow-up*."	"*Unlike participants in the HALO-EM trial, the difference in the number of participants exhibiting a ≥50% reduction in migraine days between fremanezumab and placebo was not reported separately at one, two, and three* ***months*** *follow-up*."	Typographical error whereby apostrophe used incorrectly		
p118, para 5 "*For the CM population, the male population was higher among the two fremanezumab groups compared to placebo, also not statistically significant* [redacted] *for the quarterly and monthly regimen, respectively*."	"*For the CM population, the male population was higher among the two fremanezumab groups compared to placebo, also not statistically significant* [redacted]***)*** *for the quarterly and monthly regimen, respectively*."	Typographical error whereby close bracket missed		
p130, para 3 "*Posttreatment data for EM patients who have used three or more prior preventative therapies*…"	"***Post treatment*** *data for EM patients who have used three or more prior preventative therapies*…"	Typographical error whereby space missing		
p135, para 1 "*The most common individual AEs were injection site related and were comparable between fremanezumab groups and placebo except for duration which was significantly higher*…"	"*The most common individual AEs were injection site related and were comparable between fremanezumab groups and placebo except for* ***induration*** *which was significantly higher*…"	Typographical error		

p138, para 4 "*Clinical advice to the ERG suggested that practices in north America are more likely to use opioids*…"	"*Clinical advice to the ERG suggested that practices in **North** America are more likely to use opioids*…"	Typographical error North America not capitalised		
p140, para 2 "*The CS stated that feasibility was assessed for two outcomes (CS, Appendix D., p. 333):*"	"*The CS stated that feasibility was assessed for two outcomes (CS, **Appendix D**, p. 333)"*	Erroneous full stop included		
p149, para 2 "*In the CS (CS Appendix D, p 333), the*…"	"*In the CS (CS**, Appendix** D, p 333), the*…"	Typographical error whereby comma missing		
p163, para 1 "*A single model handed both analyses*."	"*A single model **handled** both analyses*."	Typographical error		
p164, para 3 "*The ERG considered believed a cohort model to restrict*…"	"*The ERG **considered a** cohort model to restrict*…"	Erroneous inclusion of believed		
p172, para 1 "*The combined effect can't be estimated by the ERG, but the combined uncertainty is large and significant*."	"*The combined effect **cannot** be estimated by the ERG, but the combined uncertainty is large and significant*."	Typographical error whereby apostrophe used		
p173, para 1 "*A mapping technique (Model 1; [49]) was used to transform pooled EM and CM scores to utility values on the EQ-5D-3L scale*."	"*A mapping technique (**Model 1[49])** was used to transform pooled EM and CM scores to utility values on the EQ-5D-3L scale*."	Erroneous inclusion of semi colon		

p175, para 1 "*However, a comparison shows disparity, particularly across at the high severity end of the range*."	"*However, a comparison shows disparity, **particularly at** the high severity end of the range*."	Erroneous inclusion of across		
p175, para 1 "*The ERG note the concern of the NICE appraisal committee of TA260 that even their estimates may represent over-estimates*."	"*The ERG note the concern **of the** NICE appraisal committee of TA260 that even their estimates may represent over-estimates*."	Typographical error whereby extra space included		
p192, para 1 "*I.e. the time horizon (scenarios 1 and 2); the positive stopping rule and long-term treatment effect (scenarios 3, 4, 7 and 8).*"	"*I.e. the time horizon (scenarios 1 and 2); the positive stopping rule **and long-term** treatment effect (scenarios 3, 4, 7 and 8).*"	Typographical error whereby extra space included		
p192, para 2 "*The company have not provided adequate description of the methods for the implementation of less obvious*."	"*The company have not provided adequate description of the methods for the implementation of less obvious **scenarios***."	Typographical error whereby word missing, Teva assumes that this word should be "scenarios"		
p195, para 4 " *Version 1 of the economic model was received by the ERG on 1 May 2019*."	"***Version 1** of the economic model was received by the ERG on 1 May 2019*."	Typographical error whereby extra space included		
p197, para 2 "*Table 70 Effect size estimators versus FOCUS trial outcomeTable 70 presents the result of a simple comparison of effect estimators used in the model with respective outcomes from the FOCUS trial*."	"***Table 70 presents the result of a simple comparison of effect estimators used in the model with respective outcomes from the FOCUS trial.***"	Erroneous inclusion of duplicated text		

p199, Figure 19 refers to results as "*Net monetary benefit*"	Change figure labelling to refer to ICER rather than net monetary benefit, as the ERG have presented results as ICERs	Typographical error of data labelling		
p 200, Figure 20 refers to results as "*Net monetary benefit*"	Change figure labelling to refer to ICER rather than net monetary benefit, as the ERG have presented results as ICERs	Typographical error of data labelling		
p207, para 2 "*…in terms of the percentage of CM people who had a reduction of 50% or more in average MMD although, this was not statistically significant..*"	"*… in terms of the percentage of CM people who had a reduction of 50% or more in average MMD although, this was not statistically* ***significant.***"	Erroneous inclusion of extra full stop		
p213, reference 53 "*53. costs NIR. National Schedule of Reference Costs. 2017/2018*."	"*53.* ***Costs*** *NIR. National Schedule of Reference Costs. 2017/2018*."	Typographical error whereby costs not capitalised		

Issue 16 Consistency errors throughout document

Description of problem	Description of proposed amendment	Justification for amendment	ERG response	Action required
Inconsistent use of dash types (*e.g.* page 19, para 4)	Keep usage of chosen dash consistent	Consistency/formatting	Issue 16 does not contain factual inaccuracy.	None
Missing colons in table titles (*e.g.* Tables 43, 47, 70, 71, 72, 76, 77, 78)	Ensure table titles include a colon after the table number	Consistency/formatting		
Inconsistent use of 'versus' and 'vs' within titles and main text	Keep usage of chosen term consistent	Consistency/formatting		

Inconsistent use of space between signs and numbers ‘>50’ and ‘> 50’	Keep usage of chosen term consistent	Consistency/formatting		
Inconsistent capitalisation of ‘Search A’ and ‘search C’ *etc.*	Keep usage of chosen term consistent	Consistency/formatting		
Inconsistent use of abbreviations; some duplicated (*e.g.* CGRP, MMD, MOH) or missed (*e.g.* SIGN, CADTH, PRISMA)	Ensure all abbreviations are written in full before first use and then used throughout document	Consistency/formatting		
Inconsistent use of spaces between figures and units *e.g.* ‘675 mg’ and ‘675mg’	Ensure all measurements written as ‘675mg’ with no spaces	Consistency/formatting		

Erratum to:

Fremanezumab for preventing migraine [ID1368]

Section, page	Description of change
Section 1.4, p. 21	Replaced "The PSA of the EM analysis found that in [redacted] of simulations fell below £20,000 per QALY gained, and [redacted] below £30,000 per QALY gained. The respective predictions for CM were [redacted] and [redacted] versus BSC, and [redacted] and [redacted] versus OBA." with "The PSA of the EM analysis found that in [redacted] of simulations fell below £20,000 per QALY gained, and [redacted] below £30,000 per QALY gained. The respective predictions for CM were [redacted] and [redacted] versus BSC, and [redacted] and [redacted] versus OBA."
Section 1.5, p. 23	Replaced "Slightly fewer QALYs are gained in the CM analysis, at similar cost, so the predicted probability of fremanezumab being the more cost effective than BSC decreased" with "Slightly more QALYs are gained in the CM analysis, at similar cost, so the predicted probability of fremanezumab being the more cost effective than BSC increased".
Section 4.1.2, p. 44	Deleted "People with MOH are rarely seen in UK practice, due to the reduced use of opiod therapy in the UK compared with other countries."
Section 4.2.2.1, p. 50	Replaced "…….for the first three-months." with "…….throughout the trial."
Section 4.2.2.2, p. 54	Replaced CS reference "CS p. 48" with "CS p. 47" Replaced "……ineligibility in…" with "……eligibility for…"
Section 4.2.2.2, p. 55	Deleted "People with MOH are also seen rarely in clinical practice in the UK as compared to the US, due to variation in the prescription of opiates."
Section 4.2.2.2, p. 58	Replaced "Participants with EM received a dose of 900 mg of fremanezumab; either in one quarterly administration, or in a dose of 675 mg at baseline, followed by two monthly administrations of 225 mg." with "Participants with CM received a dose of 675 mg of fremanezumab as one quarterly administration, or a dose of 675 mg at baseline, followed by two monthly administrations of 225 mg."
Section 4.2.2.4, p. 63	Replaced "In participants with EM, HALO EM and FOCUS also evaluated the Migraine Disability Assessment (MIDAS), while in participants with CM, HALO CM and FOCUS evaluated the six-item Headache Impact Test (HIT -6)." with "In participants with EM, HALO EM also evaluated the Migraine Disability Assessment (MIDAS), while in participants with CM, HALO CM evaluated the six-item Headache Impact Test

	(HIT-6). FOCUS evaluated HIT-6 and MIDAS in both EM and CM patients" Replaced "The distinction between…… vomiting, photophobia, or phonophobia." with "Standard definitions of migraine and headache in line with ICHD-3 criteria were used, and were calculated based on the headache information (time, severity, duration, presence of migraine symptoms etc.) recorded within participants headache diaries."
Section 4.2.2.4, p. 67 Table 9	Deleted footnote "The CS reports that data for AEs experienced by ≥5% of any treatment group was also assessed (p.101), but the data was not reported in the CS."
Section 4.2.4.1.2, p. 87 Table 14	Added minus to median MMD change for placebo.
Section 4.2.4.2.1, p. 97	Replaced 31.1% with 30.1%
Section 4.2.4.2.3, p. 104	Replace "-0.9 to -1.7" with "-0.2 to -2.7"
Section 4.2.4.2.3, p. 107	Replaced "…..while it was evaluated in the HALO-EM trial…" with "….while it was evaluated in the HALO-CM trial……"
Section 4.2.4.2.4, p. 109	Values edited as suggested by the company.
Section 4.2.4.3.1, p. 112	Replaced [redacted] with [redacted]
Section 4.2.4.3.2, p. 115	Replaced both HALO-EM in the paragraph with HALO-CM Deleted "Notably, active rollover participants who received monthly fremanezumab exhibited a significant jump in response rates ([redacted] to [redacted]) between one and 12 months (i.e. four and 15 months), which is not replicated in other groups. It's unclear whether this is an anomaly or whether this represents a true differential effect of fremanezumab in this group." and "Overall mean values appear similar between the two arms, and are consistent with data from"
Section 4.2.4.3.3, p. 116	Deleted "HALO-EM; the data appears to show that improvements in outcomes in newly treated participants remains relatively stable between one and 12 months, while active rollover participants show a trend for a small but steady improvement between one and 12 months (i.e. four and 15 months). As no comparable time points are reported, it was not possible to determine whether this effect is statistically significant. Notably, active rollover participants who received monthly fremanezumab exhibited a significant jump in response rates ([redacted] to [redacted]) between one and 12 months (i.e. four and 15 months), which is not replicated in other groups. It is unclear whether this is an anomaly or whether this represents a true differential effect of fremanezumab in this group."

Section 4.2.4.3.3, p. 118	Replaced HALO-EM with HALO-CM
Section 4.2.4.5, p. 135	Replaced “p = 0.006” with “p = 0.007”
Section 4.2.5, p. 139	Replaced ““[redacted] with ““[redacted]”
Section 4.6, p. 153	Marked “..[redacted]..” as AIC
Section 5.2.4, p. 166	Replaced “ICERs are seen to reduce only marginally.” with “ICERs are seen to increase only marginally.”
Section 5.2.10.1, p. 186	Replaced “Fremanezumab is predicted to be the most cost-effective option versus BSC in [redacted] of simulations when using a £20,000 per QALY gained WTP threshold; and [redacted] of simulations using the £30,000 threshold. Versus OBA the respective probabilities are [redacted] and [redacted].” with “Fremanezumab is predicted to be the most cost-effective option versus BSC in [redacted] of simulations when using a £20,000 per QALY gained WTP threshold; and [redacted] of simulations using the £30,000 threshold. Versus OBA the respective probabilities are [redacted] and [redacted].”
Section 5.2.10.3, p. 194 Table 67	(12) Marked [redacted] as AIC (13) Marked [redacted] as AIC
Section 5.2.12.3, p. 197 Table 69	Removed the part of the footnote stating “Not presented in the company report but extracted from the CEM”.
Section 8, p. 207	Marked “…..[redacted].” As AIC

SECTION 1.4, p. 21

QALY gained. The company base case for CM found that over 10 years the average cost per person of fremanezumab was [redacted], some [redacted] more than BSC and [redacted] more than OBA. Fremanezumab QALYs over ten years were [redacted], a gain of [redacted] QALYs over BSC. The same pattern of incremental QALYs being gained ahead of costs was observed in CM as seen in EM. The ICER for fremanezumab versus BSC was £11,825 per QALY gained; and for fremanezumab versus OBA was £16,227 per QALY gained. Results using the company base case assumptions and parameters support the company conclusion that over 10 years fremanezumab is cost-effective in episodic migraine versus BSC, and chronic migraine versus BSC and OBA. The company's tests for stability in the ICERs towards changes in the input parameters led to their conclusion that the ICERs are stable. The PSA of the EM analysis found that in [redacted] of simulations fell below £20,000 per QALY gained, and [redacted] below £30,000 per QALY gained. The respective predictions for CM were [redacted] and [redacted] versus BSC, and [redacted] and [redacted] versus OBA.

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

The structure of the cost-effectiveness searches was poor, which is likely to produce ill-defined search results. There were poorly presented, hard to follow, were limited in ways that are not evidence-based, and deviated from recognised and validated economics or health utilities filter. The ERG cannot be confident that all relevant records would have been picked up in the search results.

The model structure was restrictive since it did not allow for natural history modelling. An individual patient simulation would have been more appropriate, providing a framework attuned to alternative assumptions concerning long-term outcomes. It was, however, structurally similar to the models of NICE TA260[2] for OBA and the ongoing appraisal of erenumab (NICE ID1188). Fremanezumab was modelled using a subgroup of adults with CM or EM who have used three or more preventative therapies; this subgroup was narrower than specified in the NICE final scope and narrower than the marketing authorisation. Effectiveness, utility, and resource use parameters were estimated from multiple different populations, creating inconsistencies, in particular the extent of prior prophylactic treatment. The modelling of OBA contrasted its licence, since the positive stopping rule was defined in terms of headache not migraine, and discontinuation was not implemented as headache/migraine frequency fell below the definition of CM. A 10-year time horizon was a plausible compromise to capture most long-term treatment effects on a background of increasing uncertainty in terms of the extrapolation of short-term evidence.

SECTION 1.5, p. 23

Resource modelling was broadly appropriate. The ERG believed that the assumption of 100% self-administration is unlikely but noted a minimal impact on the ICER. There was some concern that resource consumption rates were based on a study of a general migraine population, and that they were based on headaches not migraines. Therefore consumption rates may have been underestimated, which would introduce a small conservative bias. Whilst the exclusion of adverse events may be acceptable in the context of evidence collected in short-term trials, the ERG are concerned that the impact of as yet unknown long-term safety is not included in the model.

Company base case parameters and assumptions give rise to the conclusion that fremanezumab is cost-effective versus BSC for both the episodic and chronic conditions. ICERs were £13,954 and £11,825 per QALY gained, respectively. Incremental costs were gained early and incremental QALYs gained relatively late as a consequence of low long-term discontinuation and positive stopping rule effect of benefit with no cost. Probabilistic sensitivity analysis (PSA) findings were consistent with the deterministic findings, but QALY variation shows sensitivity to the effectiveness variables. PSA simulations of the episodic migraine analysis predicted a [redacted] probability of fremanezumab being cost-effective versus BSC at the £20,000 threshold. Slightly more QALYs are gained in the CM analysis, at similar cost, so the predicted probability of fremanezumab being the more cost effective than BSC increased to [redacted] (same threshold). The comparison versus OBA was deeply flawed but the respective probability lower mainly due to smaller QALY gain ([redacted]). The subgroup analysis of high frequency EM, based on alternative effect size estimates, produced similar incremental costs and QALYs, and therefore ICER, to the analysis of episodic migraine. This outcome was subject to uncertainty as the main analyses, although the company did not present sensitivity analyses specific to the subgroup.

With regard to the validity of results, the ERG found that the utility calculation contained a small error, and the intended three month assessment period to be implemented as two months. These were corrected and a revised set of results produced. The ERG was concerned with redundant content and code, unnecessarily formula complexity, absent/poor labelling, and overly brief method description hindered model validation. Also, the absence in the model of separate calculation sheets for responders and non-responders added complexity to model validation. External validation of model outputs from the company were not presented, and the one-way uncertainty parameters did not include the key effectiveness inputs, leading to an optimistic conclusion of ICER stability.

SECTION 4.1.2, p. 44

A number of other discrepancies in the SLR inclusion criteria were noted by the ERG. It is unclear from the CS whether only full-text publications were eligible for inclusion in the SLR, or whether conference abstracts were also eligible. In an additional literature search to identify trials evaluating OBA, which may have been missed or excluded from the company's search strategy (see Section 4.4.1), the ERG identified several conference abstracts[28-32] reporting evidence from a comparison between fremanezumab and placebo in patients who had previously received OBA. Based on the SLR inclusion criteria stated by the company, the ERG also consider that evidence from these abstracts should have been included in the CS. Further, the company do not provide a rationale for restricting the inclusion of observational trials to anti-CGRP interventions only (i.e. fremanezumab, erenumab, and galcanezumab). Crucially, this decision may have led to the exclusion of phase II trials for OBA as fourth line therapy, which may have provided comparative clinical efficacy and safety evidence.

The SLR specified that participants with medication overuse headache (MOH) were eligible for inclusion. At clarification the company stated that no studies included in the SLR recruited people with MOH, however two thirds of participants in the FOCUS trial were stated to have 'medication overuse status' ([redacted]). The ERG were unclear about whether this referred to the number of participants who had experienced MOH in the past, or whether this number of participants developed this during the trial.

ERG comment:

Contrary to the NICE scope, the CS omits evidence for comparator interventions used prior to fourth line therapy, and thus limits the focus of this submission to the fourth line population. However, even in this population, the ERG considered that evidence was scantily reported and may exclude key relevant evidence. In particular, the ERG were troubled by the limited evidence presented for OBA, which is currently available as fourth line therapy for people with chronic migraine. As a consequence of this omission from the CS, the ERG considered that it was not possible to fully evaluate the relative clinical efficacy and safety of fremanezumab and OBA in the target population. The ERG also noted that the evidence for fremanezumab in the fourth-line population is derived from a subgroup of the FOCUS trial, and therefore does not retain randomisation.

SECTION 4.2.2.1, p. 50

appear similar, although factors by which participants were stratified varied (see discussion in Section 4.2.4.1.1, 4.2.4.2.1, & 4.2.4.4.1).

The majority of treating centres for the HALO trials were in the US (HALO EM = 88/136; 64.7%; HALO CM = 87/132; 65.9%), whereas less than one-third of treating centres in FOCUS were based in the US (30/113; 26.5%), and the remainder were based in Europe (83/113; 73.5%). None of the participants included in the HALO trials were based in the UK. The number of participants in FOCUS that were based in the UK was not reported in the CS, although the CS reported that 6/113 (5.3%) of sites used in the FOCUS were in the UK. The geography of centres used in the HALO extension was not reported, although likely included many of the centres used in the HALO trials.

Notably, FOCUS was a considerably smaller trial (EM N=329; CM N=509) than the main HALO EM (N=875) and HALO CM (N=1130) trials. All three trials met their target sample size according to the power calculations reported (CS, p 38-40), although (as opposed to the HALO trials) the criteria used to calculate power in the FOCUS trial combined patients with EM and CM into the same treatment group. When EM and CM populations are analysed separately, FOCUS is underpowered to detect an effect; although the ERG noted that assumptions in the power calculation were reached comfortably, which adds greater confidence in the findings. Power calculations used to target additional recruitment for the HALO extension were not reported.

In the HALO-extension, participants in the original HALO EM and HALO CM trials were eligible to opt into a 12-month extension to evaluate the long-term efficacy and safety of fremanezumab. New participants were also recruited to the extension phase, and were subject to the same eligibility criteria as the main trial. Participants who participated in the original trial and who received fremanezumab continued on the same dosing schedule; while placebo participants and new participants were randomly assigned to either monthly or quarterly fremanezumab. Treatment with fremanezumab was delivered open label in the extension, although participants were blinded to the dose (monthly or quarterly administration) that they were receiving throughout the trial.

A lead-in phase of 28 days was used to establish baseline severity in both the HALO and FOCUS trials. Follow-up in the main trials was 12 weeks. Longer-term data, at 12 months (15 months for those in the original trials) is provided by the HALO extension. An open-label extension phase is also underway for FOCUS, which will evaluate the longer-term efficacy

and safety of fremanezumab; however, the results of this extension will not be available until late 2019 (CS, p. 112).

SECTION 4.2.2.2, p. 54

preventative therapy (as defined by different medication groupings). The HALO trials determined line of treatment based on four medication clusters:

- cluster A: divalproex sodium and sodium valproate
- cluster B: flunarizine and pizotifen
- cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine
- cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol.

Participants were excluded from the HALO trials if they had received medications in two or more clusters. Notably, however, these clusters did not include topiramate or OBA, and so the ERG considered it possible that a minority of participants included in the trials may have previously received three preventative therapies for migraine, including a medication in one of the clusters, plus both topiramate and OBA. At clarification, the company submitted data suggested that 21.3% (186/875) of participants in HALO-EM and 35.3% (399/1130) of participants in HALO-CM had received between one and three preventative therapies, including OBA, topiramate, or other.

The CS states that eligibility for the FOCUS trial was determined by having previously used two to four classes of preventative therapies, defined as:

- beta-blockers (propranolol, metoprolol, atenolol, and bisopropol)
- anticonvulsants (topiramate)
- tricyclics (amitriptyline)
- calcium channel blocker (flunarizine)
- angiotensin II receptor antagonist (candesartan)
- OBA
- valproic acid.

The clusters used in FOCUS overlapped with those used for HALO, but were extended to include angiotensin II receptor antagonists, topiramate, and OBA. There were also some alterations in the specific drugs that were included within each class.

As noted in Section 4.1.2, participants with ‘other migraine disorder’, described elsewhere in the CS as ‘medication overuse headache’ (MOH) were also eligible for inclusion in the trials (CS p.47). At clarification, the company advised that no participants recruited to any of the

included trials were classified as having MOH. However, the majority of participants in the FOCUS trial who had previously used ≥3 preventative therapies for migraine were identified

SECTION 4.2.2.2, p. 55

by the company as having overused acute medication status [redacted]). The ERG are unsure whether this refers to participants who have previously been classified as having MOH and have resolved this, or whether they developed MOH during the trial. Clinical advice to the ERG is that MOH complicates treatment of migraine as it changes the nature of the headaches people experience. As it is unclear whether 'medication overuse status' refers to present or previous MOH, it is unclear whether this may affect the applicability of the evidence included.

Trial inclusion is limited to those between the ages of 18 and 70 years. This excluded people aged between 16 and 18 years, who are treated in adult services in the UK, and older adults, who may constitute a significant minority of people with migraine treated in the UK (clinical advice to the ERG suggests approximately 15% of people will be over age 70 years, although this will vary by region). Clinical advice to the ERG is that evidence from the included trials may be generalised to people between 16 and 18 years of age, although may be less appropriate for people over 70 years of age, due to variation in metabolism.

Population inclusion criteria for the HALO and FOCUS trials, aside from criterion for line of treatment, were generally comparable.

Table 6: Population Inclusion/Exclusion Criteria of the included Trials

	HALO EM and HALO CM	FOCUS
Inclusion criteria	• Aged 18 to 70 years • Migraine onset at or prior to age 50 • History of migraine based on ICHD-3 beta criteria or clinical judgement suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for at least 12 months prior to screening • Meets trial criteria for EM or CM (see Table 7) • ~85% diary compliance • Not using preventive medications (i.e. at least 5 half-lives have passed since last use) or using no more than 1 preventive medication for migraine [f]or other medical conditions (e.g. propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to	• Aged 18 to 70 years • Migraine onset at or prior to age 50 • History of migraine based on ICHD-3 beta criteria or clinical judgement suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for at least 12 months prior to screening • Meets trial criteria for CM or EM (see Table 7) • ~85% diary compliance • Documented inadequate response to 2 to 4 classes of prior preventive migraine medications within the past 10 years (defined as a lack of a clinically meaningful improvement after at least 3 months of therapy, intolerance to the treatment or contraindication/unsuitability for a treatment) Classes as follows: o beta-blockers (propranolol, metoprolol, atenolol, and bisopropol) o anticonvulsants (topiramate) o tricyclics (amitriptyline)

	beginning the 28-day run-in period	

SECTION 4.2.2.2, p. 58

Abbreviations: CM, chronic migraine; EM, episodic migraine; ICHD-3, The international classification of headache disorders 3rd edition.
Source: CS, Appendix L p 3-11.

ERG comment:

Aside from the line of treatment participants received in the trials, population inclusion criteria were comparable between the HALO and FOCUS trials, and were generally consistent with the SLR inclusion criteria.

The ERG considered it unlikely that there would be significant implications of defining prior line of treatment based on clusters of therapies, rather than on individual medicines. However, it was not clear whether there would be a difference in treatment effect between participants in the studies who have experienced different treatment pathways. Moreover, in both studies participants were permitted to have previously received OBA: at clarification, the company reported that amongst participants in FOCUS who had received ≥3 prior therapies, 33/127 (26.0%) of participants with EM and 138/293 (47.1%) of participants with CM had previously received OBA. As the company wish to position fremanezumab as an alternative to OBA, this means that a significant minority of participants in the key trial are at a different position in the treatment pathway. The ERG also noted that there is an overlap in the populations treated in HALO and FOCUS, with a minority of participants in HALO having previously received between one and three treatments.

It is unclear from the CS whether a significant number of participants in the FOCUS trial developed MOH during the trial. If true, this could affect the generalisability of the treatment effect to the UK population, although the ERG were unable to determine from the information provided in the CS and at clarification if this was the case. All exclusions from the trials were considered to be appropriate, although clinical advice to the ERG is that the evidence may be less generalisable to people with migraine over the age of 70 years.

4.2.2.3 Intervention characteristics

Intervention characteristics used in the included trials are summarised in Table 8 below.

In all trials, participants with EM received a dose of 675 mg of fremanezumab; either in one quarterly administration, or as in three monthly administrations of 225 mg. Participants with CM received a dose of 675 mg of fremanezumab as one quarterly administration, or a dose of 675 mg at baseline, followed by two monthly administrations of 225mg. The ERG noted that the initial dose of 675 mg used for CM participants on monthly treatment exceeded the

marketing authorisation for fremanezumab. A matching placebo (not described) was arranged to blind participants to treatment allocation, and was delivered using the same schedule in both trials.

SECTION 4.2.2.4, p. 63

4.2.2.4 Outcome assessment

The outcomes evaluated in the included trials are summarised in Table 9, and methods of statistical analysis used to analyse the trial data are reported in Table 10.

All trials evaluated the mean change in monthly migraine days (MMDs), monthly headache hours, mean change in the monthly use of acute headache medication, and the proportion of participants who experienced a 50% reduction in MMDs at 12 weeks. As its primary outcome, HALO CM also evaluated the change in headache days of at least moderate severity at 12 weeks; this outcome was prioritised in a change to the study protocol (as reported on clinicaltrials.gov on June 12, 2017). All clinical outcomes were evaluated using participants' diary entries: participants completed daily electronic diaries of their symptoms. Standard definitions of migraine and headache in line with ICHD-3 criteria were used, and were calculated based on the headache information (time, severity, duration, presence of migraine symptoms etc) recorded within participants headache diaries. The CS did not provide detail on the methods of assessing HRQoL and functional outcomes, although participants were stated to be seen by trial personnel at screening and baseline, followed by weeks four, eight, and twelve and/or discontinuation (HALO EM and HALO CM) or weeks four, eight, twelve, sixteen, and twenty and/or discontinuation (FOCUS; CS p. 32).

With regards to HRQoL, the three main trials all evaluated the Migraine-Specific Quality of Life Questionnaire (MSQoL). In participants with EM, HALO EM also evaluated the Migraine Disability Assessment (MIDAS), while in participants with CM, HALO CM evaluated the six-item Headache Impact Test (HIT-6). FOCUS evaluated HIT-6 and MIDAS in both EM and CM patients. HRQoL as evaluated by generic tools was not reported in the CS, and no HRQoL outcomes were evaluated in the HALO extension. The CS did not report validated minimally important differences (MIDs) for the three scales. The ERG was able to identify MIDs for the MSQoL and HIT-6 (reported in Table 9).

Measures of AEs were consistent across the trials, and were assessed as: any AE; treatment-related AEs; SAEs; discontinuation due to AEs; and any AE experienced by more than 2% of any group.

SECTION 4.2.2.4, p. 67

	HALO EM	HALO CM	HALO Extension	FOCUS EM	FOCUS CM
Final follow-up	**12 weeks**	**12 weeks**	**1 year**	**12 weeks**	**12 weeks**
Additional Analyses	• Patients with past topiramate and/or OBA use			• HFEM • Patients who have previously received 3 or more classes of preventative migraine treatment • Patients with HFEM who have previously received 3 or more classes of preventative migraine treatment	

Abbreviations: AE, adverse event; ALT, Alanine transaminase; AST, Aspartate transaminase; CM, chronic migraine; CS, company submission; EM, episodic migraine; ERG, Evidence Review Group; HFEM, high-frequency episodic migraine; HIT-6,six-item headache impact test; HRQoL, health-related quality of life; INR, international normalised ratio; MID, minimally important difference; MIDAS, migraine disability assessment; MMDs, mean monthly migraine days; MSQoL, migraine-specific quality of life questionnaire; NR, not reported; OBA, onabotulinum toxin A; SAE, serious adverse event; ULN, upper limit of normal.

Notes: * Note that within HALO EM and HALO CM, all pre-planned subgroup analyses were stated to have been conducted for 2 outcomes only: monthly average number of migraine days and the monthly average number of headache days of at least moderate severity.

^Protocol-defined AEs of special interest included ophthalmic adverse events of at least moderate intensity, events of possible drug-induced liver injury (AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN or INR >1.5), Hy's Law events, or events of suspected anaphylaxis and severe hypersensitivity reactions.

Source: CS, p. 29-33, 52; 74-93; clarification question A26.

SECTION 4.2.4.1.2, p. 87

Finally, in terms of adherence, only a small minority of participants in the trial were reported to be non-compliant with treatment (1% of quarterly fremanezumab participants, and 2% of both placebo and fremanezumab monthly participants).

Table 14: HALO EM Main Efficacy Outcomes

	Placebo (n=290)	Fremanezumab quarterly (n=288)	Fremanezumab monthly (n=287)
MMDs			
Baseline (SD)	9.1 (2.7)	9.3 (2.7)	8.9 (2.6)
Median change (IQR)	-2.7 (-4.7 to -0.5)	-4.0 (-6.4 to -1.9)	-4.2 (-6.2 to -2.0)
LSM change (95% CI)	-2.2 (-2.68 to -1.71)	-3.4 (-3.94 to -2.96)	-3.7 (-4.15 to -3.18)
Difference vs placebo (95% CI)		-1.3 (-1.79 to -0.72)	-1.5 (-2.01 to -0.93)
P-value vs placebo		<0.0001	<0.0001
Patients with at least 50% reduction in MMDs			
Number achieving endpoint (%)	81 (27.9%)	128 (44.4%)	137 (47.7%)
Difference vs placebo (%; 95% CI)		16.5 (8.9 to 24.1)	19.8 (12.0 to 27.6)
P-value vs placebo		<0.0001	<0.0001
Mean monthly days of use of any acute headache medication			
Baseline (SD)	7.7 (3.6)	7.8 (3.7)	7.7 (3.4)
Median (IQR)	-1.7 (-4.0 to 0.0)	-3.0 (-5.6 to -0.8)	-3.2 (-5.2 to -1.2)
LSM change (95% CI)	-1.6 (-2.04 to -1.20)	-2.9 (-3.34 to -2.48)	-3.0 (-3.41 to -2.56)
Difference vs placebo (95% CI)		-1.3 (-1.76 to -0.82)	-1.4 (-1.84 to -0.89)
P-value vs placebo		<0.0001	<0.0001
Mean change in monthly average number of headache days of at least moderate severity			
Baseline	6.9 (3.1)	7.2 (3.1)	6.8 (2.9)
LSM difference vs placebo (95% CI)	-	-1.5 (-1.96 to -1.04)	-1.5 (-1.92 to -0.99)
P-value vs placebo		<0.0001	<0.0001
Mean change in monthly average headache hours of any severity			
Baseline	NR	NR	NR
LSM difference vs placebo (95% CI)		-8.8 (-13.28 to -4.32)	-12.5 (-16.99 to -8.03)
P-value vs placebo		0.0001	<0.0001

Abbreviations: CI, confidence interval; EM, episodic migraine; IQR, interquartile range; LSM, least squares mean; MMDs, mean monthly migraine days; NR, not reported; SD, standard deviation; vs, versus.
Source: CS, Table 14, p. 50 – 51; p. 55.

SECTION 4.2.4.2.1, p. 97

were female, and had been diagnosed with migraines between one and 61 years prior to the trial (mean 19.7 – 20.1; SD 12.0 – 12.9). The line of treatment of participants in the trial was not reported in the CS, although at clarification the company submitted that 35.3% (399/1130) of participants in the trial had previously received between one and three preventative therapies, which may include OBA or topiramate. Topiramate was commonly used amongst these patients: the CS reports that (21.2%, 239/1130) of participants had previously received topiramate. The CS further reports that 30.1% (340/1130) of participants were receiving another preventative therapy for migraine in the run-up period to the trial. Evidence from the trial CSR[39] (p. 111) suggests that the majority of these participants continued their preventative therapy during the main trial ([redacted]).

Assessment of disease severity at baseline, as reported in the CS, was based on participant reports during the lead-in phase of the trial (28 days). Participants reported a mean of 16.0 – 16.7 migraine days (range 5 – 28; SD 4.9 – 5.2) and a mean of 12.8 – 13.3 moderately severe or severe headache days (range 0 – 28; SD 5.5 – 5.8). Participants reported using acute headache medication on 13.0 – 13.1 days (range 0 - 28; SD 6.8 – 7.2), and acute migraine-specific medications on 10.7 – 11.3 days (range 1 – 28; SD 6.0 – 6.3). Mean HIT-6 scores ranged between 64.1 – 64.6 (range 42 - 78; SD 4.4 – 4.8), indicating a mean score in the severe impact category for all trial arms.

Participant characteristics at baseline were similar across trial arms, with no significant differences between trial arms.

Table 20: Baseline Characteristics of Patients Included in HALO-CM

HALO CM Baseline characteristic	Placebo (n=375)	Fremanezumab quarterly (n=376)	Fremanezumab monthly (n=379)
Age, years			
Mean (SD)	41.4 (12.0)	42.0 (12.4)	40.6 (12.0)
Median (range)	41.0 (19-70)	43.0 (18-71)	40.0 (18-70)
Sex, n (%)			
Male	45 (12)	45 (12)	49 (13)
Female	330 (88)	331 (88)	330 (87)
Weight, kg			
Mean (SD)	72.6 (15.6)	72.4 (15.8)	72.5 (16.4)
Median (range)	71.2 (45-119)	70.5 (45-132)	69.8 (44-119)
Time since initial migraine diagnosis, years			
Mean (SD)	19.9 (12.9)	19.7 (12.8)	20.1 (12.0)

HALO CM Baseline characteristic	Placebo (n=375)	Fremanezumab quarterly (n=376)	Fremanezumab monthly (n=379)
Median (range)	17.0 (1-57)	18.0 (1-61)	18.0 (1-55)
Preventive medication use during run-in period, n (%)			

SECTION 4.2.4.2.3, p. 104

subgroups, mean improvements in outcomes ranged between -0.2 to -2.7 for monthly migraine days and -0.9 to -1.7 for monthly headache days of at least moderate severity. The latter does not include mean values reported for prior topiramate and OBA use, which have been excluded due to the lack of variance data and risk of reporting bias.

The CS does not report the outcomes of any statistical tests to evaluate whether the effect of fremanezumab varies between different subgroups. Based on the data reported, it was not possible for the ERG to conduct these analyses. However overall, there appeared to be a trend for the effect of fremanezumab to be greater relative to placebo in the following subgroups: participants aged between 18 and 45 years (compared to >45 years); Caucasians (compared to non-Caucasians); females (compared to males); and participants receiving concomitant preventative therapies (compared to not).

As for HALO-EM, data is not reported for two of the subgroups: prior topiramate and prior OBA use. A footnote to the table explains that this was because the sample size for each was too small to perform the analysis; however, this explanation is inconsistent with the sample sizes reported for other reported subgroups. Further, an adjusted (LSM) treatment difference without 95% confidence intervals was reported for prior topiramate use, suggesting that this analysis was conducted and not reported. At clarification, the company provided a subgroup analysis that included participants who had previously used topiramate, OBA and/or another preventative treatment, for the outcome of the change from baseline in monthly average number of headache days of at least moderate severity. The results of this analysis are presented in Table 23, and appear to show a larger effect of fremanezumab on headache days than in the main trial population. As the company did not provide any further outcome data, it was not possible for the ERG to determine whether this was a trend across all outcomes.

SECTION 4.2.4.2.3, p. 107

ERG comment:

Subgroup analyses for HALO-CM demonstrated a consistent benefit of fremanezumab monthly and quarterly compared to placebo for both mean monthly migraine days and mean headache days of at least moderate severity. This difference was statistically significant across most subgroups. No statistical tests were reported in the CS to compare the effect of fremanezumab with placebo between subgroups; however the ERG noted that the effect of fremanezumab as compared to placebo appeared greater for participants receiving concomitant preventative therapy. Further differences between subgroups noted were considered to likely be random, as clinical advice to the ERG is that there is no known clinical rationale for these differences. Participants in the placebo arm across all subgroups also demonstrated improvements across both outcomes.

4.2.4.2.4 Quality of life and patient reported outcomes (PRO)

Quality of life and PRO are reported in Table 24. MSQoL was the company's chosen methods for evaluating HRQoL in this population, however while it was evaluated in the HALO-CM trial, the data is not reported in the CS. Rather, the company reported a qualitative summary of the data (CS, p. 61) stating that 'differences' from placebo were demonstrated for fremanezumab across the three domains. The company went on to state that LSM differences for role function-restrictive were stated to be statistically significant (p<.0001). LSM differences with placebo were reported (6.1 for quarterly and 6.9 for monthly), which are both above the recommended MID of 3.2[34], although with no accompanying variance data. Mean values for the other domains were not reported and it is unclear whether the differences stated in these domains were above the scale MID or statistically significant.

With regards to the HIT-6 scale, improvements in the impact of migraines on everyday functioning above the recommended scale MID of 2.3[35] were exhibited across all three trial arms. Fremanezumab was associated with a greater improvement in HIT-6 scores than placebo (a difference of -1.9 and -2.4 for fremanezumab quarterly and monthly, respectively), which was statistically significant. All three treatment groups also demonstrated improvements in EQ-5D VAS, indicating improvements in HRQoL. Patients in the fremanezumab arms showed a statistically significant greater improvement in EQ-5D VAS scores than placebo.

SECTION 4.2.4.2.4, p. 109

the placebo arm may undermine the validity of the absolute data (including the absolute change relative to the scale MIDs).

4.2.4.3 HALO Extension

A total of [redacted]/2,005 ([redacted]) patients from the HALO trials (including [redacted]/875 [redacted] patients with EM and [redacted]/1,130 [redacted] patients with CM) elected to participate in the HALO extension phase. An additional [redacted] new patients ([redacted] with EM and [redacted] with CM) were also recruited. Based on information provided in Table 20 and 21 of the CS (p.72 and 74) the ERG estimates that [redacted]/581 ([redacted]%) of patients with EM and [redacted]/755 ([redacted]%) of patients with CM who were receiving fremanezumab in the main trial continued with the extension. A total of [redacted]/669 ([redacted]%) patients who received placebo in the main trial opted to join the extension.

4.2.4.3.1 Baseline Characteristics

The baseline characteristics of patients who were included in the HALO trials are reported in Table 25 and for participants with EM and Table 26 for participants with CM.

A total of 780 participants with episodic migraine participated in the HALO extension phase. Patients were aged between 18 and 71 years, with a mean age of between [redacted] years (SD [redacted]). The majority of participants ([redacted]780) were female, and had been diagnosed with migraines between 1 and 65 years prior to the trial (mean [redacted]; SD [redacted]). The line of treatment of participants in the trial was not reported, nor was the number of participants who were receiving another preventative therapy for migraine in the lead-in phase. It was reported that [redacted]/780) of participants had previously received topiramate.

Disease severity at baseline was based on participants' reports during the lead-in phase of the trial (28 days). Participants reported a mean of [redacted] migraine days (range [redacted]), and a mean of [redacted] moderately severe or severe headache days (range [redacted]; SD [redacted]). Participants reported using acute headache medication on [redacted] days (range [redacted]; SD [redacted]). The number of acute migraine-specific medications and mean migraine disability assessment scores were not reported at baseline.

No significant differences in population characteristics were reported between patients who received fremanezumab quarterly and monthly in the extension.

SECTION 4.2.4.3.1, p. 112

participants in the extension than in the main trial; specifically, the number of headaches of any severity, previous use of OBA, baseline MIDAS/HIT-6 scores, and information on line of treatment were not reported for those entering the extension phase. It is possible that there are further differences between participants in the main trials and the extension on these characteristics that the ERG has been unable to review.

Population characteristics between participants receiving fremanezumab monthly and quarterly in the extension phase were similar, with no differences reported.

4.2.4.3.2 Clinical Outcomes – episodic migraine

Clinical outcome data for the extension phase of HALO EM is reported in Table 27. Outcomes are reported separately for participants who continued to receive fremanezumab in the main trial ('active rollover' participants with 12 weeks of existing fremanezumab therapy) and those who were naïve to fremanezumab at the start of the trial (either because they received placebo in the main trial or they were newly recruited). It is unclear why outcome data for the combined population is not reported. A further limitation of the data reported is that there are no comparable time points between newly treated and active rollover participants reported in the CS to allow comparison. Those who rolled over into the extension received an additional three months of treatment (i.e. one-month follow-up is a total of four-months of treatment for those in the active rollover arm). A total of [redacted] of patients in the extension phase were included in final follow-up at 12 months (final sample size not stated in the CS, so this figure is based on the sample size reported for the proportion of patients exhibiting a 50% reduction in migraine days).

Overall the data (Table 27) shows improvements in all outcomes from baseline for both groups at one, three, six, and 12 months (the ERG have assumed that baseline scores displayed in Table 27 for active rollover participants are at baseline of the main trial, and not of the extension). No statistical tests were reported; however, all 95% confidence intervals are consistent with statistically significant changes from baseline in all continuous outcomes. At 12 months, the data indicated that participants receiving fremanezumab exhibited a [redacted] to [redacted] day reduction in mean monthly migraine days compared to baseline, and between [redacted] [redacted] of patients reported a 50% reduction in monthly migraine days ([redacted] of all patients in the extension phase). Reductions are similar in headache days of at least moderate severity, which reduced from [redacted] to [redacted] days at 12 months from baseline, and participants reported between [redacted] and [redacted] fewer days using acute headache medication.

No statistical tests were reported to compare outcomes between newly treated and active rollover participants. Overall, outcomes were relatively similar between active rollover and

SECTION 4.2.4.3.2, p. 115

ERG comment:

The data from the extension phase to HALO-EM suggests that reductions in improvements in clinical outcomes persist until final follow-up at 12 and 15 months for newly recruited and active rollover participants, respectively. Clinical advice to the ERG is that changes in outcomes between baseline and follow-up represent a clinically meaningful difference.

Generally, the ERG noted that the CS contains very limited discussion of the results from the extension phase of HALO, and provides no discussion of any trends in the data.

4.2.4.3.3 Clinical Outcomes – chronic migraine

Clinical outcome data for the extension phase of HALO CM is reported in Table 28. No statistical tests were reported to compare outcomes between newly treated and active rollover participants. Overall mean values appear similar between the two arms and are consistent with data from HALO-CM; the data appears to indicate that outcome data in newly treated participants remains relatively stable between one and 12 months, while active rollover participants show a trend for a small but steady improvement between one and 12 months (i.e. four and 15 months). As no comparable time points are reported, it was not possible to determine whether this effect is statistically significant.

As with HALO EM, outcomes are reported separately for participants who continued to receive fremanezumab in the main trial (active rollover participants) and those who were naïve to fremanezumab at the start of the trial (either because they received placebo in the main trial or they were newly recruited). Outcome data for the combined population are also not reported. A total of [redacted] of participants in the extension phase were included in final follow-up at 12 months (again, the final sample size was not reported in the CS and so this figure is based on numbers reported for the proportion of participants exhibiting a 50% reduction in migraine days).

Overall the data shows improvements in all outcomes from baseline for both groups at 1, 3, 6, and 12 months (the ERG have assumed that baseline scores displayed for active rollover participants are at baseline of the main trial, and not of the extension). No statistical tests were reported to compare outcomes between newly treated and active rollover participants.

SECTION 4.2.4.3.3, p. 116

No statistical tests are reported, however upper and lower 95% confidence intervals are consistent with statistically significant changes from baseline in all continuous outcomes. At 12 months, the data indicates that participants receiving fremanezumab exhibit a [redacted] day reduction in mean monthly migraine days compared to baseline, and between [redacted] of participants reported a 50% reduction in monthly migraine days ([redacted] of all participants in the extension phase). Reductions are similar in headache days of at least moderate severity, which reduced from [redacted] to [redacted] days at 12 months from baseline, and participants used acute headache medication for between [redacted] and [redacted] fewer days.

SECTION 4.2.4.3.3, p. 118

ERG comment:

The data from the extension phase to HALO-CM suggest that improvements in clinical outcomes persist until final follow-up at 12 and 15 months, for newly recruited and active rollover participants, respectively. Clinical advice to the ERG is that changes in outcomes between baseline and follow-up all represent a clinically meaningful difference. The ERG noted that for all arms, there was a trend for improvements in outcomes to increase slightly over time.

4.2.4.4 FOCUS

The company stated in clarification that the data provided for FOCUS was the final cut for the double-blind part of the trial.

4.2.4.4.1 Baseline characteristics

In the overall population, the baseline characteristics of participants in the FOCUS trial were comparable between the three randomised groups of fremanezumab quarterly, fremanezumab monthly and the placebo groups (CS, p. 37).

For the EM population, the mean age of participants in the placebo group [redacted] mean age of the fremanezumab monthly group but [redacted] the mean age in the fremanezumb quarterly group, albeit [redacted] (CS, Appendix M, p. 5). The female population also [redacted] in the fremanezumab monthly group compared to the placebo group [redacted] The mean MIDAS scores for both fremanezumab groups [redacted] mean MIDAS score for the placebo group [redacted], for quarterly and monthly groups respectively).
[redacted]. The differences and similarities [redacted] for the HFEM subgroup of the total EM population.

For the CM population, the male population [redacted] the two fremanezumab groups compared to placebo, also [redacted] for the quarterly and monthly regimen, respectively.
[redacted]

The comparison of baseline characteristics for the EM population who have used three or more classes of migraine preventative therapies [redacted]. This was [redacted] for the HFEM population who have used three or more classes of migraine preventative therapies. For the CM population who have used three or more classes of

migraine preventative treatment, [redacted] **SECTION 4.2.4.5, p. 135**

4.2.4.5 Adverse events – HALO and FOCUS trials

In the HALO EM trial, the overall adverse event (AE) rate ($p = 0.05$) and proportion of participants with at least one treatment-related AE ($p < 0.02$) were significantly higher in both fremanezumab groups compared to placebo (Table 37). Few patients had serious adverse events (SAEs) in both fremanezumab groups (1.0%) and in the placebo group (2.4%). The most common individual AEs were injection site related and were comparable between fremanezumab groups and placebo except for duration which was significantly higher in the fremanezumab monthly group compared to the placebo group ($p = 0.007$) (CS, Section B 2.10.1, p. 101).

For the HALO CM trial, the fremanezumab groups also had a higher rate of overall AEs compared to placebo ($p = 0.059$ and 0.034 for the quarterly and monthly groups respectively) (Table 38). Treatment-related AEs were also higher in the fremanezumab groups than placebo ($p = 0.052$ and 0.016 for the quarterly and monthly groups respectively). Participants with SAEs and participants with at least one AE leading to study discontinuation were evenly distributed among treatment groups. One death, deemed unrelated to the study medication, was recorded in the CM fremanezumab quarterly group. All individual AEs were evenly distributed among the three groups. The most common individual AEs were also injection site related including pain, induration and erythema (CS, p. 104).

In the FOCUS trial, the data from the whole population show that participants with at least one AE, participants with at least one treatment-related AEs and participants with at least one SAE, [redacted] (Table 40). All individual AE rates [redacted] Most common individual AEs [redacted] (CS, p. 105-106). For the relevant subgroup population who have used three or more classes of preventative therapies, [redacted] for participants who had at least one AE compared to the overall FOCUS population, [redacted] FOCUS EM and FOCUS CM population who had used three or more preventative therapies. Regarding the individual incidence of AEs,

[redacted]

[redacted]. Over the 12 months extension, participants with at least one AE [redacted] treatment-related AE (Table 39). The proportion of participants with at least one SAE [redacted]

SECTION 4.2.5, p. 139

analysis for the FOCUS patients from the six UK centres [redacted]

The preventative therapies used in the FOCUS subgroup who have used three or more [redacted]. Thus, it appears that the overall proportion of the first three lines of preventative therapies used in the UK constituted [redacted] the prior therapies received by the FOCUS population. This may reflect some [redacted] in the other centres compared to the UK. It is unclear whether the types of therapy received by people with migraine may affect subsequent treatment efficacy, although clinical advice to the ERG suggested that there are various reasons for stopping preventative therapies (including both tolerability and contraindication issues), which influence how people progress to different lines in the pathway. The FOCUS [redacted] in the study sample. There is no evidence on how these factors may impact on treatment effects at later lines of therapy, and therefore this is a key uncertainty in the applicability of the FOCUS data to the UK target population.

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

The CS reports that "A network meta-analysis was conducted to compare relevant treatment within the population of interest for this appraisal (patients who have failed three or more classes of preventive therapies)" (CS, p. 94).

4.3.1 Search strategy

The company did not provide a separate search strategy for the ITC in the submission.

ERG comment:

The ERG assumed that the ITC also used the SLR broad search strategy as all relevant comparators stated in the final scope were include in search C of the company's search strategy (CS, Appendix D, p. 7).

SECTION 4.6, p. 153

4.6 Conclusions of the clinical effectiveness section

The population specified in the company's SLR was broader than was specified in the NICE final scope, but the evidence presented in the CS was for a narrower population. In all, four trials were presented: HALO EM, HALO CM, HALO extension and the FOCUS trials. The ERG identified two additional Phase II trials which were considered to meet the specified inclusion criteria; however, these were not included by the company. The final NICE scope specified "adults with chronic or episodic migraine" while the CS focused on a subgroup of people with EM and CM who have used three or more preventative treatments. Thus, the company considered only the FOCUS trial to be directly relevant to the population of interest. The FOCUS population appeared more representative of the UK population involving 85% of participants from Europe. Thus it's largely comparable to the UK population in respect of baseline demographic and clinical characteristics except for potential differences in the classes and types of drugs previously used.

Data from the HALO EM, HALO CM and FOCUS trials demonstrated better treatment effects in EM and CM for both fremanezumab quarterly and monthly regimens versus placebo across reported outcomes. The HALO extension trial also demonstrated significant improvement in all clinical outcomes compared to the baseline. Treatment effects appear consistent across EM and CM populations in the FOCUS as well as in the subgroup that have used three or more preventative therapies, albeit with reduced precision. The comparative effect versus placebo also appeared generally greater in the FOCUS population than in the HALO population. The ERG believed that the placebo in the FOCUS trial appeared more representative of best supportive care compared to the placebo group in the HALO trials because concomitant preventative therapies were allowed in 20% of the participants in HALO but not in FOCUS. No direct evidence comparing fremanezumab and comparators was found. The ITC containing a network of fremanezumab, erenumab and OBA and placebo, showed there was no statistically significant advantage between either of the two fremanezumab dosing regimens and OBA, though both dosing regimens of fremanezumab were numerically superior to OBA in terms of percentage of patients with at least 50% reduction in monthly average number of migraine days. The ITC estimates were confirmed by the ERG.

The HRQoL assessments broadly showed significant improvement compared to the placebo arms for both fremanezumab groups in both EM and CM populations and in the population, who have used three or more preventive therapies. The AE profile showed fremanezumab to

be largely tolerable with treatment discontinuation rate due to AEs of 3% at 12 months. Overall, both fremanezumab regimens are likely to be beneficial in the EM and CM

SECTION 5.2.4, p. 166

negative stopping rule (12 weeks for fremanezumab; 24 weeks for OBA). Discontinuation was applied in the episodic migraine analysis for the proportion failing to reduce MMDs by ≥50% versus baseline; and ≥30% MMDs in the chronic migraine analysis.

A strategy of best supportive care was compared to fremanezumab in both analyses. The effectiveness of BSC was informed by the placebo control arm of FOCUS, which did not allow active prophylactic treatment but did allow acute headache and migraine specific medication. Like the prophylactic strategies, BSC was also modelled in terms of response and non-response. OBA was included as a second comparator to fremanezumab in the chronic migraine analysis, since it is recommended as an option for the prophylaxis of headaches in adults with CM that have not responded to at least three prior pharmacological prophylaxis therapies.[47] They must have headaches on at least 15 days per month, of which at least 8 days are with migraine, a definition consistent with fremanezumab. In the model, the negative stopping rule was applied should inadequate response be measured at initial assessment (24 weeks), defined as failing to reach ≥50% reduction in MMDs.

The company did not present a comparison versus other preventative treatments topiramate, propranolol, amitriptyline or gabapentin. This is in line with their recommendation as earlier options in the treatment pathway.

ERG comment:

That three-monthly fremanezumab administration would be no more resource intensive than monthly administration is a reasonable and potentially conservative assumption, but the plausibility of all patients self-administering fremanezumab is doubtful. The ERG presents a scenario analysis in which 10% of patients receive nursing support is presented in Section 5.3.3. ICERs are seen to increase only marginally.

The stopping rule described in the OBA license refers to headache days not migraine days; and that discontinuation should follow a change in the condition to episodic frequency, defined as <15 headache days per month for three consecutive months. It is worth noting therefore that the stopping rule of the model is defined in terms of migraine days per month; and OBA is not discontinued when the intensity of the condition improves such that it is no longer defined as chronic. The ERG is concerned therefore that the evaluation fremanezumab versus OBA is inconsistent with its licence with implication at decision level.

5.2.5 Perspective, time horizon and discounting

The analyses assumed the perspective of the NHS and Personal Social Services (PSS), and future costs and benefits were discounted at 3.5% per annum. The time horizon of the base

SECTION 5.2.10.1, p. 186

Figure 11: Cost-effectiveness acceptability curve for EM, fremanezumab vs. BSC

Figure redacted - CIC

Table 65 presents the mean results of the PSA of the CM analysis, including the comparison with OBA; Figure 12 and Figure 13 show the plots of each iteration on the cost-effectiveness plane, for the comparison versus BSC and OBA, respectively. Mean findings are consistent with the deterministic CM analysis. Both plots show that QALY gain is highly sensitive to variation across the effectiveness variables relative to incremental costs, as was seen in the EM analysis. Figure 14 and Figure 15 illustrate the cost-effectiveness acceptability curves versus BSC and OBA, respectively (and separately). Fremanezumab is predicted to be the most cost-effective option versus BSC in [redacted] of simulations when using a £20,000 per QALY gained WTP threshold; and [redacted] of simulations using the £30,000 threshold. Versus OBA the respective probabilities are [redacted] and [redacted].

SECTION 5.2.10.3, p. 194

Table 67: Result of scenario analyses in the chronic migraine analysis

Scenario	ICER, Frem vs. BSC	ICER Frem vs. OBA
Base case	£11,825	£16,825
(1) Time horizon reduced from 10 to 5 years	£19,328	£27,517
(2) Time horizon increased from 10 years to lifetime (57.8 years)	£4,085	£5,555
(3) Linear waning of active treatment effect to BSC level over 10 years post discontinuation.	£12,017*	£16,382*
(4) Lifetime horizon and 10-year waning of active treatment effect to BSC level	£4,131	£5,589
(5) Treatment administration costs included for fremanezumab (monthly: £1.85 per cycle)	£11,907	£16,380
(6) Treatment administration costs included for fremanezumab (quarterly: £0.62 per cycle)	£11,853	£16,278
(7) Positive stopping rule affects only 10% of currently treated patients rather than 20% in the base case	£14,017	£19,634
(8) No positive stopping applied at annual assessment due to sustained treatment effect	£16,951	£24,756
(9) Impact of lost work days included in cost analysis	Dominates	Dominates
(10) Use of quarterly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£12,243	£17,325
(11) Use of monthly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£11,462	£15,326
(12) Proportion of patients responding to OBA increased to from [redacted] to [redacted]	£11,825	£22,411
(13) Proportion of patients responding to OBA decreased from [redacted] to [redacted]	£11,825	£12,742
(14) 50% reduction in MMDs used as response threshold in CM rather than 30%	£10,724	£17,155

Abbreviations: BSC, best supportive care; CM, chronic migraine; Frem, fremanezumab; ICER, incremental cost-effectiveness ratio; MMDs, monthly migraine days; OBA, onabotulinum toxin A.
*A modelling error was identified in the calculation of these estimates. Further, the ERG advise caution with this result which appears to wane patients on prophylaxis as well as those with positive discontinuation.

5.2.11 Subgroup analysis of high frequency episodic migraine (HFEM)

This analysis used efficacy data from the FOCUS clinical trial in patients with 8-14 monthly headache days. This patient group was assumed to have baseline characteristics of the

overall EM population. Responders had baseline mean MMDs of [redacted] compared to [redacted] for non-responders. The fremanezumab treatment effect compared to BSC was [redacted] MMDs

SECTION 5.2.12.3, p. 197

respective strategy level findings of the two appraisals, albeit that the comparison in this submission is simplified and reliant on OBA effectiveness equated to that of fremanezumab. The exception is that response at the 30% threshold level in CM was an outcome of the NMA and therefore drew on the findings of the OBA pivotal trials PREEMPT I and II. Table 69 compares the findings of the respective economic analyses and finds consistency across the ratio of costs and effects in each analysis. Since the time horizon of the TA260 cost-effectiveness analysis was just two years compared to ten, strategy cost and QALY totals are lower in the TA260 analysis, as would be expected in the context of the assumption around long-tern effectiveness of OBA in this analysis (sustained full effect of OBA prophylaxis and no positive discontinuation).

Table 69: Comparison of findings across appraisals, OBA vs. BSC

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus BSC (£/QALY)
BSC	[redacted]	[redacted]	-	-	**-**
OBA	[redacted]	[redacted]	[redacted]	[redacted]	**£6,777****
*BSC TA 260**	£1,895	1.20			
*OBA TA260**	£2,438	1.09	£543	0.09	**£6,083**

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; OBA, onabotulinum toxin A; QALY, quality adjusted life year; TA, technology appraisal.
Notes: *For a population whose condition failed to respond to at least three prior preventive medications.
Source: NICE TA260 FAD 3.16.

5.2.12.4 Model versus trial outcomes

Table 70 presents the result of a simple comparison of effect estimators used in the model with respective outcomes from the FOCUS trial. The weighted estimators, using response rates used in the model, are higher than published figures for both fremanezumab and BSC/placebo strategies.

Table 70: Effect size estimators versus FOCUS trial outcome

MMD reduction at response assessment	Model						FOCUS trial**	
	Non-responder		Responder		Weighted*			
	EM	CM	EM	CM	EM	CM	EM	CM
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC/Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BSC, best supportive care; CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days; OBA, onabotulinum toxin A. *Weights were ITC responder rates: CM: Frem =54.25%; BSC = 21.69%; EM: Frem = 59.56%, BSC = 10.17%. ** CS B 2.6.2 Table 17.

SECTION 8, p. 207

8 Overall conclusion

The ERG reviewed the clinical and cost-effectiveness evidence for fremanezumab in adults with chronic or episodic migraine. The company has provided evidence focused on a narrower population of people who have used three or more prior preventative therapies, using subgroup data mainly from the FOCUS trial. The evidence showed potentially substantial benefit for both fremanezumab monthly and quarterly regimens compared to placebo across all clinical outcomes. Fremanezumab also appeared to be highly tolerable with low discontinuation rates due to adverse events. The ERG is concerned about the differences in the types of drugs previously used by the FOCUS trial population which created some doubts about the positioning of fremanezumab as a fourth line therapy in the migraine preventative treatment pathway.

No direct evidence comparing fremanezumab and comparators was found. The ITC showed that fremanezumab demonstrated numerically superior clinical benefits compared to OBA in terms of the percentage of CM people who had a reduction of 50% or more in average MMD although, this was not statistically significant. However, the ITC conducted was restricted to monthly migraine days; other important clinical outcomes, for example, number of headache hours and acute medication use, were not considered.

As a consequence, only monthly migraine days provided clinical effectiveness inputs into the cost-effectiveness model. The company's base case assumptions and parameters support the conclusion that fremanezumab is cost effective versus best supportive care (BSC) in episodic migraine and versus BSC and OBA in chronic migraine. The ERG found that uncertainty is most profound in the base case assumptions relating to the positive stopping rule and response to BSC. For people experiencing chronic migraine the ERG conducted a substantial scenario analysis which incorporated a five year wane to baseline of fremanezumab effect for people who positively discontinued fremanezumab treatment. This was coupled with treatment re-initiation at the point when half of treatment effect is lost relative to baseline. Within the same scenario, the treatment effect of BSC was linearly waned to baseline for all responders. Combined, this had an impact on the company base chronic migraine ICER of [redacted]% (£13,836 per QALY gained) for the comparison of fremanezumab versus BSC ([redacted] including the ERG fixes), which provides some reassurance. The comparison of fremanezumab with OBA is deemed weak in the absence of reliable estimates of relative effectiveness. Assuming equivalent effect size and a lower probability of response to OBA, the approximated ICER is indicative of cost-effectiveness but

the ERG have not tested this under the assumption of bilateral waning and re-commencement. In the analysis of fremanezumab for episodic migraine, the ERG's ICER.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Fremanezumab for preventing migraine [ID1368]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm on Monday 23 September 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Thomas Jouini**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Teva UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Treatment stopping rules	
1. Is treatment stopped when people respond positively to treatment and migraine frequency decreases?	The expert clinical advice given to Teva was that patients that respond positively to treatment typically have their medication stopped, following appropriate review and in consultation with the patient. It was advised that oftentimes preventive treatment is used to cover periods of migraine exacerbation and that treatment is stopped once the patient no longer requires it. Thus, it is not accepted practice in the treatment of migraine for patients to remain on preventive treatment indefinitely. It is expected that a similar clinical practice would be adopted with anti-CGRP therapies, as has been highlighted by the European Headache Federation recommendations on the use of anti-CGRP therapies. These opinions are consistent with the submissions to this appraisal by the Association of British Neurologists and British Association for the Study of Headache, with both groups stating that the need for ongoing treatment should be assessed after one year. The SmPC for fremanezumab states that the need to continue treatment should be reviewed regularly based on an individual patient basis. Therefore, Teva believes that there is clear clinical opinion that treatment will be stopped (at an appropriate time) in patients who respond positively to treatment with fremanezumab.
2. Annually, what proportion of people on therapy will stop treatment because of a positive response?	There is currently no empirical evidence that can be used to show the proportion of patients who would stop treatment following a positive response. The consensus of clinical opinion gathered by Teva was that 20% was a reasonable estimate in the absence of any other data. Some headache specialists contacted expressed an opinion that this figure was a conservative estimate and lower than they would expect. The submission from the British Association for the Study of Headache also states that "*We anticipate that no more than two years treatment may be required in the vast majority*", implying expectation of a much higher annual stopping percentage. The value of 20%, used as a base case assumption by Teva, can be considered to be a conservative assumption in light of the expert opinion.
3. Will the treatment effect be maintained indefinitely after treatment is stopped? If not, how long would you expect treatment effect to	There are no data to demonstrate that treatment effect will not be maintained after discontinuation and, for any observed rises in migraine frequency, the time period in which this would occur is unclear. The natural history of migraine is such that the condition has periods where it is better or

continue following treatment stopping (after a positive response)?	worse than what is normal for an individual patient. This can be exacerbated by life events and natural changes in frequency of migraines over the course of a patient's life. Expert opinion expressed to Teva is that there is an expectation that treatment with fremanezumab should allow patients to gain control over their migraines (when they often feel out of control), and, once this control is established, there would be an expectation that these improvements would be maintained.
4. Will treatment be restarted if treatment effect diminishes after stopping treatment? If yes, by how much would treatment effect have to diminish before treatment is restarted?	Teva finds that it is plausible that treatment would be restarted in patients who have been positively stopped and experienced a subsequent deterioration in their condition. However, the modelling in these scenarios is based on assumptions, as no data are available on which patients will stop and then restart treatment, or the time period between these events. In addition, this does not consider the unpredictable nature of migraine and the impact of life events on this condition. However, the assumptions made by the ERG in consultation with clinical experts (that treatment effect may wane over a number of years after a positive stop and that people may restart treatment when the treatment effect has diminished) appear to be reasonable and plausible.
5. Will treatment be stopped if people do not respond to treatment? What proportion of people do you expect to stop treatment following a negative treatment response?	All clinical experts consulted by Teva have expressed a clear view that no physician would continue prescribing an ineffective treatment. It is therefore entirely rational and plausible that treatment would be stopped in patients who do not respond to treatment (with these definitions in line with those previously preferred by NICE, namely at least a 50% reduction in monthly migraine days for episodic migraine and at least a 30% reduction in monthly migraine days for chronic migraine). The proportion of patients that would stop under these criteria can be taken directly from the FOCUS clinical trial data, with the subgroup analysis on the three or more treatment failure group providing the directly relevant data for the population of interest in this appraisal.
• **Issue 2: The model time horizon**	
6. Will all the costs and benefits of fremanezumab be captured over 10 years?	A 10-year time horizon is sufficient to capture all meaningful differences in costs and QALYs between treatments. This horizon is supported by the fact that only a very small number of patients remain on treatment at the end of this time horizon. This position is also supported by the submission from the British Association for the Study of Headache, which states "*We anticipate that no more than two years treatment may be required in the vast majority.*" The ERG also agreed in their report that a 10-year horizon is a reasonable assumption.
7. Is a lifetime model time horizon more appropriate than 10 years?	Whilst migraine is a chronic condition, a 10-year time horizon is more appropriate than a lifetime horizon in this case for a number of reasons. As outlined in the response above, a 10-year time

	horizon is sufficient to capture all meaningful differences in costs and QALYs between treatments, with only a small number of patients remaining on treatment at the end of this time horizon. Extending the time horizon without including the impact of the natural history of migraine will introduce unnecessary uncertainty into the model. Whilst it would be highly desirable to include the natural history of migraine within the model, there is a lack of available evidence for modelling such scenarios and no previous economic models found within the literature reviewed by Teva have shown any migraine models that have included this factor within their analyses. Therefore, Teva agrees with the ERG that a 10-year horizon becomes the most appropriate compromise given the available data, as this provides sufficient time to capture all meaningful differences between treatments, but minimises the unnecessary uncertainty from a longer time horizon (associated with the inability to include modelling of the natural history of migraine within the model). To understand the implications of using a lifetime horizon, the ERG undertook some scenario analyses. One scenario analysis involved fremanezumab responders who discontinue treatment reverting to the baseline MMDs of non-responders after this discontinuation (ERG Scenario 9 within ERG model). Teva believes that this is not clinically justifiable, in that these patients have responded to treatment and would therefore be likely to maintain some treatment effect (based on the expert opinion received by Teva that fremanezumab should allow patients to gain control over their migraines during periods of high migraine activity). In addition, some patients are likely to respond to best supportive care once they discontinue fremanezumab treatment, with the potential that these previously responding patients (who have stopped treatment for reasons other than due to a lack of efficacy) may be more likely to respond to a subsequent line of preventive treatment (best supportive care in this case). Teva is of the opinion that ERG Scenario 10 (within ERG model, where consideration of responder status was included) is a more reasonable and justifiable approach to the issue than ERG Scenario 9; although other approaches should potentially be considered to find the most plausible and clinically justifiable approach.
• **Issue 3: Utility values used in the economic model**	
8. Is the Migraine-Specific Quality of Life Questionnaire (MSQoL) used to measure the quality of life of people with migraine in clinical	The HIT-6 and MIDAS tools are commonly used within clinical practice due to their simplicity and ease of administration, whilst giving sufficient information to allow for the clinical management of patients. In comparison to these two tools, the MSQoL is a more detailed measure that fully assesses the quality of life in patients with migraine (including an assessment of their emotional

practice? If not, what alternative measure(s) are used?	state, which is not included in either of the other measures). This measure has therefore been widely used in clinical trials and has demonstrated reliability, validity, and responsiveness in assessing the quality of life in patients with migraine. The MSQoL should, therefore, be considered as the most appropriate measure of overall quality of life in migraine. In addition, it is noted that the HIT-6 is not considered an appropriate measure in episodic migraine, due to its focus solely on the frequency of headache impacts which are much greater in chronic migraine. The applicability of the MSQoL as a measure of quality of life in migraine has been previously recognised by NICE within the onabotulinumtoxin A and the erenumab appraisals.
9. The NICE reference case and current position statement on the EQ-5D-5L, state a preference for the use of EQ-5D-3L for base-case analyses. Is the EQ-5D-3L insensitive to changes in quality of life caused by migraine attacks?	The EQ-5D (and particularly in the way administered during the clinical trials of fremanezumab) is not sensitive to changes in quality of life caused by migraine attacks. The EQ-5D data in FOCUS were collected during clinic visits within the clinical trial and measured the quality of life only on that day. Should a patient be experiencing a migraine attack, it is unlikely that they would have visited the clinic that day and, thus, the full impact of migraine on quality of life is missed through the EQ-5D measure. There was a lack of correlation found between EQ-5D results and the number of monthly migraine days in the FOCUS results. There is strong evidence to show that the number of monthly migraine days are strongly correlated with quality of life in migraine, and therefore this lack of correlation demonstrates that these EQ-5D data have not adequately captured the quality of life impact of migraine within the clinical trial. Therefore, as the full quality of life impacts are not captured within the EQ-5D, Teva believes that this is not an appropriate methodology for consideration in this appraisal.
10. Are utility values mapped from the MSQoL to EQ-5D-3L more appropriate than those mapped from EQ-5D-5L to EQ-5D-3L?	As explained in the responses to questions 8 & 9 (above), the MSQoL can be considered to be superior to the EQ-5D at measuring quality of life in patients with migraine. The EQ-5D is not sensitive to changes in quality of life caused by migraine attacks, and as EQ-5D data in FOCUS were collected during clinic visits, this measure assesses the quality of life only on that day. Should a patient be experiencing a migraine attack, it is unlikely that they would visit the clinic that day and, thus, the full impact of migraine on quality of life is missed through the EQ-5D measure. In contrast, the MSQoL is a detailed measure of quality of life in patients with migraine that has been widely used and has demonstrated reliability, validity, and responsiveness. The MSQoL includes a four-week recall period and thereby assesses the patient's overall quality of life, including the impact of migraine attacks and their quality of life during the interictal period. The publication (Gillard *et al*. 2012) which defined the algorithm for mapping utility values from MSQoL to EQ-5D included a second version of the algorithm which accounted for various patient

	baseline demographic characteristics. The baseline data available from the FOCUS trial were not collected in a suitable format to use with this second algorithm. Therefore, the mapping has been carried out using the simpler version of the algorithm and this represents the best available data for utilities. Teva note that this approach was also used by the company within the ongoing NICE appraisal of erenumab for the mapping of utilities, with similar justification to that presented here. Therefore, utility values mapped from the MSQoL are the most representative for the overall quality of life for people with migraine and the most appropriate to be used in this appraisal.
11. Are utility values estimated from the full FOCUS trial population (≥2 prior preventative therapies) generalisable to the population of interest (≥3 prior preventative therapies)?	Utility values from the whole FOCUS population were used in order to increase the robustness and reliability of the results, as the estimation of utility values was required for all health states (0-28 monthly migraine days) included within the model. The larger dataset utilising the full population of the FOCUS trial therefore provided a dataset of a sufficient size for a robust analysis to be conducted. In addition, the evidence from the FOCUS trial (as presented in the company submission) showed a good consistency between results for the overall trial population and the ≥3 prior preventative therapies population. This provides further reassurance that the utilities derived from the overall trial population are representative of the ≥3 prior preventative therapies population. The ERG was of a similar opinion and stated that this inconsistency in populations would not be expected to have a significant effect on the utility values.
12. Do preventative therapies result in quality of life improvements beyond those achieved by reducing the frequency of migraine days?	The values used for this appraisal are derived from the double-blind FOCUS trial data. The difference in quality of life is taken directly from these data and provides evidence that preventative therapies do result in quality of life improvements beyond those achieved by reducing the frequency of migraine days. The difference in utilities between on and off treatment patients reflects the additional benefits of migraine treatment not captured within MMD numbers (such as reducing nausea, reducing recovery time after a migraine attack, shortening a migraine attack). These benefits were recognised in the clinical expert opinion submitted to NICE as part of this appraisal.
Issue 4: The high-frequency episodic migraine subgroup	
13. Is the high-frequency episodic migraine (HFEM) subgroup recognised in clinical practice?	The opinion given to Teva by headache specialists is that high-frequency episodic migraine is a recognised and clinically distinct subgroup. This view was echoed in the expert advice given to the ERG and in the expert submissions to this appraisal. Teva finds that it is unfortunate that there has been no internationally agreed definition for this group of patients who endure a substantial impact on their quality of life (which can be seen to be similar to the impact seen in

	chronic migraine) and who currently have restricted treatment options and therefore a very high unmet need for treatment. High-frequency episodic migraine is a widely accepted clinically distinct subgroup by UK based headache experts and the lack of a clear definition should not, Teva believes, be used to exclude this group from consideration.
14. If yes, what definition of "high-frequency" is used in clinical practice?	There is no internationally agreed definition of high-frequency episodic migraine, and a variety of definitions have been used in clinical practice. The most widely used definitions are based on monthly headache days, with a frequency of 8-14 or 10-14 most commonly used as the definition of high-frequency episodic migraine. Teva believes that a definition of 8-14 best encompasses the entirety of this population, but accepts that it is a matter of clinical debate. Teva also notes that a cost-effectiveness analysis in the 10-14 monthly headache day group would be expected to show greater cost effectiveness (lower ICER values *versus* BSC) than was seen in the 8-14 monthly headache day group presented within the company submission (as these patients will have a higher disability and so a relatively greater impact from treatment).
Issue 5: Resource use and costs	
15. Will everyone be capable of self-administering fremanezumab? If not, what proportion do you expect will need their treatment administered for them?	It is reasonable to assume that not every patient will be capable of self-administering fremanezumab. It is expected, as this is a disease that most commonly affects working age people with few additional disabilities, that the proportion who cannot self-administer will be low. In addition, as fremanezumab is administered as a single injection once *per* month or as three injections once every three months, the headache specialists consulted by Teva have indicated that they would expect that many patients unable to self-administer will be able to have their treatment administered by a partner or carer. As fremanezumab requires only infrequent administration it is likely that this could be arranged by most patients, and is likely to be the preference for many patients unable to self-administer; as this would allow them to avoid the inconvenience of attending a clinic for administration of their medication and enable them to have it administered within their own home. The proportion of patients requiring their treatment to be administered was assumed to be 10%, as a conservative assumption within the modelled scenario included within our submission. As the clinical expert opinion gathered by NICE has reported that only around 5% of patients may not be able to self-administer, additional analyses have been conducted to investigate the impact of this scenario. Using a proportion of 5% of patients requiring treatment to be administered by a health professional (cost of 91p *per* cycle for monthly administration and 31p *per* cycle for

	quarterly administration) increased the ICER *versus* best supportive care in episodic migraine by 0.4% for monthly administration and by 0.1% for quarterly administration. In chronic migraine *versus* best supportive care, ICER values were raised by 0.3% for monthly administration and by 0.1% for quarterly administration; the increase when compared to onabotulinumtoxin A was 0.5% for monthly administration and by 0.2% for quarterly administration. Therefore, it can be seen that conservative assumptions around patients requiring treatment to be administered for them have negligible impacts on the cost-effectiveness.
Issue 6: Network meta-analysis for chronic migraine	
16. Is fremanezumab more effective at preventing migraines than onabotulinumtoxin A?	The NMA conducted by Teva is the best available evidence for a comparison between fremanezumab and onabotulinumtoxin A, in the absence of any head-to-head studies. Other approaches were considered, but Teva believes that the NMA undertaken for this appraisal is the strongest analysis that could be run given the available data. For example, a placebo-adjusted analysis has been suggested as a potential approach by NICE, but Teva note that the ERG have considered such an approach and did not consider it feasible based on the available data. The NMA that has been presented shows an additional benefit for fremanezumab over onabotulinumtoxin A across all endpoints analysed. It was not possible for further endpoints to be analysed within this NMA as no further data for onabotulinumtoxin A was available in the ≥3 prior preventative therapies population (the population of interest for this appraisal). Whilst Teva recognises that there are weaknesses in this NMA (as identified within the company submission), a number of these act in favour of onabotulinumtoxin A. The fact that onabotulinumtoxin A data was only available at 24 weeks rather than at 12 weeks (as utilised for fremanezumab) would make onabotulinumtoxin A appear more effective than had 12-week data been used; the published results of the PREEMPT trials show that the efficacy of onabotulinumtoxin A continued to increase between week 12 and week 24. For the comparison between "at least a 50% reduction in monthly migraine/headache days", a reduction in migraine days (fremanezumab) can be seen to be a more challenging endpoint than a reduction in monthly headache days (onabotulinumtoxin A), with migraine days representing a higher burden on patients. Therefore,

the comparisons within the NMA can be seen to be conservative and likely to underestimate the relative efficacy of fremanezumab in comparison to onabotulinumtoxin A.

Given these facts, it is unreasonable to assume that there is no additional treatment benefit for fremanezumab over onabotulinumtoxin A and to override the NMA results that provide the best available evidence for this comparison. It is also worthy of note that many other appraisals conducted by NICE have accepted differences in treatment effect based on NMA results which did not show a significant difference between treatments. What our NMA indicates is that the probability of having a response to fremanezumab was greater than that of the comparators, which may be of clinical significance and should be used to drive the cost-effectiveness comparisons. Additionally, as there is evidence that the relative treatment effect is underestimated (conservative) for fremanezumab in this comparison to onabotulinumtoxin A, this means that it is likely that the true relative treatment effect favours fremanezumab more than has been reported by the NMA.

Teva has also been made aware of some concerns from NICE around the inclusion of patients who have previously failed onabotulinumtoxin A in the NMA data. These data were taken from the FOCUS trial, which was an international trial that included patients who may have had previous exposure to onabotulinumtoxin A at various lines. The subgroup analyses of the overall FOCUS data showed that in patients with prior onabotulinumtoxin A exposure, fremanezumab had a similar efficacy compared to the overall trial results, which included prior and no prior onabotulinumtoxin A use (data within Appendix on recent Lancet publication). Similar results were also seen in the three or more preventive treatment failures group as well (see below). Therefore, the incorporation of data for patients with prior onabotulinumtoxin A use should have no major impact on the NMA results.

Prior onabotulinumtoxin A use: Summary of efficacy outcomes for patients with chronic migraine who have failed three or more classes of preventive therapy 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 50% 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]

No prior onabotulinumtoxin A use: Summary of efficacy outcomes for patients with chronic migraine who have failed three or more classes of preventive therapy 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 50% 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] Teva would also like to take this opportunity to reaffirm the strengths in the design of the FOCUS clinical trial and highlight important features of this trial. The FOCUS study is a strong, robust study with large patient numbers that provides the best available data for fremanezumab in the relevant population of interest (three or more prior preventive treatment class failures) for the treatment of both chronic and episodic migraine. Approximately half of the population of the overall FOCUS study were of the relevant population of interest in this appraisal (three or more preventive treatment failures). There is evidence to show that the chronic and episodic migraine subpopulations do have differences in their disease pathophysiology, burden, disability and quality of life, which is fully captured within the FOCUS clinical trial by the inclusion of both populations. For inclusion within FOCUS, documented evidence had to be provided for inadequate response to pharmacological classes of preventive treatment, which means that patients can be assumed to have had difficult to treat migraine. To be classed as having a migraine day, patients had to have a calendar day with at least four consecutive hours of a migraine with or without aura as *per* ICHD-3 diagnostic criteria (no more than one ICHD-3 migraine criterion missing), or a headache of any duration treated with migraine-specific acute medications (triptans or ergot compounds); meaning that the FOCUS definition aligns with the stringent ICHD-3β migraine diagnostic criteria. Teva also notes that there is an error in the technical report (page 8 and page 29) where it states "no evidence available for people for whom 4 or more preventative treatments have failed"; this is not correct. The FOCUS clinical trial includes patients who had failed two to four previous classes of preventive treatment, and, therefore, FOCUS data includes patients with four treatment class failures which may include (in some cases) more than four individual treatments.
17. Is it reasonable to assume monthly headache days will be equivalent to monthly migraine days?	Whilst monthly migraine days and monthly headache days cannot be seen to be directly equivalent, they are related measures. Teva agrees with the expert clinical opinion submitted to NICE as part of this appraisal that headache days are less impactful for patients, and, therefore, that migraine days can be considered more burdensome with a greater impact on quality of life. The comparison between monthly headache days (onabotulinumtoxin A) and monthly migraine days (fremanezumab) was only carried out for the analysis of "at least a 50% reduction in monthly migraine/headache days" (the analysis of "reduction in monthly migraine days" used data on monthly migraine days for both treatments). This analysis was conducted using a mix of

	definitions (as there are no other data available) and, thus, provides the best comparison possible for the at least a 50% reduction endpoint. It should also be noted that as headache days are a less stringent endpoint, at least a 50% reduction in monthly migraine days would be a more challenging endpoint to meet than at least a 50% reduction in monthly headache days. Therefore, this assumption is likely to underestimate the relative efficacy of fremanezumab in this comparison to onabotulinumtoxin A either directly through the comparison between these endpoints, or indirectly through the greater quality of life benefits that will be seen by patients for at least a 50% reduction in monthly migraine days compared to those seen with at least a 50% reduction in monthly headache days. It is reasonable to assume that monthly headache days are equivalent to monthly migraine days, if not slightly easier an outcome to achieve in terms of response.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Fremanezumab for preventing migraine [ID1368]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm on Monday 23 September 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Association of British Neurologists Headache and Pain advisory group**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**nil**

Questions for engagement

Issue 1: Treatment stopping rules	
1. Is treatment stopped when people respond positively to treatment and migraine frequency decreases?	Yes: this applies to all preventative treatment for patients with migraine; 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. A 'drug holiday' is recommended to confirm whether or not ongoing treatment is 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 6-12months before treatment break (Diener et al Lancet Neurol. 2007 Dec;6(12):1054-62)
2. Annually, what proportion of people on therapy will stop treatment because of a positive response?	The data on the sub-cohort analysis of those on ≥3 preventives which is the population in question to be able to determine this. Longer term 1year data of those on concomitant preventive treatment (no breakdown according to the number of preventives but with 35-38% having had prior topiramate and 30-32 % prior Botox) (data presented at International Headache Society Conference 2019 Poster: Goadsby et al IHC-DP-035, *available on request*) showed that 48-53% of patients had ≥50% reduction in average monthly migraine days according to differing monthly versus quarterly treatment paradigms. Data on number of patients that on stopping maintain treatment response for >6months will allow more robust prediction of annual cohort that stop treatment because of positive response. There is lack of published data on long term outcome for those that have stopped treatment following successful conversion from chronic to episodic migraine. The only data available is for

	patients receiving Botox treatment for chronic migraine from a UK headache centre presented in at the International Headache Congress in Dublin 2019. 1. 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). 2. 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 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, Topiramate).
3. Will the treatment effect be maintained indefinitely after treatment is stopped? If not, how long would you expect treatment effect to continue following treatment stopping (after a positive response)?	At present there is no data on whether treatment effect is maintained. In migraine there is the confounding issue of natural history influencing likely outcome e.g. any women will have an increase in their migraines at the perimenopausal period with a reduction in migraine frequency post-menopause. Data available is for patients with chronic migraine receiving Botox from a UK headache centre (as per Q.2 response). 1. 2 year data shows of 228 patients who came off treatment after an initial response, 61 relapsed (26.75%) and restarted Botox treatment. 112 patients out of 380 (29.7%) showed a sustained response and remained episodic (Ahmed et al, IHC-PO-418). 2. 5 year data shows that of 160 patients who came off treatment after an initial response, 18 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)

4. Will treatment be restarted if treatment effect diminishes after stopping treatment? If yes, by how much would treatment effect have to diminish before treatment is restarted?	Yes: we would suggest a lower threshold for restarting treatment as it is unreasonable to wait for reversion back to former state of maximal disability e.g. in chronic migraineurs that improved to episodic state would consider re-embarking on therapy when converting to high frequency episodic as the disability of this group is already evident.
5. Will treatment be stopped if people do not respond to treatment? What proportion of people do you expect to stop treatment following a negative treatment response?	Yes- provided given sufficient time course for cumulative benefits to be seen. We expect 100% to stop if negative treatment response unless confounding circumstance at time of evaluating treatment response eg. 'flu/ concussive head injury etc. where one would treat for a further quarter and then re-evaluate response.
Issue 2: The model time horizon	
6. Will all the costs and benefits of fremanezumab be captured over 10 years?	No but very difficult to model over life time.
7. Is a lifetime model time horizon more appropriate than 10 years?	Yes but this will be difficult given the dynamic course.
Issue 3: Utility values used in the economic model	
8. Is the Migraine-Specific Quality of Life Questionnaire (MSQoL) used to measure the quality of life of people with migraine in clinical practice? If not, what alternative measure(s) are used?	In clinical practice HIT6 and MIDAS is used in preference to MSQoL. Recent paper looking at utility of patient reported outcome measures (Haywoood et al. Cephalagia.2018; 38(7):1374-1386) looking at patient reported outcome measures for headaches, found evidence of reliability and validity for HIT6 and the MSQoL.
9. The NICE reference case and current position statement on the EQ-5D-5L, state a preference for the use of EQ-5D-3L for base-case analyses.	Uncertain: not as yet used in routine practise.

Is the EQ-5D-3L insensitive to changes in quality of life caused by migraine attacks?	
10. Are utility values mapped from the MSQoL to EQ-5D-3L more appropriate than those mapped from EQ-5D-5L to EQ-5D-3L?	Not necessarily
11. Are utility values estimated from the full FOCUS trial population (≥2 prior preventative therapies) generalisable to the population of interest (≥3 prior preventative therapies)?	It is generalizable provided awareness that the full FOCUS population is likely to represent the better utility values as about 50% of the population have tried only 2 treatments: those who have tried more preventative treatments may have been seeking a greater level of medical input which may reflect on the functional impact given that this is strongly related to health utilisation.
12. Do preventative therapies result in quality of life improvements beyond those achieved by reducing the frequency of migraine days?	Yes. Significant functional impact from reducing headache 'load', i.e. measure of both severity and duration of migraine, which is not captured using standard migraine/ headache days. It also does not recognise the most bothersome symptom which is not always pain (eg nausea/emesis, cognitive dysfunction) and arguably will have a greater impact on QoL.
Issue 4: The high-frequency episodic migraine subgroup	
13. Is the high-frequency episodic migraine (HFEM) subgroup recognised in clinical practice?	Yes and often challenging to treat.
14. If yes, what definition of "high-frequency" is used in clinical practice?	>10 – 14 days per month.
Issue 5: Resource use and costs	
15. Will everyone be capable of self-administering fremanezumab? If not, what proportion do you expect will need their treatment administered for them?	5-10% that may need Rx administered for them due to eg. needle phobia/ elderly.
Issue 6: Network meta-analysis for chronic migraine	

16. Is fremanezumab more effective at preventing migraines than onabotulinumtoxin A?	Unknown as no head to head. Information from a cohort sub-analysis of a 1yr extension study on the use of Fremanezumab, presented as poster, Cowan et al IHC 2019 (*available on request*), of the n253 patients, n28 had been treated with Botox previously with 23 out of 28 preferring fremanezumab with preference given by patients being that of greater efficacy (with over 70% reporting reduced attack frequency and intensity).
17. Is it reasonable to assume monthly headache days will be equivalent to monthly migraine days?	No: this is a matter of severity - non-migraine headache days will be of a lower severity/impact than migraine days; impact of treatment may be more apparent on the migraine days rather than headache days. Both parameters should be used to assess response rate as reduction in severity may be more sensitive in identifying a response than number of headache days

NICE National Institute for Health and Care Excellence

Technical engagement response form

Fremanezumab for preventing migraine [ID1368]

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	[redacted]
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.	**Nil**

Questions for engagement

Issue 1: Treatment stopping rules	
1. Is treatment stopped when people respond positively to treatment and migraine frequency decreases?	In general the answer is YES. However, it depends on whether patient has episodic or chronic migraine. Patients with episodic migraine are usually given treatment for a period of 6-12 months following achievement of 50% reduction in headache frequency or severity. Treatment is gradually weaned off and those where headache frequency start to rise again, a further 6-12 months of treatment is advised. Those with chronic migraine are treated until they are converted to low frequency episodic migraines i.e. 8 days or less in a month. As the condition is very disabling, a minimum one year of treatment is usually advised by the headache experts before weaning off the treatment. 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 (Diener et al Lancet Neurol. 2007 Dec;6(12):1054-62)
2. Annually, what proportion of people on therapy will stop treatment because of a positive response?	There is lack of long term published data on patients who failed at least three preventatives. The data from UK headache centre on Botox presented in the recent International Headache Congress indicates that 60% of patients were able to stop treatment at two years (228 out of 380) and 76% of patients were off treatment at 5 years (142/186) (Ahmed et al, IHC-PO-418 and 419). Data on Fremaanezumab in episodic and chronic migraine treated for a year showed 48-53% of patients had 50% or more reduction in the monthly migraine days. (Goadsby et al, IHC-PO-035). A follow up of these patients will provide data on how many will remain in remission following discontinuation of treatment.

	It is anticipated that very few patients in this group will require this drug as most patients respond well to the first line treatments of tricyclic antidepressants, beta-blockers, topiramate and candesartan.
3. Will the treatment effect be maintained indefinitely after treatment is stopped? If not, how long would you expect treatment effect to continue following treatment stopping (after a positive response)?	There is lack of published data on long term outcome for those that have stopped treatment following successful conversion from chronic to episodic migraine. The only data available is for Botox from a UK headache centre presented in the recent International Headache Congress in Dublin. Around 60% of patients (228/380) were able to stop treatment at two years. 61 of those who stopped treatment (N=228) relapsed (26.75%). 112 out of 380 (29.7%) showed a sustained response and remained episodic (Ahmed et al, IHC-PO-418). At five years 142/186 were able to stop treatment and 44 were still on treatment that included 18 that had relapsed following successful withdrawal. 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)
4. Will treatment be restarted if treatment effect diminishes after stopping treatment? If yes, by how much would treatment effect have to diminish before treatment is restarted?	Yes. Treatment is re-commenced and continued for another year. Experts recommend commencing treatment when patient are in high frequency episodic migraine as this group of patient have the same disability to those with chronic migraine.
5. Will treatment be stopped if people do not respond to treatment? What proportion of people do you expect to stop treatment following a negative treatment response?	Yes. It is suggested that the treatment is given for three months and evaluated for a response. Those with less than 30% response would be stopped treatment. The earlier published data on various CGRP MAB have shown a response rate of around 50% so half of the patient would be stopped treatment.
Issue 2: The model time horizon	
6. Will all the costs and benefits of fremanezumab be captured over 10 years?	For this to occur, studies would need to be set up that would capture both clinical efficacy and the cost-saving. Some data is captured through Phase IV. The industry will have to gear such study as it will be very difficult to set this up within the NHS (High cost).

7. Is a lifetime model time horizon more appropriate than 10 years?	Ideally yes but again, extremely difficult. Five years is a reasonable horizon. Given the natural history of migraine lifetime is too long- most get better with time, and frequency does wax and wane. Serrano D, Lipton RB, Scher AI, Reed ML, Stewart WBF, Adams AM, et al. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. J Headache Pain. 2017;18(1):101
Issue 3: Utility values used in the economic model	
8. Is the Migraine-Specific Quality of Life Questionnaire (MSQoL) used to measure the quality of life of people with migraine in clinical practice? If not, what alternative measure(s) are used?	MS QoL is a validated tool and has recently been reported in patient reported outcome measure (Haywood et al, Cephalalgia 2018;38(7):1374-1386. HIT-6, MIDAS and EQ-5D are other measures used in clinical practice.
9. The NICE reference case and current position statement on the EQ-5D-5L, state a preference for the use of EQ-5D-3L for base-case analyses. Is the EQ-5D-3L insensitive to changes in quality of life caused by migraine attacks?	We don't think although in clinical practice this is used less than other validated tools.
10. Are utility values mapped from the MSQoL to EQ-5D-3L more appropriate than those mapped from EQ-5D-5L to EQ-5D-3L?	Not necessarily.
11. Are utility values estimated from the full FOCUS trial population (≥2 prior preventative therapies) generalisable to the population of interest (≥3 prior preventative therapies)?	Those who tried 3 or more preventive treatments are more refractory to those with failure of 2 treatments, hence they are not comparable and utility value for this group will be different.

12. Do preventative therapies result in quality of life improvements beyond those achieved by reducing the frequency of migraine days?	Clinicians often measure response through Headache 'load' that takes into account the frequency and severity of headache over a period of time. Response to treatment includes improvement in the quality of life measured through validated tools like HIT-6
Issue 4: The high-frequency episodic migraine subgroup	
13. Is the high-frequency episodic migraine (HFEM) subgroup recognised in clinical practice?	Yes and it is strongly believed by the clinicians to have similar disability to those with chronic migraine.
14. If yes, what definition of "high-frequency" is used in clinical practice?	Some clinicians believe 10-14 while others quote figures of 8-14.
Issue 5: Resource use and costs	
15. Will everyone be capable of self-administering fremanezumab? If not, what proportion do you expect will need their treatment administered for them?	We feel the treatment will be self-administered by vast majority (> 95%)
Issue 6: Network meta-analysis for chronic migraine	
16. Is fremanezumab more effective at preventing migraines than onabotulinumtoxin A?	There is no head to head study comparing fremanezumab and Botox. Patients may prefer Fremanezumab than Botox because of number of injections and ability to self-administer (Fremanezumab). This was noticed by Cowan et al in their recent study on Fremanezumab one year extension study (IHC-PO-403,404)

17. Is it reasonable to assume monthly headache days will be equivalent to monthly migraine days?	No – Headache days include any day with headache that could even be mild. Migraine days are moderate to severe headache days that has features of migraine i.e., nausea, vomiting, sensitivity to light and sound and aggravation with physical activity.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS England**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NA**

Questions for engagement

Issue 1: Treatment stopping rules	
1. Is treatment stopped when people respond positively to treatment and migraine frequency decreases?	
2. Annually, what proportion of people on therapy will stop treatment because of a positive response?	
3. Will the treatment effect be maintained indefinitely after treatment is stopped? If not, how long would you expect treatment effect to continue following treatment stopping (after a positive response)?	
4. Will treatment be restarted if treatment effect diminishes after stopping treatment? If yes, by how much would treatment effect have to diminish before treatment is restarted?	
5. Will treatment be stopped if people do not respond to treatment? What proportion of people do you expect to stop treatment following a negative treatment response?	Engagement with clinicians when drafting NHS England BIT suggested that agreement of and adherence to stopping rules is important; to ensure treatment is used appropriately and to help manage capacity issues. They advised that patients should be reviewed after a minimum of 3 months from starting treatment, with treatment stopped if deemed a non-responder
Issue 2: The model time horizon	
6. Will all the costs and benefits of fremanezumab be captured over 10 years?	

7. Is a lifetime model time horizon more appropriate than 10 years?	There should be consistency between the model time horizon used for erenumab (ID1188) and fremanezumab. As a lifetime model time horizon was used in ID1188, it would seem reasonable to use for fremanezumab.
Issue 3: Utility values used in the economic model	
8. Is the Migraine-Specific Quality of Life Questionnaire (MSQoL) used to measure the quality of life of people with migraine in clinical practice? If not, what alternative measure(s) are used?	It would seem reasonable to expect a consistent approach to determine utility values across the appraisals for treatments used in the prophylaxis of migraine.
9. The NICE reference case and current position statement on the EQ-5D-5L, state a preference for the use of EQ-5D-3L for base-case analyses. Is the EQ-5D-3L insensitive to changes in quality of life caused by migraine attacks?	
10. Are utility values mapped from the MSQoL to EQ-5D-3L more appropriate than those mapped from EQ-5D-5L to EQ-5D-3L?	
11. Are utility values estimated from the full FOCUS trial population (≥2 prior preventative therapies) generalisable to the population of interest (≥3 prior preventative therapies)?	
12. Do preventative therapies result in quality of life improvements beyond those achieved by reducing the frequency of migraine days?	
Issue 4: The high-frequency episodic migraine subgroup	

13. Is the high-frequency episodic migraine (HFEM) subgroup recognised in clinical practice?	When discussed with clinicians – they referred to high frequency episodic migraine, suggesting this was 10 monthly migraine days or more
14. If yes, what definition of "high-frequency" is used in clinical practice?	When discussed with clinicians – they referred to high frequency episodic migraine, suggesting this was 10 monthly migraine days or more
Issue 5: Resource use and costs	
15. Will everyone be capable of self-administering fremanezumab? If not, what proportion do you expect will need their treatment administered for them?	Based on other injectable products suitable for self-administration, it is reasonable to estimate that some patients will not be willing/able to self-administer treatment. I have not been able to find evidence for expected proportion of people who would require the treatment to be administered. Has NICE applied a % for patients unable to self-administer sc products for other agents? If so, it may be reasonable to apply the same %.
Issue 6: Network meta-analysis for chronic migraine	
16. Is fremanezumab more effective at preventing migraines than onabotulinumtoxin A?	
17. Is it reasonable to assume monthly headache days will be equivalent to monthly migraine days?	

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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

Questions for engagement

Issue 1: Treatment stopping rules

1. Is treatment stopped when people respond positively to treatment and migraine frequency decreases?	▪ In clinical practice, among chronic migraine (CM) patients who have failed 3 or more oral preventive treatments, a positive stopping rule is applied, as recommended by NICE TA260. Treatment is stopped in people whose condition has changed from chronic to episodic migraine for 3 consecutive months; defined as fewer than 15 headache days per month, of which at least 8 days are with migraine. ▪ Recently published consensus statement from the European Headache Federation recommends that treatment should be stopped in patients with a reduction to less than 10 headache days per month for 3 months.
2. Annually, what proportion of people on therapy will stop treatment because of a positive response?	▪ The proportion of patients who will stop treatment annually in clinical practice, as a result of the positive stopping rule is unknown for fremanezumab.
3. Will the treatment effect be maintained indefinitely after treatment is stopped? If not, how long would you expect treatment effect to continue following treatment stopping (after a positive response)?	▪ NICE TA 10302 in migraine concluded that the "treatment effect [of a migraine therapy] is unlikely to be maintained indefinitely therefore a constant treatment effect is implausible". ▪ The assumption in TEVA's economic model that the treatment benefit of fremanezumab in patients who discontinue (because of the positive stopping rule) is maintained indefinitely at a zero cost is highly optimistic and cannot be substantiated. This assumption does not reflect clinical practice and will lead to underestimation of ICERs. ▪ Evidence from the galcanezumab trials EVOLVE 1 and EVOLVE 2 in which galcanezumab was administered for 6 months and then discontinued shows a reduction in efficacy after discontinuation. Patients were followed up for 4 months after discontinuation: ▪ Efficacy results for EVOLVE 1: ▪ Galcanezumab 120 mg: decrease of efficacy after discontinuation was seen from 5.2 reduction of monthly migraine days (MMD) versus baseline at month 6 to 4.1 at month 10 ▪ Galcanezumab 240 mg: decrease of efficacy after discontinuation, from 5.3 reduction of MMD versus baseline at month 6 to 3.8 at month 10

	▪ Placebo: Efficacy was stable, with respectively 3.4 and 3.3 MMD reduction of MMD versus baseline at months 6 and 10 ▪ Similar efficacy results were found for EVOLVE 2 ▪ Unlike fremanezumab, the long-term efficacy and tolerability of onabotulinumtoxinA in CM has been demonstrated in both clinical trials as well as large real-world studies across different clinical settings: ▪ A prospective analysis of a total of over 650 CM patients treated by the HULL Migraine Clinic going back to 2010 and providing data for patients in some cases treated for as long as two years (n=508) and as long as five years (n=211). 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. ▪ Two-year outcomes from the REPOSE study involving over 600 patients in seven European countries, including 94 from the UK ▪ 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 CM from 7 private neurology practices in Australia ▪ In addition to PREEMPT 1 and 2 a Phase IV clinical trial (COMPEL) further demonstrates the long-term effectiveness of onabotulinumtoxinA in patients with CM, including those with/without concomitant oral preventive treatment and acute medication overuse at baseline (108 week follow-up of over 700 patients in the USA, Australia and Korea)
4. Will treatment be restarted if treatment effect diminishes after stopping treatment? If yes, by how much would treatment effect have to diminish before treatment is restarted?	▪ The assumption that the patients who stop treatment due to positive response would never recommence the treatment when the symptoms return is not substantiated by evidence.

	Evidence suggests that there is loss of efficacy after treatment discontinuation and subsequently, there may be a need for patients to re-initiate treatment. ▪ Andreou et al reported a total of 20% of patients in whom onabotulinumtoxinA treatment was discontinued due to a positive stopping rule relapsed to a chronic pattern after 4 months and hence treatment with onabotulinumtoxinA was resumed. ▪ TEVA's model does not consider a scenario in which a proportion of patients restart their treatment. This overestimates the benefits and underestimates the cost of fremanezumab, which leads to underestimation of ICERs.
5. Will treatment be stopped if people do not respond to treatment? What proportion of people do you expect to stop treatment following a negative treatment response?	▪ The following responder rates are considered clinically relevant for the treatment of migraine in clinical practice (TA10302 and TA260): ▪ CM: ≥30% reductions of headache frequency from baseline to 12 weeks ▪ EM: ≥50% reductions of headache frequency from baseline to 12 weeks ▪ As a result, in clinical practice a negative stopping rule is applied where treatment is discontinued in patients - with EM or CM - who do not achieve the above responder rates. ▪ The proportion of people expected to stop treatment with fremanezumab following a negative treatment response in clinical practice is unknown.

▪ Issue 2: The model time horizon	
6. Will all the costs and benefits of fremanezumab be captured over 10 years?	▪ The model does not fully capture all costs associated with the administration of fremanezumab. The assumption in TEVA's economic model that the treatment benefit of fremanezumab in patients who discontinue (because of the positive stopping rule) is maintained indefinitely at a zero cost is unrealistic and overly optimistic. While there may be some basis to extrapolate the benefit for a specified duration of time, assuming that it is maintained indefinitely does not reflect clinical practice and it may lead to underestimation of ICERs. ▪ The uncertainty that originates from the short-term fremanezumab trials and from the assumptions around the positive and negative stopping rules, further contribute to the uncertainty of the cost-effectiveness results.
7. Is a lifetime model time horizon more appropriate than 10 years?	▪ A lifetime model time horizon is not more appropriate than a 10-year model given the degree of uncertainty with respect to several key model assumptions. There is significant uncertainty in terms of treatment discontinuation and the corresponding impact on clinical effectiveness in a lifetime model. A shorter time horizon would result in more robust estimates, discriminating more accurately between treatments based upon observed clinical evidence and allowing for informed decision-making.
▪ Issue 3: Utility values used in the economic model	
8. Is the Migraine-Specific Quality of Life Questionnaire (MSQoL) used to measure the quality of life of people with migraine in clinical practice? If not, what alternative measure(s) are used?	▪ The MSQv2.1 is a reliable and valid migraine specific health-related quality of life measure and has been used extensively in clinical trials of migraine preventive treatments. ▪ The International Headache Society Clinical Trials Subcommittee Guidelines recommend as useful efficacy endpoints in migraine both the HIT-6 test and the MIDAS questionnaire.

9. The NICE reference case and current position statement on the EQ-5D-5L, state a preference for the use of EQ-5D-3L for base-case analyses. Is the EQ-5D-3L insensitive to changes in quality of life caused by migraine attacks?	▪ The EQ-5D data is collected during clinic visits and therefore, does not capture the full impact of migraine attacks on a patient's health-related quality of life. While there are recognized challenges with the valuation set for the EQ-5D-5L, as noted in the position statement, the EQ5D-5L given the psychometric properties can be expected to be a more sensitive measure than the EQ5D-3L.
10. Are utility values mapped from the MSQoL to EQ-5D-3L more appropriate than those mapped from EQ-5D-5L to EQ-5D-3L?	▪ The MSQv2.1 is a reliable and valid migraine specific health-related quality of life measure and has been used extensively in clinical trials of migraine preventive treatments. ▪ Mapping has limitations and direct elicitation using a sensitive utility measure is preferable.
11. Are utility values estimated from the full FOCUS trial population (≥2 prior preventative therapies) generalisable to the population of interest (≥3 prior preventative therapies)?	▪ There may be an additional uncertainty associated with applying utility values from a different trial subpopulation; however, the exact impact on the model results remains unknown.
12. Do preventative therapies result in quality of life improvements beyond those achieved by reducing the frequency of migraine days?	▪ Clinically meaningful improvements from baseline in quality of life (QoL) and disability were experienced after onabotulinumtoxinA treatment for CM in both clinical trials as well as large real-world studies across different clinical settings: ▪ In PREEMPT 1 and 2, onabotulinumtoxinA significantly reduced headache severity (as measured by improved HIT-6 scores at all time points) compared with placebo. ▪ In the REPOSE study, MSQ scores showed significant reductions from baseline in Role Function-Restrictive domain at each follow-up session. ▪ An interim analysis of the PREDICT study showed that MSQ scores significantly increased post-treatment compared with baseline, indicating improved QoL, across all role function domains.

	▪ In Santoro et al. 2017 (Italy) onabotulinumtoxinA effectively reduced headache-related disability and improved patients' quality of life. ▪ In the Sant Andrea Hospital study, onabotulinumtoxinA reduced the mean HIT-6 score during all the treatment period up to 2 years. ▪ In the Australian RWE study, reductions in the adverse impact of headaches, reflected in significant mean (SD) changes in HIT-6 scores of –11.7 (9.8) after 2 treatment cycles (n=80; p<0.001) and –11.8 (12.2) at final follow-up (n=68; p<0.001), respectively, represent a clinically meaningful reduction in HIT-6 scores. ▪ In a retrospective study of 94 patients in Taiwan onabotulinumtoxinA significantly improved MIDAS score from 60 at baseline to 30 at 12 weeks. ▪ OnabotulinumtoxinA treatment for CM reduced symptoms of comorbid conditions such as depression and anxiety: ▪ Results from the COMPEL study show that approximately 80% of patients treated with onabotulinumtoxinA experience a clinically meaningful improvement in comorbid depression and anxiety. ▪ In the 529 COMPEL patients with mild or worse depressive symptoms at baseline (PHQ-9 ≥5), the mean (SD) PHQ-9 scores were reduced from baseline at all timepoints measured (up to week 108). ▪ Among 175 patients with clinically significant baseline anxiety (GAD ≥10), the mean (SD) GAD-7 scores were reduced from baseline at all timepoints (up to Week 108). At Week 12, 69.3% had clinically meaningful improvements in anxiety symptoms, increasing to 78.0% at Week 48 and 81.5% at Week 108. ▪ OnabotulinumtoxinA treatment for CM is associated with reductions in the impact of headache on daily activities and work productivity: ▪ Analysis of secondary endpoints in the FORWARD study showed mean baseline scores on the WPAI-SHP were 4.8 in the onabotulinumtoxinA group and 5.1 in the topiramate group. At Week 12, the scores had improved to 3.3 and 4.4 respectively, and at Week 36, to 3.5 and 4.4, respectively, a significant and clinically meaningful difference.

▪ **Issue 4: The high-frequency episodic migraine subgroup**	
13. Is the high-frequency episodic migraine (HFEM) subgroup recognised in clinical practice?	▪ Unlike CM, there is no standardised definition of HFEM in the International Classification of Headache Disorders (ICHD-3). Epidemiology studies show that CM may be more difficult to treat, associated with more comorbidities, with more severe and longer lasting migraine headaches, and great functional impact than EM. Different studies have used frequencies from 8 to 14 and 10 to 14 migraine headache days per month to define HFEM: Katsarava et al. 2011; Maleki et al. 2012; Torres-Ferrús et al. 2017.
14. If yes, what definition of "high-frequency" is used in clinical practice?	▪ There is no agreed definition in clinical guidelines. In the published literature and clinical trials, HFEM has been defined as 8-14, 9-14 and also 10-14 headache days per month for at least 3 months. ▪ In Scotland, the Scottish Intercollegiate Guidelines Network (SIGN) guidelines (Feb 2018) define HFEM as between 10-14 monthly migraine days.
Issue 5: Resource use and costs	
15. Will everyone be capable of self-administering fremanezumab? If not, what proportion do you expect will need their treatment administered for them?	▪ The assumption that all patients (100%) will self-administer fremanezumab 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). ▪ It is more realistic to expect that i) no patient would be expected to self-administer right from the start, ii) a number of patients will need their treatment to be administered for them and iii) patients to be monitored by specialists in order to ensure compliance with monthly fremanezumab and to evaluate response to the treatment. ▪ EHS consensus statement recommends an evaluation of response to onabotulinumtoxinA treatment after each treatment cycle. TEVA's economic model should also account for similar hospital visits to evaluate the response to monthly fremanezumab (at similar intervals recommended by EHS for onabotulinumtoxinA). TA10302 also recommends regular evaluation of monthly erenumab treatment.

	▪ In summary, TEVA's assumption of a zero-cost administration of fremanezumab - as applied in the economic model - is highly optimistic and does not reflect the actual healthcare resources needed in "real-life" to administer fremanezumab to all the eligible patients.
Issue 6: Network meta-analysis for chronic migraine	
16. Is fremanezumab more effective at preventing migraines than onabotulinumtoxinA?	▪ There is no robust evidence that fremanezumab is more clinically effective than onabotulinumtoxinA in people with CM. In the Pooled Analyses of the 56-Week PREEMPT Clinical Program, 48% of patients had ≥50% reduction in mean MMDs from baseline to week 24 (quarterly onabotulinumtoxinA). In FOCUS study, 34% of patients had ≥50% reduction in mean MMDs from baseline to week 12 (either with quarterly or monthly fremanezumab) ▪ In the absence of comparative RCT data, the relative treatment effect of the two therapies - in patients who have failed three or more prior migraine preventive therapies - has to be estimated via a network meta-analysis (NMA). However, the lack of quality evidence in the NMA produced by TEVA for CM accounting for differences in trial populations, assessment timepoints and outcomes lead to high uncertainties, which prevent a robust indirect comparison of treatment effects between fremanezumab and onabotulinumtoxinA. ▪ Also, unlike fremanezumab there is long-term evidence to support the value of onabotulinumtoxinA in CM. In clinical trials and observational studies, the clinical efficacy of onabotulinumtoxinA is sustained or improved in patients over an extended period of treatment, as well as onabotulinumtoxinA 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. ▪ A prospective analysis of a total of over 650 CM patients treated by the HULL Migraine Clinic going back to 2010 and providing data for patients in some cases treated for as long as two years (n=508) and as long as five years (n=211). ▪ Two-year data from the prospective observational REPOSE study, involving over 600 patients in seven European countries, including 94 from the UK.

	▪ Two-year data from the Phase IV long-term open label prospective COMPEL study, involving over 700 patients in the USA, Australia and Korea. ▪ Two-year data from a prospective observational study of 275 patients treated at the Sant Andrea Hospital in Italy between 2010 and 2015.
17. Is it reasonable to assume monthly headache days will be equivalent to monthly migraine days?	▪ Headache days and monthly migraine days are distinct endpoints that they are clearly defined in clinical trials for preventive treatment in migraine. Depending on the patient sample and frequency of monthly headache days, these endpoints may or may not be equivalent.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Fremanezumab for preventing migraine [ID1368]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm on Monday 23 September 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Treatment stopping rules	
1. Is treatment stopped when people respond positively to treatment and migraine frequency decreases?	In the appraisal of erenumab for preventing migraine (ID1188, Appraisal Consultation Document [ACD], pg 13 and Final Appraisal Document (FAD), pg 17-18), the Committee concluded that a positive discontinuation scenario in which patients who are responding positively to therapy stop their treatment was not appropriate for consideration. The committee considered that there was no evidence on either the proportion of patients that would stop treatment or the continuation of treatment benefit once treatment had stopped. Given that Teva has not presented evidence that demonstrates maintenance of treatment effect upon positive discontinuation (Teva submission Section B.3.6.2: "limited data are available for patients once they have discontinued treatment"), the same considerations should apply for this appraisal of fremanezumab in order to ensure consistency of decision-making. Therefore, the Committee should conclude that modelling of positive discontinuation similarly cannot be considered in the appraisal of fremanezumab.
2. Annually, what proportion of people on therapy will stop treatment because of a positive response?	Please see response to Question 1.
3. Will the treatment effect be maintained indefinitely after treatment is stopped? If not, how long would you expect treatment effect to continue following treatment stopping (after a positive response)?	Please see response to Question 1. In addition, we note from Tables 1a-1c in the Technical Engagement papers that a "preferred assumption" of the NICE Technical Team is "without treatment waning". This is in the context of the NICE Technical Team also preferring an assumption of "no positive stopping rule" (which Novartis agrees with). Therefore, this presumably relates to the Technical Team's preferences regarding the modelling of maintenance of treatment effect over time in general for patients who remain on treatment. The long-term data for fremanezumab is limited to 15 months.
4. Will treatment be restarted if treatment effect diminishes after stopping treatment? If yes, by	Please see response to Question 1.

how much would treatment effect have to diminish before treatment is restarted?	
5. Will treatment be stopped if people do not respond to treatment? What proportion of people do you expect to stop treatment following a negative treatment response?	Based on current clinical practice for migraine it is anticipated that treatment will be stopped in patients who do not respond to treatment. The proportion of people expected to stop treatment following a negative treatment response will be dependent on the data on response rates from the Teva clinical trials. This is consistent with the wording of the marketing authorisation for fremanezumab, which states "The treatment benefit should be assessed within 3 months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter."
Issue 2: The model time horizon	
6. Will all the costs and benefits of fremanezumab be captured over 10 years?	The erenumab ACD (pg 12) and FAD (pg13) note that the Committee preferred a lifetime time horizon over the base case 10 year time horizon selected by the manufacturer (Novartis). This was because the Committee felt that a lifetime time horizon would fully capture the costs and benefits associated with treatment. Given that the justifications for a 10 year time horizon in the fremanezumab submission are not materially different to those in the erenumab appraisal, a consistent approach should be used between the two appraisals.
7. Is a lifetime model time horizon more appropriate than 10 years?	Please see response to Question 6.
Issue 3: Utility values used in the economic model	
8. Is the Migraine-Specific Quality of Life Questionnaire (MSQoL) used to measure the quality of life of people with migraine in clinical practice? If not, what alternative measure(s) are used?	No comment.

9. The NICE reference case and current position statement on the EQ-5D-5L, state a preference for the use of EQ-5D-3L for base-case analyses. Is the EQ-5D-3L insensitive to changes in quality of life caused by migraine attacks?	No comment.
10. Are utility values mapped from the MSQoL to EQ-5D-3L more appropriate than those mapped from EQ-5D-5L to EQ-5D-3L?	No comment.
11. Are utility values estimated from the full FOCUS trial population (≥2 prior preventative therapies) generalisable to the population of interest (≥3 prior preventative therapies)?	No comment.
12. Do preventative therapies result in quality of life improvements beyond those achieved by reducing the frequency of migraine days?	No comment.
Issue 4: The high-frequency episodic migraine subgroup	
13. Is the high-frequency episodic migraine (HFEM) subgroup recognised in clinical practice?	In the appraisal of erenumab for preventing migraine the Committee did not view "high-frequency episodic migraine" (HFEM) as a clinically defined population and did not consider the cost-effectiveness results for this subgroup in the ACD (pg10) or FAD (pg 8-9). A consistent approach to consideration of the HFEM subgroup should be used between the two appraisals (erenumab and fremanezumab).
14. If yes, what definition of "high-frequency" is used in clinical practice?	Please see response to Question 13.
Issue 5: Resource use and costs	
15. Will everyone be capable of self-administering fremanezumab? If not, what proportion do you	Administration of fremanezumab on a quarterly basis will involve a patient administering 3 pre-filled syringes to achieve a 675 mg dose (each pre-filled syringe contains 225 mg), which may be difficult for some patients. Additionally, where multiple injections are needed the Summary of

expect will need their treatment administered for them?	Product Characteristics (SmPC) for fremanezumab recommends that injection sites should be alternated; again, this may be difficult for some patients. The device is a pre-filled syringe which means that the needle is visible to patients. This could present difficulties with administration for patients with needle phobia. Furthermore, the syringe is made from glass which means this will need to be handled by patients with care. In the fremanezumab clinical trials treatment was administered in the clinical setting; therefore, the clinical trials do not demonstrate that patients can competently and consistently administer fremanezumab themselves. Fremanezumab may be kept in the original carton at room temperature up to 25°C (77°F) for a maximum of 24 hours. After removal from the refrigerator, fremanezumab must be used within 24 hours or discarded. Therefore, patients need to have appropriate storage arrangements and be sufficiently organised with regards to timing of administration on removal from refrigeration.
Issue 6: Network meta-analysis for chronic migraine	
16. Is fremanezumab more effective at preventing migraines than onabotulinumtoxin A?	In the appraisal of erenumab (ACD, pg 10 and FAD, pg 11), the indirect treatment comparison (ITC) demonstrates an odds ratio that favours erenumab over onabotulinumtoxin A but which is not statistically significant. The ITC conducted for the fremanezumab appraisal similarly demonstrates a result for fremanezumab versus onabotulinumatoxin A that is numerically favourable but not statistically significant. Furthermore, the ITC conducted for the fremanezumab appraisal is associated with the same limitations as that conducted for the erenumab appraisal, namely: • Differences in timepoint of outcomes assessment (24 weeks for onabotulinumtoxinA versus 12 weeks for fremanezumab) • Difficulties in understanding heterogeneity in baseline characteristics between the subgroups for fremanezumab and onabotulinumtoxin A used in the ITC, given that the baseline characteristics of the 3 prior treatment failures subgroup for onabotulinumtoxin A are not published. • In both the fremanezumab and onabotulinumtoxin Type A studies, patients were not stratified by previous prophylactic use at randomisation. Therefore, subgroup analyses in

	each study break randomisation and may be associated with imbalances between the active intervention arm and the placebo arm. Given this, if the Committee's conclusion regarding the relative effectiveness of erenumab versus onabotulinumtoxin A remains as per the ACD (pg10) and FAD (pg 13-14) for erenumab (that "there [is] no robust evidence that erenumab is more clinically effective than botulinum toxin Type A for chronic migraine"), then the Committee should similarly conclude that there is no robust evidence that fremanezumab is more clinically effective than onabotulinumtoxin Type A.
17. Is it reasonable to assume monthly headache days will be equivalent to monthly migraine days?	The ITC of erenumab versus onabotulinumtoxin A conducted for the erenumab appraisal similarly included an analysis that compared an outcome of monthly headache days with one of monthly migraine days. The assumption of equivalence between monthly headache days and monthly migraine days inherent in this was noted as a limitation by the committee in the ACD (pg 11) and FAD (pg 11). The Committee should be consistent in their considerations of this assumption between the two appraisals (erenumab and fremanezumab).

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

ERG response to technical engagement response

1 October 2019

1 Introduction

The Evidence Review Group (ERG) critique addresses Teva's response to issues raised by the technical engagement process. The issues include: 1) treatment stopping rules; 2) the model time horizon; 3) utility values used in the economic model; 4) the high-frequency episodic migraine subgroup; 5) resource use and costs; and, 6) network meta-analysis (NMA) for chronic migraine.

2 Issue 1: Treatment stopping rules

2.1 Is treatment stopped when people respond positively to treatment and migraine frequency decreases?

Company response: The expert clinical advice given to Teva was that patients that respond positively to treatment typically have their medication stopped, following appropriate review and in consultation with the patient. It was advised that oftentimes preventive treatment is used to cover periods of migraine exacerbation and that treatment is stopped once the patient no longer requires it. Thus, it is not accepted practice in the treatment of migraine for patients to remain on preventive treatment indefinitely. It is expected that a similar clinical practice would be adopted with anti-CGRP therapies, as has been highlighted by the European Headache Federation recommendations on the use of anti-CGRP therapies. These opinions are consistent with the submissions to this appraisal by the Association of British Neurologists and British Association for the Study of Headache, with both groups stating that the need for ongoing treatment should be assessed after one year. The SmPC for fremanezumab states that the need to continue treatment should be reviewed regularly based on an individual patient basis. Therefore, Teva believes that there is clear clinical opinion that treatment will be stopped (at an appropriate time) in patients who respond positively to treatment with fremanezumab.

The ERG believe that the need for continued therapy in people who respond to fremanezumab after three months would be assessed annually in line with current practice for onabotulinum toxin A (OBA). The ERG consider that an assessment period of three months off treatment to monitor migraine frequency, and a proportion for whom treatment effect is sustained following discontinuation, are reasonable positions given current clinical practice and experience.

2.2 Annually, what proportion of people on therapy will stop treatment because of a positive response?

Company response: There is currently no empirical evidence that can be used to show the proportion of patients who would stop treatment following a positive response. The consensus of clinical opinion gathered by Teva was that 20% was a reasonable estimate in the absence of any other data. Some headache specialists contacted expressed an opinion that this figure was a conservative estimate and lower than they would expect. The submission from the British Association for the Study of Headache also states that "*We anticipate that no more than two years treatment may be required in the vast majority*", implying expectation of a much higher annual stopping percentage. The value of 20%, used as a base case assumption by Teva, can be considered to be a conservative assumption in light of the expert opinion.

In the absence of empirical evidence the ERG are satisfied with the approach of the company in the determination of this estimate (20%) but note that this crude method renders the estimate uncertain. Consensus of much broader clinical opinion would be preferable in the absence of empirical or real world data.

2.3 Will the treatment effect be maintained indefinitely after treatment is stopped? If not, how long would you expect treatment effect to continue following treatment stopping (after a positive response)?

Company response: There are no data to demonstrate that treatment effect will not be maintained after discontinuation and, for any observed rises in migraine frequency, the time period in which this would occur is unclear. The natural history of migraine is such that the condition has periods where it is better or worse than what is normal for an individual patient. This can be exacerbated by life events and natural changes in frequency of migraines over the course of a patient's life. Expert opinion expressed to Teva is that there is an expectation that treatment with fremanezumab should allow patients to gain control over their migraines (when they often feel out of control), and, once this control is established, there would be an expectation that these improvements would be maintained.

This is a highly uncertain aspect of the company's model. In view of the ERG clinical opinion, the ERG has provided scenarios to explore outcomes when waning of effect is applied for those who positively stop. The ERG has not included scenarios exploring waning of effect while patients are on-treatment, or when fremanezumab is discontinued in the responder population.

2.4 Will treatment be restarted if treatment effect diminishes after stopping treatment? If yes, by how much would treatment effect have to diminish before treatment is restarted?

Company response: Teva finds that it is plausible that treatment would be restarted in patients who have been positively stopped and experienced a subsequent deterioration in their condition. However, the modelling in these scenarios is based on assumptions, as no data are available on which patients will stop and then restart treatment, or the time period between these events. In addition, this does not consider the unpredictable nature of migraine and the impact of life events on this condition. However, the assumptions made by the ERG in consultation with clinical experts (that treatment effect may wane over a number of years after a positive stop and that people may restart treatment when the treatment effect has diminished) appear to be reasonable and plausible.

The company has correctly interpreted the ERG's scenario (which is applied to the chronic migraine population).

2.5 Will treatment be stopped if people do not respond to treatment? What proportion of people do you expect to stop treatment following a negative treatment response?

Company response: All clinical experts consulted by Teva have expressed a clear view that no physician would continue prescribing an ineffective treatment. It is therefore entirely rational and plausible that treatment would be stopped in patients who do not respond to treatment (with these definitions in line with those previously preferred by NICE, namely at least a 50% reduction in monthly migraine days for episodic migraine and at least a 30% reduction in monthly migraine days for chronic migraine). The proportion of patients that would stop under these criteria can be taken directly from the FOCUS clinical trial data, with the subgroup analysis on the three or more treatment failure group providing the directly relevant data for the population of interest in this appraisal.

The ERG is satisfied with the company's estimation of response rates with FOCUS as the source of evidence, notwithstanding the weaknesses of the NMA. For the relevant episodic migraine population, 50% in the quarterly fremanezumab group and 40% in the fremanezumab monthly grouped achieved a 50% reduction in monthly migraine days (MMD). For the relevant chronic migraine population, 44% in the quarterly fremanezumab group and 46% in the fremanezumab monthly group achieved at least a 30% reduction in the MMD.

3 Issue 2: The model time horizon

3.1 Will all the costs and benefits of fremanezumab be captured over 10 years?

Company response: A 10-year time horizon is sufficient to capture all meaningful differences in costs and QALYs between treatments. This horizon is supported by the fact that only a very small number of patients remain on treatment at the end of this time horizon. This position is also supported by the submission from the British Association for the Study of Headache, which states "*We anticipate that no more than two years treatment may be required in the vast majority.*" The ERG also agreed in their report that a 10-year horizon is a reasonable assumption.

The ERG has no further comment but refer to the previously described position in the ERG report and Addendum as follows:

> *"The ERG considered that on balance a ten-year time horizon is reasonable given the competing requirements of capturing long-term treatment effect and avoiding increasing uncertainty as extrapolation lengthens. Importantly, the company state that the natural history of the condition is not considered in the simulation (due to a lack of informative evidence). This position becomes increasingly simplistic and uncertain with time horizons beyond ten-years, whilst shorter time-horizons may not be fully representative. By the end of the time horizon here patients exceed 50 years, at which age the onset of menopause in the female contingent becomes relevant. Since this is not accounted for the estimates of cost-effectiveness may be biased."* (Main report, Section 5.2.5)

> *"The ERG note that whilst long time-horizons could better reflect the long-term nature of the condition, the degree of uncertainty around the ICER increases. This is because increasingly long extrapolations are required of short-term trial evidence; because the model does not adjust for changes in the natural history of disease; and because some assumptions increasingly favour fremanezumab. In particular, that all patients respond to BSC after fremanezumab discontinuation"* (Addendum 1)

3.2 Is a lifetime model time horizon more appropriate than 10 years?

Company response: Whilst migraine is a chronic condition, a 10-year time horizon is more appropriate than a lifetime horizon in this case for a number of reasons. As outlined in the response above, a 10-year time horizon is sufficient to capture all meaningful differences in costs and QALYs between treatments, with only a small number of patients remaining on treatment at the end of this time horizon. Extending the time horizon without including the impact of the natural history of migraine will introduce unnecessary uncertainty into the model. Whilst it would be highly desirable to include the natural history of migraine within the model, there is a lack of available evidence for modelling such scenarios and no previous economic models found within the literature reviewed by Teva have shown any migraine models that have included this factor within their analyses. Therefore, Teva agrees with the ERG that a 10-year horizon becomes the most appropriate compromise given the available data, as this provides sufficient time to capture all meaningful differences between treatments, but minimises the unnecessary uncertainty from a longer time horizon (associated with the inability to include modelling of the natural history of migraine within the model).

To understand the implications of using a lifetime horizon, the ERG undertook some scenario analyses. One scenario analysis involved fremanezumab responders who discontinue treatment reverting to the baseline MMDs of non-responders after this discontinuation (ERG Scenario 9 within ERG model). Teva believes that this is not clinically justifiable, in that these patients have responded to treatment and would therefore be likely to maintain some treatment effect (based on the expert opinion received by Teva that fremanezumab should allow patients to gain control over their migraines during periods of high migraine activity). In addition, some patients are likely to respond to best supportive care once they discontinue fremanezumab treatment, with the potential that these previously responding patients (who have stopped treatment for reasons other than due to a lack of efficacy) may be more likely to respond to a subsequent line of preventive treatment (best supportive care in this case). Teva is of the opinion that ERG Scenario 10 (within ERG model, where consideration of responder status was included) is a more reasonable and justifiable approach to the issue than ERG Scenario 9; although other approaches should potentially be considered to find the most plausible and clinically justifiable approach.

The ERG consider the extension of the model time horizon beyond ten years to further exacerbate the issues contributing to uncertainty in the model outcomes. The modelling of

migraine frequency after fremanezumab/OBA failure is of particular concern. The ERG have highlighted the importance of fully understanding the nature of best supportive care (BSC) as applied the model's strategies, in particular how it has been included as the 5th treatment line after fremanezumab discontinuation. In Addendum #2 the ERG have presented scenarios including two alternative approaches to modelling this situation. These highlight the sensitivity of results to the management of migraine after fremanezumab/OBA failure when long time horizons are selected.

4 Issue 3: Utility values used in the economic model

4.1 Is the Migraine-Specific Quality of Life Questionnaire (MSQoL) used to measure the quality of life of people with migraine in clinical practice? If not, what alternative measure(s) are used?

Company response: The HIT-6 and MIDAS tools are commonly used within clinical practice due to their simplicity and ease of administration, whilst giving sufficient information to allow for the clinical management of patients. In comparison to these two tools, the MSQoL is a more detailed measure that fully assesses the quality of life in patients with migraine (including an assessment of their emotional state, which is not included in either of the other measures). This measure has therefore been widely used in clinical trials and has demonstrated reliability, validity, and responsiveness in assessing the quality of life in patients with migraine. The MSQoL should, therefore, be considered as the most appropriate measure of overall quality of life in migraine. In addition, it is noted that the HIT-6 is not considered an appropriate measure in episodic migraine, due to its focus solely on the frequency of headache impacts which are much greater in chronic migraine. The applicability of the MSQoL as a measure of quality of life in migraine has been previously recognised by NICE within the onabotulinumtoxin A and the erenumab appraisals.

The ERG note that Headache Impact Test (HIT-6) and Migraine Disability Assessment (MIDAS) may be used in clinical practice to evaluate the impact of migraine on patients' daily functioning; however the ERG do not consider either to be appropriate measures of quality of life. The ERG agree that the Multiple Sclerosis Quality of Life (MSQoL) provides a more appropriate measure of quality of life in these patients. The ERG also consider that the 14-item short form of the MSQoL used within the company submission (the **Migraine**-Specific Quality of Life Questionnaire version 2.1 [MSQ v2.1]) is a reasonable approach for evaluating quality of life for patients with migraine.

4.2 The NICE reference case and current position statement on the EQ-5D-5L, state a preference for the use of EQ-5D-3L for base-case analyses. Is the EQ-5D-3L insensitive to changes in quality of life caused by migraine attacks?

Company response: The EQ-5D (and particularly in the way administered during the clinical trials of fremanezumab) is not sensitive to changes in quality of life caused by migraine attacks. The EQ-5D data in FOCUS were collected during clinic visits within the clinical trial and measured the quality of life only on that day. Should a patient be experiencing a migraine attack, it is unlikely that they would have visited the clinic that day and, thus, the full impact of migraine on quality of life is missed through the EQ-5D measure. There was a lack of correlation found between EQ-5D results and the number of monthly migraine days in the FOCUS results. There is strong evidence to show that the number of monthly migraine days are strongly correlated with quality of life in migraine, and therefore this lack of correlation demonstrates that these EQ-5D data have not adequately captured the quality of life impact of migraine within the clinical trial. Therefore, as the full quality of life impacts are not captured within the EQ-5D, Teva believes that this is not an appropriate methodology for consideration in this appraisal.

The ERG believe that the company's selection of MSQoL derived data over directly gathered EQ-5D data [form the FOCUS trial] was reasonable.

4.3 Are utility values mapped from the MSQoL to EQ-5D-3L more appropriate than those mapped from EQ-5D-5L to EQ-5D-3L?

Company response: As explained in the responses to questions 8 & 9 (above), the MSQoL can be considered to be superior to the EQ-5D at measuring quality of life in patients with migraine. The EQ-5D is not sensitive to changes in quality of life caused by migraine attacks, and as EQ-5D data in FOCUS were collected during clinic visits, this measure assesses the quality of life only on that day. Should a patient be experiencing a migraine attack, it is unlikely that they would visit the clinic that day and, thus, the full impact of migraine on quality of life is missed through the EQ-5D measure. In contrast, the MSQoL is a detailed measure of quality of life in patients with migraine that has been widely used and has demonstrated reliability, validity, and responsiveness. The MSQoL includes a four-week recall period and thereby assesses the patient's overall quality of life, including the impact of migraine attacks and their quality of life during the interictal period.

The publication (Gillard *et al*. 2012) which defined the algorithm for mapping utility values from MSQoL to EQ-5D included a second version of the algorithm which accounted for

various patient baseline demographic characteristics. The baseline data available from the FOCUS trial were not collected in a suitable format to use with this second algorithm. Therefore, the mapping has been carried out using the simpler version of the algorithm and this represents the best available data for utilities. Teva note that this approach was also used by the company within the ongoing NICE appraisal of erenumab for the mapping of utilities, with similar justification to that presented here.

Therefore, utility values mapped from the MSQoL are the most representative for the overall quality of life for people with migraine and the most appropriate to be used in this appraisal.

While the ERG considered that the company's selection of MSQoL as the elicitation tool was reasonable, it also noted that the absence of adjustment for baseline characteristics was a potential source of bias.

4.4 Are utility values estimated from the full FOCUS trial population (≥2 prior preventative therapies) generalisable to the population of interest (≥3 prior preventative therapies)?

Company response: Utility values from the whole FOCUS population were used in order to increase the robustness and reliability of the results, as the estimation of utility values was required for all health states (0-28 monthly migraine days) included within the model. The larger dataset utilising the full population of the FOCUS trial therefore provided a dataset of a sufficient size for a robust analysis to be conducted. In addition, the evidence from the FOCUS trial (as presented in the company submission) showed a good consistency between results for the overall trial population and the ≥3 prior preventative therapies population. This provides further reassurance that the utilities derived from the overall trial population are representative of the ≥3 prior preventative therapies population. The ERG was of a similar opinion and stated that this inconsistency in populations would not be expected to have a significant effect on the utility values.

No further remarks.

4.5 Do preventative therapies result in quality of life improvements beyond those achieved by reducing the frequency of migraine days?

Company response: The values used for this appraisal are derived from the double-blind FOCUS trial data. The difference in quality of life is taken directly from these data and provides evidence that preventative therapies do result in quality of life improvements beyond

those achieved by reducing the frequency of migraine days. The difference in utilities between on and off treatment patients reflects the additional benefits of migraine treatment not captured within MMD numbers (such as reducing nausea, reducing recovery time after a migraine attack, shortening a migraine attack). These benefits were recognised in the clinical expert opinion submitted to NICE as part of this appraisal.

The examples, given by the company, of contributory factors to improved wellbeing when on-treatment, compared to off-treatment, are not directly measured by the MSQoL elicitation tool, but are indirectly captured by much broader questions relating to wellbeing. For example, 'is it is important to avoid changes in the pace of my life because of migraines?' (Copyright 1994, Burroughs Wellcome Co. and The Wellcome Foundation Ltd; University of Washington and Galen Research, authors). Whether it is reasonable to assume that the impact of such contributory factors are not fully captured by the MSQoL is uncertain, and it was not possible to explore this issue in depth given the time constraints of the review.

5 Issue 4: The high-frequency episodic migraine subgroup

5.1 Is the high-frequency episodic migraine (HFEM) subgroup recognised in clinical practice?

Company response: The opinion given to Teva by headache specialists is that high-frequency episodic migraine is a recognised and clinically distinct subgroup. This view was echoed in the expert advice given to the ERG and in the expert submissions to this appraisal. Teva finds that it is unfortunate that there has been no internationally agreed definition for this group of patients who endure a substantial impact on their quality of life (which can be seen to be similar to the impact seen in chronic migraine) and who currently have restricted treatment options and therefore a very high unmet need for treatment. High-frequency episodic migraine is a widely accepted clinically distinct subgroup by UK based headache experts and the lack of a clear definition should not, Teva believes, be used to exclude this group from consideration.

Clinical advice to ERG suggested that the HFEM subgroup is a clinically relevant subgroup. There is no consensus on the cut-off definition for HFEM but the ERG's understanding is that the most commonly documented definition in the literature is a monthly headache day frequency of 10-14.[1-3] The ERG is unaware of any evidence on the comparison of the impact of migraine on the quality of life between chronic migraine and HFEM. Clinical advice to the ERG suggested that HFEM is biologically distinct from chronic migraine.

5.2 If yes, what definition of "high-frequency" is used in clinical practice?

Company response: There is no internationally agreed definition of high-frequency episodic migraine, and a variety of definitions have been used in clinical practice. The most widely used definitions are based on monthly headache days, with a frequency of 8-14 or 10-14 most commonly used as the definition of high-frequency episodic migraine. Teva believes that a definition of 8-14 best encompasses the entirety of this population, but accepts that it is a matter of clinical debate. Teva also notes that a cost-effectiveness analysis in the 10-14 monthly headache day group would be expected to show greater cost effectiveness (lower ICER values *versus* BSC) than was seen in the 8-14 monthly headache day group presented within the company submission (as these patients will have a higher disability and so a relatively greater impact from treatment).

Clinical advice to the ERG and the literature suggest that HFEM may be more commonly defined with a monthly headache day frequency of 10-14 in clinical practice. The ERG concurs that, all other considerations being equal, fremanezumab would be of greater benefit to a high-frequency episodic migraine (HFEM) subgroup defined by 10-14 migraine headache days (MHDs) compared to 8-14 MHDs; however, is subject to the many sources of uncertainty highlighted within the cost-effectiveness model.

6 Issue 5: Resource use and costs

6.1 Will everyone be capable of self-administering fremanezumab? If not, what proportion do you expect will need their treatment administered for them?

Company response: It is reasonable to assume that not every patient will be capable of self-administering fremanezumab. It is expected, as this is a disease that most commonly affects working age people with few additional disabilities, that the proportion who cannot self-administer will be low. In addition, as fremanezumab is administered as a single injection once *per* month or as three injections once every three months, the headache specialists consulted by Teva have indicated that they would expect that many patients unable to self-administer will be able to have their treatment administered by a partner or carer. As fremanezumab requires only infrequent administration it is likely that this could be arranged by most patients, and is likely to be the preference for many patients unable to self-administer; as this would allow them to avoid the inconvenience of attending a clinic for administration of their medication and enable them to have it administered within their own home.

The proportion of patients requiring their treatment to be administered was assumed to be 10%, as a conservative assumption within the modelled scenario included within our submission. As the clinical expert opinion gathered by NICE has reported that only around 5% of patients may not be able to self-administer, additional analyses have been conducted to investigate the impact of this scenario. Using a proportion of 5% of patients requiring treatment to be administered by a health professional (cost of 91p *per* cycle for monthly administration and 31p *per* cycle for quarterly administration) increased the ICER *versus* best supportive care in episodic migraine by 0.4% for monthly administration and by 0.1% for quarterly administration. In chronic migraine *versus* best supportive care, ICER values were raised by 0.3% for monthly administration and by 0.1% for quarterly administration; the increase when compared to onabotulinumtoxin A was 0.5% for monthly administration and by 0.2% for quarterly administration. Therefore, it can be seen that conservative assumptions around patients requiring treatment to be administered for them have negligible impacts on the cost-effectiveness.

The ERG has adapted the company model to provide scenarios in which 5% or 10% of patients are unable to self-administer fremanezumab.

7 Issue 6: Network meta-analysis for chronic migraine

7.1 Is fremanezumab more effective at preventing migraines than onabotulinumtoxin A?

Company response: The NMA conducted by Teva is the best available evidence for a comparison between fremanezumab and onabotulinumtoxin A, in the absence of any head-to-head studies. Other approaches were considered, but Teva believes that the NMA undertaken for this appraisal is the strongest analysis that could be run given the available data. For example, a placebo-adjusted analysis has been suggested as a potential approach by NICE, but Teva note that the ERG have considered such an approach and did not consider it feasible based on the available data.

The NMA that has been presented shows an additional benefit for fremanezumab over onabotulinumtoxin A across all endpoints analysed. It was not possible for further endpoints to be analysed within this NMA as no further data for onabotulinumtoxin A was available in the ≥3 prior preventative therapies population (the population of interest for this appraisal). Whilst Teva recognises that there are weaknesses in this NMA (as identified within the company submission), a number of these act in favour of

onabotulinumtoxin A. The fact that onabotulinumtoxin A data was only available at 24 weeks rather than at 12 weeks (as utilised for fremanezumab) would make onabotulinumtoxin A appear more effective than had 12-week data been used; the published results of the PREEMPT trials show that the efficacy of onabotulinumtoxin A continued to increase between week 12 and week 24. For the comparison between "at least a 50% reduction in monthly migraine/headache days", a reduction in migraine days (fremanezumab) can be seen to be a more challenging endpoint than a reduction in monthly headache days (onabotulinumtoxin A), with migraine days representing a higher burden on patients. Therefore, the comparisons within the NMA can be seen to be conservative and likely to underestimate the relative efficacy of fremanezumab in comparison to onabotulinumtoxin A.

Given these facts, it is unreasonable to assume that there is no additional treatment benefit for fremanezumab over onabotulinumtoxin A and to override the NMA results that provide the best available evidence for this comparison. It is also worthy of note that many other appraisals conducted by NICE have accepted differences in treatment effect based on NMA results which did not show a significant difference between treatments. What our NMA indicates is that the probability of having a response to fremanezumab was greater than that of the comparators, which may be of clinical significance and should be used to drive the cost-effectiveness comparisons. Additionally, as there is evidence that the relative treatment effect is underestimated (conservative) for fremanezumab in this comparison to onabotulinumtoxin A, this means that it is likely that the true relative treatment effect favours fremanezumab more than has been reported by the NMA.

Teva has also been made aware of some concerns from NICE around the inclusion of patients who have previously failed onabotulinumtoxin A in the NMA data. These data were taken from the FOCUS trial, which was an international trial that included patients who may have had previous exposure to onabotulinumtoxin A at various lines. The subgroup analyses of the overall FOCUS data showed that in patients with prior onabotulinumtoxin A exposure, fremanezumab had a similar efficacy compared to the overall trial results, which included prior and no prior onabotulinumtoxin A use (data within Appendix on recent Lancet publication). Similar results were also seen in the three or more preventive treatment failures group as well (see below). Therefore, the incorporation of data for patients with prior onabotulinumtoxin A use should have no major impact on the NMA results.

Prior onabotulinumtoxin A use: Summary of efficacy outcomes for patients with chronic migraine who have failed three or more classes of preventive therapy 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 50% 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]

No prior onabotulinumtoxin A use: Summary of efficacy outcomes for patients with chronic migraine who have failed three or more classes of preventive therapy 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 50% 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]

Teva would also like to take this opportunity to reaffirm the strengths in the design of the FOCUS clinical trial and highlight important features of this trial. The FOCUS study is a strong, robust study with large patient numbers that provides the best available data for fremanezumab in the relevant population of interest (three or more prior preventive treatment class failures) for the treatment of both chronic and episodic migraine. Approximately half of the population of the overall FOCUS study were of the relevant

population of interest in this appraisal (three or more preventive treatment failures). There is evidence to show that the chronic and episodic migraine subpopulations do have differences in their disease pathophysiology, burden, disability and quality of life, which is fully captured within the FOCUS clinical trial by the inclusion of both populations. For inclusion within FOCUS, documented evidence had to be provided for inadequate response to pharmacological classes of preventive treatment, which means that patients can be assumed to have had difficult to treat migraine. To be classed as having a migraine day, patients had to have a calendar day with at least four consecutive hours of a migraine with or without aura as *per* ICHD-3 diagnostic criteria (no more than one ICHD-3 migraine criterion missing), or a headache of any duration treated with migraine-specific acute medications (triptans or ergot compounds); meaning that the FOCUS definition aligns with the stringent ICHD-3β migraine diagnostic criteria.

Teva also notes that there is an error in the technical report (page 8 and page 29) where it states "no evidence available for people for whom 4 or more preventative treatments have failed"; this is not correct. The FOCUS clinical trial includes patients who had failed two to four previous classes of preventive treatment, and, therefore, FOCUS data includes patients with four treatment class failures which may include (in some cases) more than four individual treatments.

The ERG has no further comments on the network meta-analysis.

In further subgroup analysis presented by the company (prior use of OBA), the ERG noted a substantial difference for the fremanezumab monthly group in the monthly migraine days reduction versus placebo, compared with no prior use of OBA. The efficacy appeared reduced for participants who have had prior OBA treatment in the fremanezumab monthly group.

7.2 Is it reasonable to assume monthly headache days will be equivalent to monthly migraine days?

Company response: Whilst monthly migraine days and monthly headache days cannot be seen to be directly equivalent, they are related measures. Teva agrees with the expert clinical opinion submitted to NICE as part of this appraisal that headache days are less impactful for patients, and, therefore, that migraine days can be considered more burdensome with a greater impact on quality of life. The comparison between monthly headache days (onabotulinumtoxin A) and monthly migraine days (fremanezumab) was only carried out for the analysis of "at least a 50% reduction in monthly migraine/headache days" (the analysis of "reduction in monthly migraine days" used data on monthly migraine days for

both treatments). This analysis was conducted using a mix of definitions (as there are no other data available) and, thus, provides the best comparison possible for the at least a 50% reduction endpoint. It should also be noted that as headache days are a less stringent endpoint, at least a 50% reduction in monthly migraine days would be a more challenging endpoint to meet than at least a 50% reduction in monthly headache days. Therefore, this assumption is likely to underestimate the relative efficacy of fremanezumab in this comparison to onabotulinumtoxin A either directly through the comparison between these endpoints, or indirectly through the greater quality of life benefits that will be seen by patients for at least a 50% reduction in monthly migraine days compared to those seen with at least a 50% reduction in monthly headache days. It is reasonable to assume that monthly headache days are equivalent to monthly migraine days, if not slightly easier an outcome to achieve in terms of response.

The ERG differ that it is reasonable to assume that monthly headache days are equivalent to monthly migraine days. Migraine headaches may coexist with other headache types for example, chronic tension-type headache.[4] The number of monthly headache days are likely to be almost always higher than the number of monthly migraine days which is why the classification of migraine types takes into account both the number of monthly headache days and the number of monthly migraine days as joint criteria.

References

1. Bigal ME, Lipton RB. Clinical course in migraine: conceptualizing migraine transformation. Neurology. 2008;71(11):848-55.

2. Lipton RB. Tracing transformation: chronic migraine classification, progression, and epidemiology. Neurology. 2009;72(5 Suppl):S3-7.

3. Silberstein SD, Lee L, Gandhi K, Fitzgerald T, Bell J, Cohen JM. Health care Resource Utilization and Migraine Disability Along the Migraine Continuum Among Patients Treated for Migraine. Headache. 2018;58(10):1579-92.

4. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia : an international journal of headache. 2013;33(9):629-808.

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

Addendum #1

Additional scenario analyses and erratum pages

19/08/2019

1 Introduction

This addendum was produced in response to a request from NICE for additional scenario analyses combining previous scenario approaches (Section 1). The ERG has responded to further queries from NICE in Section 2 and Section 3.

In setting up the scenario analyses, the ERG identified wiring errors in the model. These have been corrected and provided as erratum pages in Section 4.

2 Scenario analyses exploring utility, self-administration, and treatment effect waning

Features common to all additional scenarios include:

- Implementation of ERG model fixes identified in original ERG report.
- No utility premium for prophylaxis as compared to BSC / off-prophylaxis.
- 10% of fremanezumab patients unable to self-administer, attracting a new cost.

Features specific to added scenarios (all concerning waning of treatment effect):

- **Scenario 1:** No waning of effect (company base case retained)
- **Scenario 2a:** Fremanezumab MMD effect waned linearly to BSC over 10 years whether on or off treatment (company alternative approach)
- **Scenario 2b:** Fremanezumab MMD effect waned to baseline on five-year linear trajectory but treatment restarted when half of full effect is lost (ERG alternative approach). And BSC effect waned linearly to baseline over five-years.

The ERG note that whilst long time-horizons could better reflect the long-term nature of the condition, the degree of uncertainty around the ICER increases. This is because increasingly long extrapolations are required of short-term trial evidence; because the model does not adjust for changes in the natural history of disease; and because some assumptions increasingly favour fremanezumab. In particular, that all patients respond to BSC after fremanezumab discontinuation (See Section 2.1.1). Included as part of Scenario 2a is a coding correction of an introduced error which returns the waning effect to the fremanezumab responder cohort. This impacted the coding of cells Q9:Q775 in worksheet <Tx1 Calculations (Ch)> only (ERG model version). Scenario 2b includes waning of fremanezumab for positive stoppers, and BSC effect in all responders, with fremanezumab being restarted when half of effect is lost. This was implemented through ten years, by which time few patients remain alive on treatment, so complex implementation was not performed for longer time horizons. The scenario was not run for episodic migraine due to some patients not being eligible for treatment re-start having fallen below the indication MMD threshold of four migraines per month (and being off-treatment).

2.1 Scenario analyses exploring utility, self-administration, and treatment effect waning

2.1.1 Incremental results of scenario analyses

The ICERs for each scenario base case and extended time horizons are presented in Table 1 for the comparison of fremanezumab versus BSC, in both episodic and chronic migraine. Note that Scenario 2b is run in chronic migraine and only over a 10-year time horizon, as explained above.

Table 1: Summary results of additional scenario analyses, fremanezumab vs. BSC (probabilistic ICER in parenthesis)

Preferred assumption	ICER vs, BSC, £/QALY	+/- ICER, £	Proportional impact, %
Company base case, EM	£13,954 (£14,038)	-	-
Company base case, CM	£11,825 (£11,896)	-	-
Scenario 1. ERG fixes, no utility premium for prophylaxis, 10% unable to self-administer, no waning of effect applied to either strategy.			
	Episodic migraine		
10 year time horizon	£16,029 (£16,062)	£2,075	15%
20 year time horizon	£8,811 (£8,902)	-£5,143	-37%
40 year time horizon	£5,633 (£5,693)	-£8,322	-60%
	Chronic migraine		
10 year time horizon	£13,047 (£13,112)	£1,222	10%
20 year time horizon	£7,294 (£7,349)	-£4,532	-38%
40 year time horizon	£4,742 (£4,814)	-£7,084	-60%
Scenario 2a. ERG fixes; no utility premium for prophylaxis; 10% unable to self-administer; fremanezumab MMD effect waned linearly to BSC over 10 years whether on or off treatment (company approach)			
	Episodic migraine		
10 year time horizon	£16,352 (£16,482)	£2,398	17%
20 year time horizon	£8,965 (£9,010)	-£4,989	-36%
40 year time horizon	£5,720 (£4,830)	-£8,234	-59%
	Chronic migraine*		
10 year time horizon	£13,274 (£13,338)	£1,449	12%
20 year time horizon	£7,399 (£7,461)	-£4,426	-37%
40 year time horizon	£4,800 (£5,748)	-£7,026	-59%
Scenario 2b. ERG fixes; no utility premium for prophylaxis; 10% unable to self-administer; fremanezumab MMD effect waned to baseline on 5 year linear trajectory but restarted when half of full effect is lost; and BSC effect linearly reduced to baseline over 5 years (ERG approach).			
	Chronic migraine (only)		
10 year time horizon	£15,083 (£15,265)	£3,257	28%

Abbreviations: BSC, Best supportive care; CM, Chronic migraine; EM, Episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year. Notes: *Includes a coding fix to the ERG's implementation of the company's waning scenario.

Probabilistic ICERs are close to deterministic ICERs; however, the ERG draw attention to the limited range of input parameters included in the PSA, including the omission of structural assumptions; for example, inclusion of the positive stopping rule, or the assumption of baseline migraine frequency for BSC non-responders.

The summary results of the same scenario are presented in Table 2 for the comparison of fremanezumab versus OBA in chronic migraine.

Table 2: Summary results of additional scenario analyses, fremanezumab vs. OBA (probabilistic ICER in parenthesis)

Preferred assumption	ICER vs, BSC (£/QALY)	+/- ICER (£)	Proportional impact (%)
Company base case, CM	£16,227	-	-
Scenario 1. ERG fixes, no utility premium for prophylaxis, 10% unable to self-administer, no waning of effect applied to either strategy.			
10 year time horizon	£19,980 (£20,144)	£3,753	23%
20 year time horizon	£10,438 (£10,536)	-£5,789	-36%
40 year time horizon	£6,698 (£6,803)	-£9,529	-59%
Scenario 2a. ERG fixes; no utility premium for prophylaxis; 10% unable to self-administer; fremanezumab MMD effect waned linearly to BSC over 10 years whether on or off treatment (company approach)*			
10 year time horizon	£20,192 (£20,297)	£3,965	24%
20 year time horizon	£10,521 (£10,596)	-£5,706	-35%
40 year time horizon	£6,740 (£6,830)	-£9,486	-58%

Abbreviations: BSC, Best supportive care; CM, Chronic migraine; EM, Episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, Quality-adjusted life year. Notes: *Includes a coding fix to the ERG's implementation of the company's waning scenario.

2.1.2 ICER sensitivity to length of time horizon (Fremanezumab versus BSC)

Scenarios 1 and 2a show a trend of increasing fremanezumab cost-effectiveness versus BSC as the time horizon is lengthened (Tables 1). This is due to the combination of two assumptions: a further line of intervention (BSC) was modelled for the fremanezumab strategy after discontinuation of fremanezumab in responders (~54%; by awarding BSC level MMDs not baseline MMDs); and full responder level BSC effect was awarded to *all* these individuals. Therefore in the fremanezumab strategy an increasingly large pool of patients accrue for whom BSC responder level effect is indefinitely awarded). In contrast, 78% of individuals in the BSC strategy were awarded baseline (or zero) effect at 12 weeks. Consequently there is the implicit assumption that BSC following fremanezumab has a greater effect (overall) than when fremanezumab is not used at all. Note that the positive stopping rule does not significantly impact this assumption so the same trend of improving cost-effectiveness over longer time horizons is observed with or without this rule.

Since treatment effect in the BSC strategy was modelled according to the placebo/BSC response profile in QuANTUM-R, the ERG would prefer the same for recipients of BSC after fremanezumab rather than the assumption of full responder effect for all. As this is not the underlying assumption the ERG base case is likely to bias in favour of the fremanezumab strategy both at the ten year horizon and beyond (increasingly).

3 Results of scenario analysis exploring effectiveness of OBA

Presented in Table 3 is the result of a further scenario exploring the impact of equalising the effectiveness parameters defining the fremanezumab and OBA treatment strategies; in this case it was necessary only to increase the response rate of OBA to that of fremanezumab, other parameters already aligned in the base case preference set.

Table 3: Summary results of additional scenario analysis, fremanezumab vs. OBA

Preferred assumption	ICER vs, BSC (£/QALY)	+/- ICER (£)	Proportional impact (%)
Company base case, CM	£16,227	-	-
Scenario 3. ERG fixes, no utility premium for prophylaxis, 10% unable to self-administer, no waning of effect applied to either strategy, OBA response rate increased to fremanezumab rate.			
10 year time horizon	Dominated	-	-

Abbreviations: BSC, Best supportive care; CM, Chronic migraine; EM, Episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OBA, Onabotulinumtoxin A; QALY, quality-adjusted life year.

In the company base case model, there was limited difference in simulation in chronic migraine of costs and effects of OBA compared to fremanezumab. Differences in effects were driven by more people responding to fremanezumab than to OBA (54.25% versus 35.20%), otherwise efficacy parameters were effectively the same. The longer run-in to first assessment between strategies, causing a short delay in attainment maximal effect and point at which effect may for some be lost, had minimal impact. If the response rate to OBA is raised to that of fremanezumab then a further 0.03 QALYs are gained. And in this scenario, OBA costs are only slightly increased (£81) since higher treatment costs are all but offset by a reduction in migraine related costs. The change in the ratio of costs to effects results in the domination of OBA over fremanezumab, since in comparison its costs remain lower whilst its effect becomes marginally better than parity.

4 Erratum pages

In producing the scenarios requested by NICE, the ERG identified wiring errors in the model. Table 4 highlights the affected pages and the changes that have been made, and clean versions of the corrected pages follow.

Table 4: Erratum

Section & page number	Page included in main erratum submitted 30 July 2019	Change made
Section 5.2.10.3, page 193, Table 66	No	Removal of asterisk and associated footnote
Section 5.2.10.3, page 194, Table 67.	Yes – (12) Marked [redacted] as AIC (13) Marked [redacted] as AIC	Removal of asterisk and associated footnote and correction of ICER values
Section 6, pages 203-204, Table 76, Table 78.	No	Wiring correction in model and update to +/- ICER £/QALY, Cumulative ICER £/QALY, and Cumulative +/- ICER (%) in Table 76 and Table 78

SECTION 5.2.10.3, PAGE 193

Table 66: Result of scenario analyses in the episodic migraine analysis

Scenario	ICER, Frem vs BSC
Base case	**£13,954**
(1) Time horizon reduced from 10 to 5 years	£22,598
(2) Time horizon increased from 10 years to lifetime (57.8 years)	£4,767
(3) Linear waning of active treatment effect to BSC level over 10 years post discontinuation.	£14,202
(4) Lifetime horizon and 10-year waning of active treatment effect to BSC level	£4,835
(5) Treatment administration costs included for fremanezumab (monthly: £1.85 per cycle)	£14,054
(6) Treatment administration costs included for fremanezumab (quarterly: £0.62 per cycle)	£13,987
(7) Positive stopping rule affects only 10% of currently treated patients rather than 20% in the base case	£16,620
(8) No positive stopping applied at annual assessment due to sustained treatment effect	£20,214
(9) Impact of lost work days included in cost analysis	Dominates
(10) Use of quarterly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£13,976
(11) Use of monthly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£13,909

Abbreviations: BSC, best supportive care; Frem, fremanezumab; ICER, incremental cost-effectiveness ratio.

Table 67 presents the ICER result set of the company's scenario analyses for CM. Fourteen alternative scenarios within the CM analysis were tested; including three specific to OBA and the CM analysis (Scenarios 12-14). Again, the ERG draw attention to the scenarios relating to the base case assumptions about which uncertainty is most profound: time horizon (Scenarios 1 and 2); positive stopping rule / long-run treatment effect (Scenarios 3, 4, 7 and 8). These, and their variants are discussed in Section 5.3.

SECTION 5.2.10.3, PAGE 194

Table 67: Result of scenario analyses in the chronic migraine analysis

Scenario	ICER, Frem vs. BSC	ICER Frem vs. OBA
Base case	£11,825	£16,227
(1) Time horizon reduced from 10 to 5 years	£19,328	£27,517
(2) Time horizon increased from 10 years to lifetime (57.8 years)	£4,085	£5,555
(3) Linear waning of active treatment effect to BSC level over 10 years post discontinuation.	£12,017	£16,382
(4) Lifetime horizon and 10-year waning of active treatment effect to BSC level	£4,131	£5,589
(5) Treatment administration costs included for fremanezumab (monthly: £1.85 per cycle)	£11,907	£16,380
(6) Treatment administration costs included for fremanezumab (quarterly: £0.62 per cycle)	£11,853	£16,278
(7) Positive stopping rule affects only 10% of currently treated patients rather than 20% in the base case	£14,017	£19,634
(8) No positive stopping applied at annual assessment due to sustained treatment effect	£16,951	£24,756
(9) Impact of lost work days included in cost analysis	Dominates	Dominates
(10) Use of quarterly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£12,219	£17,245
(11) Use of monthly fremanezumab dosing effectiveness data rather than combined monthly and quarterly	£11,482	£15,385
(12) Proportion of patients responding to OBA increased from [redacted]	£11,825	£22,411
(13) Proportion of patients responding to OBA decreased from [redacted]	£11,825	£12,742
(14) 50% reduction in MMDs used as response threshold in CM rather than 30%	£10,411	£14,609

Abbreviations: BSC, best supportive care; CM, chronic migraine; Frem, fremanezumab; ICER, incremental cost-effectiveness ratio; MMDs, monthly migraine days; OBA, onabotulinum toxin A.

5.2.11 Subgroup analysis of high frequency episodic migraine (HFEM)

This analysis used efficacy data from the FOCUS clinical trial in patients with 8-14 monthly headache days. This patient group was assumed to have baseline characteristics of the overall

EM population. Responders had baseline mean MMDs of [redacted] compared to [redacted] for non-responders. The fremanezumab treatment effect compared to BSC was [redacted] MMDs

SECTION 6, PAGES 203-204

6. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG identified two areas for correction following a review of the company model for coding and implementation error (See Section 5.2.12.1):

i. Correction of coding for averaging of cycle level utility.

ii. Correction of assessment period length and alignment with 24-week treatment cycles to produce a 48 week treatment year.

Table 76, Table 77 and Table 78 present the impact on the ICERs of the two corrections, which are not large and do not increase deterministic ICERs above the £20,000 per QALY threshold.

Table 5 Impact of ERG changes on EM ICER, fremanezumab versus BSC

Change	Section in ERG report	+/- ICER £/QALY	Cumulative ICER £/QALY	Cumulative +/- ICER (%)
Company base-case	5.2.9	£13,954	-	-
Correction of utility estimation	5.2.12	£14,053	£14,053	0.7%
Correction of length of positive stop assessment (2 to 3 cycles)	5.2.12	£13,440	£13,535	-3.0%

Abbreviations: BSC, best supportive care; EM, episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 6 Impact of ERG changes on CM ICER, fremanezumab versus BSC

Change	Section in ERG report	+/- ICER £/QALY	Cumulative ICER £/QALY	Cumulative +/- ICER (%)
Company base-case	5.2.9	£11,825	-	-
Correction of utility estimation	5.2.12	£11,903	£11,903	0.7%
Correction of length of positive stop assessment (2 to 3 cycles)	5.2.12	£11,412	£11,487	-2.9%

Abbreviations: BSC, best supportive care; EM, episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 7 Impact of ERG changes on CM ICER, fremanezumab versus OBA

Change	Section in ERG report	+/- ICER £/QALY	Cumulative ICER £/QALY	Cumulative +/- ICER (%)
Company base-case	5.2.9	£16,227	-	-
Correction of utility estimation	5.2.12	£16,339	£16,339	0.7%
Correction of length of positive stop assessment (2 to 3 cycles)	5.2.12	£15,453	£15,560	-4.1%

Abbreviations: BSC, best supportive care; EM, episodic migraine; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

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

Addendum #2

Scenarios prepared for the NICE technical team

01/10/2019

(updated 17/10/2019)

1 NICE technical team preferences

1.1 Assumptions diverging from the company base case

The following technical team preferences are represented:

1. Implementation of ERG coding corrections (ERG report section 5.2.12.1).
2. Lifetime horizon extended from 10 years to lifetime (58 years from starting age 41/42).
3. Removal of the utility premium for migraine prophylaxis, creating equivalent on/off treatment utilities.
4. Exclusion of the positive stopping rule, removing the annual off-drug assessment periods and any proportion who consequently retain prophylactic effect whilst off-treatment.
5. Inclusion of nursing resource to support fremanezumab administration for 10% of patients unable to self-administer.
6. Alteration of treatment type and MMD effect following the per cycle discontinuation (1.95% every 4 weeks) of prophylaxis in the responder group ('negative' discontinuation). Two options.

   Scenario A (tech team preference). No further effective therapy
   Responders who subsequently discontinue fremanezumab revert to their baseline MMD frequency for the remainder of the time horizon, there are no further treatment options. Additionally, the 'placebo' effect of BSC that is attributed to responders in the BSC strategy is linearly waned over five years from full effect to baseline MMD frequency. This attenuates the indefinite application of the BSC/placebo effect preferred in the company base case, otherwise a stark assumption against per cycle decline to baseline of the fremanezumab effect. A two year wane is also explored.

   Scenario B. Further BSC effectual for a responding proportion
   A subsequent line of BSC is applied following fremanezumab drop-out, as per company base case, but a proportion do not respond. Responders are attributed a MMD frequency reduction equal to that applied in the BSC strategy. Note that the BSC effect applied here post-discontinuation is perpetual and not waned, as per company base case assumption for the BSC strategy. Non-responders revert to baseline MMD frequency. Response rates are based on those applied to the BSC strategy. I.e. 21.69% response in episodic migraine, 10.17% response in chronic migraine.

7. For the direct comparison of prophylactics for chronic migraine, the response rate of onabotulinum toxin A was increased to match the modelled response rate of fremanezumab (54.25%). This brings to parity both the response rates and the level of MMD reduction, thereby exploring only the impact of cost disparity between strategies.

Scenario Analyses

1. Relating to point 6A above, the linear wane of BSC effect is reduced from five years to two years.

2. An alternative unit cost for triptan was explored for each of these two preference sets. In this scenario the company base cost of triptan (£1.41 per day required), based on oral administration, was replaced with a weighted cost which included both oral and injectable triptans (£7.01 per day required).

3. Positive stopping is implemented in chronic migraine at a 20% annual rate following a 12 week assessment period. For this cohort the MMD reduction of fremanezumab is waned linearly to the responder baseline effect on a five year trajectory, however at the point when half effect is lost the treatment is restarted and full effect is quickly regained. This is implemented as a single stop - re-start cycle through the first ten-years of the time horizon.

1.2 Incremental results

Table 1 presents the results for the comparison of fremanezumab versus BSC strategies, along with the results of the two scenario analyses.

Table 1 Incremental results using technical team preference sets, fremanezumab versus BSC (probabilistic ICER in parenthesis)

Preferred assumption set	Incremental QALYs	ICER vs BSC, £/QALY	Proportional impact on ICER, %
Episodic migraine			
Company base case	[redacted]	£13,954 (£13,843)	
-Technical team using scenario A	[redacted]	£53,309	282%
(No further therapy and 5yr BSC wane)		(£53,239)	
Two year BSC wane in BSC strategy	[redacted]	£49,934	258%
Revised triptan	[redacted]	£50,856	264%
-Technical team using scenario B	[redacted]	£16,902	21%
(Further BSC for respondents)		(£17,146)	
Revised triptan	[redacted]	£14,352	3%
Chronic migraine			
Company base case	[redacted]	£11,825 (£12,102)	
-Technical team using scenario A	[redacted]	£21,529	82%
(No further therapy and 5 yr BSC wane)		(£21,654)	
Two year BSC wane in BSC strategy	[redacted]	£19,745	67%
Revised triptan	[redacted]	£19,239	63%
Positive stop and restart	[redacted]	£24,426	107%
-Technical team using scenario B	[redacted]	£43,754	270%
(Further BSC for respondents)		(£43,788)	
Revised triptan	[redacted]	£41,677	252%
Positive stop and restart	[redacted]	£11,421	-3%

Abbreviations: BSC, Best supportive care; CM, Chronic migraine; EM, Episodic migraine; ICER, incremental cost-effectiveness ratio; OBA, Onabotulinum toxin A; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year.

Table 2 presents the results for the comparison of fremanezumab versus onabotulinum toxin A.

Table 2 Incremental results using technical team preference sets, fremanezumab versus OBA (probabilistic ICER in parenthesis)

Preferred assumption set	Incremental QALYs	ICER vs OBA, £/QALY	Proportional impact on ICER, %
	Chronic migraine		
Company base case	[redacted]	£16,227 (£16,654)	
-Technical team using scenario A (No further therapy and 5 yr BSC wane)	[redacted]	Dominated (Dominated)	N/a
Revised triptan	[redacted]	Dominated	N/a
Positive stop and restart	[redacted]	Dominated	N/a
-Technical team using scenario B (Further BSC for respondents)	[redacted]	Dominated	N/a
Revised triptan	[redacted]	Dominated	N/a

Abbreviations: BSC, Best supportive care; CM, Chronic migraine; EM, Episodic migraine; ICER, incremental cost-effectiveness ratio; N/a, Not applicable; OBA, Onabotulinum toxin A; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year. *This non-zero despite equal response rates and effect size due to the different times to first assessment (12 weeks fremanezumab versus 24 weeks OBA).

1.3 Incremental impact of technical team preferences

Table 3 presents the ICERs for fremanezumab versus BSC and versus OBA. The impact on respective ICERs is given for each of the seven technical team preferences as applied individually. Note that they are not mutually exclusive.

Table 3 Impact on ICER of preferences when individually applied

Issue	ICER (£/QALY)		
	EM: Frem v BSC	CM: Frem v BSC	CM: Frem v OBA
Company base case	£13,954	£11,825	£16,227
1. ERG coding fixes	£13,535	£11,487	£16,118
2. Lifetime horizon	£4,767	£4,085	£5,555
3. No prophylaxis utility premium	£16,435	£13,363	£20,681
4. No positive stopping rule	£20,214	£16,951	£24,756
5. 10% unable to self-administer fremanezumab	£14,022	£11,881	£16,332
6. No further effective therapy after fremanezumab (with BSC strategy waning)	£28,648	£19,143	£30,424
7. Frem vs. OBA: equalisation of response rates (using frem rates)	N/a	N/a	Dominated
Tech team base case (Scenario A)	£53,309	£21,529	Dominated

Abbreviations: BSC, Best supportive care; CM, Chronic migraine; EM, Episodic migraine; ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; N/a, Not applicable; OBA, Onabotulinum toxin A; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year.

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

Addendum #3

Scenarios prepared for the NICE technical team

24/10/2019

1 NICE technical team preferences

1.1 Assumptions diverging from the company base case

The following technical team preferences are represented:

1. Implementation of ERG coding corrections (ERG report section 5.2.12.1).
2. Lifetime horizon extended from 10 years to lifetime (58 years from starting age 41/42).
3. Removal of the utility premium for migraine prophylaxis, creating equivalent on/off treatment utilities.
4. Exclusion of the positive stopping rule, removing the annual off-drug assessment periods and any proportion who consequently retain prophylactic effect whilst off-treatment.
5. Inclusion of nursing resource to support fremanezumab administration for 10% of patients unable to self-administer.
6. Negative discontinuation: Alteration of migraine frequency following the per cycle discontinuation of prophylaxis from BSC MMDs to baseline MMDs. Simultaneously, the 'placebo' effect of BSC that is attributed to responders in the BSC strategy is linearly waned over one year from full effect to baseline MMD frequency.
7. Removal of residual fremanezumab effect in non-responders.
8. For the direct comparison of prophylactics in chronic migraine, the response rate of onabotulinum toxin A is increased to match the modelled response rate of fremanezumab (54.25%). This brings to parity both the response rates and the level of MMD reduction, thereby exploring only the impact of cost disparity between strategies.

1.2 Summarised strategy results

Table 1 presents the mean total migraine days, costs, and quality-adjusted life-year results for each strategy in the two migraine populations.

Table 1. Summarised strategy level results

Strategy	Migraine days	Costs	QALYs
	Episodic migraine		
Fremanezumab	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
	Chronic migraine		
Fremanezumab	[redacted]	[redacted]	[redacted]
Onabotulinumtoxin A	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, Best supportive care; QALY, Quality-adjusted life year.

1.3 Incremental results

Table 2 presents the incremental results for the comparison of fremanezumab versus BSC strategies, along with the results of the two scenario analyses.

Table 2. Incremental results of company of technical team base cases, fremanezumab versus BSC (probabilistic ICER in parentheses)

Preferred assumption set	Incremental costs	Incremental QALYs	ICER vs BSC, £/QALY	Proportional impact on ICER, %
		Episodic migraine		
Company base case	[redacted]	[redacted]	£13,954 (£13,843)	
Technical team base case	[redacted]	[redacted]	£48,996 (£49,041)	251%
		Chronic migraine		
Company base case	[redacted]	[redacted]	£11,825 (£12,102)	
Technical team base case	[redacted]	[redacted]	£19,228 (£19,401)	63%

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; OBA, Onabotulinum toxin A; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year.

Table 3 presents the incremental results for the comparison of fremanezumab versus onabotulinum toxin A.

Table 3. Incremental results of company of technical team base cases, fremanezumab versus OBA (probabilistic ICER in parentheses)

Preferred assumption set	Incremental costs	Incremental QALYs	ICER vs OBA, £/QALY	Proportional impact on ICER, %
		Chronic migraine		
Company base case	[redacted]	[redacted]	£16,227 (£16,654)	
Technical team base case	[redacted]	[redacted]	Dominated (Dominated)	N/a

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; N/a, Not applicable; OBA, Onabotulinum toxin A; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year. *This non-zero despite equal response rates and effect size due to the different times to first assessment (12 weeks fremanezumab versus 24 weeks OBA).

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Technical report

Fremanezumab for preventing migraine

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background

Migraine is primarily a headache disorder manifesting as recurring attacks usually lasting between 4 and 72 hours involving throbbing head pain of moderate to severe intensity. It is often accompanied by nausea, sometimes vomiting, sensitivity to light, sensitivity to sound, and/or other sensory stimuli. Migraine can impact the ability to carry out normal activities and working responsibilities, can lead to depression, and can adversely affect quality of life. The severity of the condition can vary over time. Chronic migraine (CM) is defined as 15 or more headache days a month with at least 8 of those having features of migraine. Episodic migraine (EM) is defined as less than 15 headache days a month; the burden on quality of life can be similar to that of chronic migraine.

1.2 Treatment pathway

NICE clinical guideline 150 recommends offering oral preventatives such as, topiramate or propranolol, and considering amitriptyline, 1st line for the prevention of migraine. After the failure of at least 3 prior preventative therapies NICE technology appraisal guidance 260 recommends botulinum toxin type A for preventing headaches in adults with chronic migraine whose condition is appropriately managed for medication overuse.

The NICE final scope defined the population as “adults with chronic or episodic migraine”, therefore did not specify a particular position for fremanezumab in the treatment pathway. The scope defined the relevant comparators as, established clinical management for migraine prevention without fremanezumab, including oral preventive treatments (such as topiramate, propranolol, amitriptyline), botulinum toxin type A, erenumab, and best supportive care (BSC). In its evidence submission the company positioned fremanezumab as a treatment option after 3 or more failed preventative therapies, at this position it considered BSC and botulinum toxin type A (CM only) as the relevant comparators.

1.3 The technology

Fremanezumab (Ajovy, Teva Pharmaceuticals) is a fully humanised monoclonal antibody that inhibits the action of calcitonin gene-related peptide (CGRP) which is believed to transmit signals that can cause severe pain. It has a marketing authorisation in the UK and is indicated for the 'prophylaxis of migraine in adults who have at least 4 migraine days per month'. Fremanezumab is administered as subcutaneous injection and has 2 dosing options: 225 mg once monthly (monthly dosing); or 675 mg every three months (quarterly dosing). According to the summary of product characteristics (SPC), treatment benefit should be assessed within 3 months after starting treatment and any decision to continue treatment should be taken on an individual patient basis. It also states that, evaluation of the need to continue treatment is recommended regularly thereafter. The list price of fremanezumab is £450 per 225 mg injection (£1350 per 675 mg). Costs may vary in different settings because of negotiated procurement discounts.

1.4 Clinical evidence

The company's systematic literature review (SLR) identified 3 randomised control trials (RCTs) in people with migraine.

- HALO EM: evaluated fremanezumab in people with episodic migraine
- HALO CM: evaluated fremanezumab in people with chronic migraine
- FOCUS: evaluated framanezumab in people with migraine.

All trials were double-blind and compared fremanezumab (quarterly or monthly dosing regimen) to placebo in adults aged 18 to 70 years across multiple international centres. The HALO and FOCUS trials were 16-weeks in length, including a 4-week run in period and a 12-week treatment period. Long-term safety and efficacy data were collected in the HALO-extension study which included people from HALO EM and HALO CM in for a further 12 months (up to 15 months total).

The FOCUS trial included people who had failed to respond to 2 to 4 preventive therapies. The population in the HALO trials excluded people who had a lack of

efficacy after 3 or more months of treatment on 2 or more classes of preventative therapy.

1.5 Key trial results

FOCUS trial efficacy outcomes at week 12

Summary of main efficacy outcomes for patients with episodic migraine in whom three or more classes of preventive therapy have failed

	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]	[redacted]
P-value *vs* placebo	[redacted]	[redacted]	[redacted]
Patients with at least 50% reduction in monthly average migraine days			
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)	[redacted]	[redacted]	[redacted]
P-value *vs* placebo	[redacted]	[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]	[redacted]
P-value *vs* placebo	[redacted]	[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]	[redacted]
P-value *vs* placebo	[redacted]	[redacted]	[redacted]
Mean monthly headache hours of at least moderate severity			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)	[redacted]	[redacted]	[redacted]
P-value *vs* placebo	[redacted]	[redacted]	[redacted]

Note: LSM, least-square mean change; SD, standard deviation; CI, confidence interval
Source: table 25 company submission (page 80)

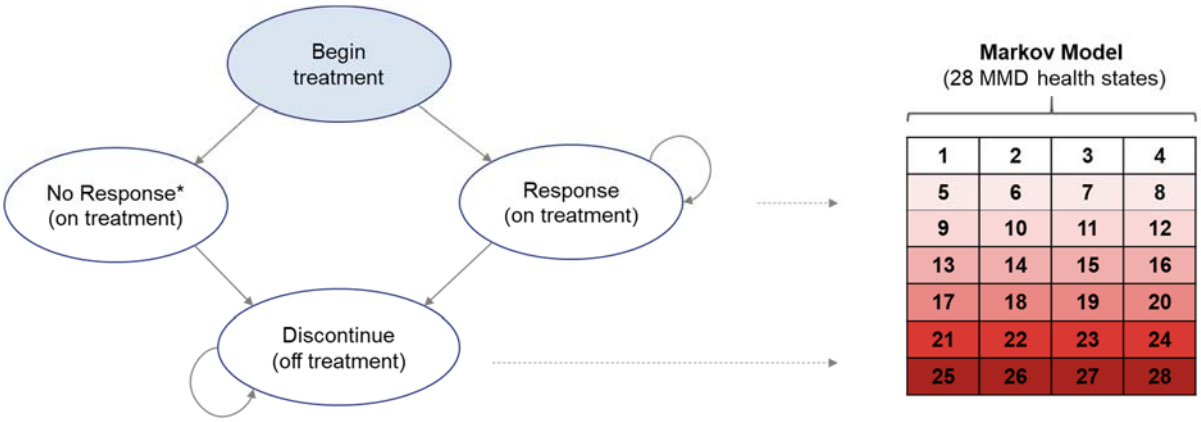
Summary of main efficacy outcomes for patients with chronic migraine for whom three or more classes of preventive therapy have failed

	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]	[redacted]
P-value *vs* placebo	[redacted]	[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]	[redacted]
P-value *vs* placebo	[redacted]	[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]	[redacted]
P-value *vs* placebo	[redacted]	[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]	[redacted]
P-value *vs* placebo	[redacted]	[redacted]	[redacted]
Mean monthly headache hours of at least moderate severity			
Baseline (SD)	[redacted]	[redacted]	[redacted]
LSM change (95% CI)	[redacted]	[redacted]	[redacted]
Difference *vs* placebo (95% CI)	[redacted]	[redacted]	[redacted]
P-value *vs* placebo	[redacted]	[redacted]	[redacted]

Note: LSM, least-square mean change; SD, standard deviation; CI, confidence interval.
Source: table 29 company submission (page 90)

1.6 Model structure

The company's economic model is a semi-Markov model. EM and CM are analysed separately, with each analysis using a dedicated set of input parameters. People in the model are split into treatment responders (defined as, 50% [for EM] or 30% [for CM] reduction in monthly migraine days (MMDs) from baseline) and non-responders. Responders remain on treatment and non-responders discontinue. Cost and utilities are exclusive to each health state. Utilities and costs are separately calculated for responders and non-responders based on the proportion of patients in each MMD health state.



Source: figure 8 company submission

1.7 Key model assumptions

The company made a number of assumptions in the design of its economic model. Key model assumptions are listed below:

- Any natural history variation in migraine is not modelled
- Base case time horizon is 10 years
- Cycle length is 4 weeks
- The distribution of MMDs obtained from fremanezumab FOCUS trial are assumed to be generalisable to other active treatments [onabotulinumtoxin A]
- The fremanezumab treatment effect does not wane over the model duration
- Placebo efficacy data is used to provide data for BSC

- Reductions in MMDs for onabotulinumtoxin A responders and non-responders are assumed equivalent to fremanezumab
- Responder rate in onabotulinumtoxin A based on data for at least a 50% reduction in MMDs (30% response rate data unavailable)
- A negative stopping rule is applied to people who do not respond to treatment
- A positive stopping rule applies in which 20% of responders positively discontinue (every 64 weeks: 52 week treatment period followed by 12 week treatment break where response is assessed)
- After treatment discontinuation: MMDs reduce to baseline levels after negative stopping; MMDs reduce to placebo (BSC) after per cycle (1.95%) discontinuation; and MMDs remain constant after positive stopping
- Migraine-specific mortality is not included
- Adverse events not included.

1.8 Overview of how quality-adjusted life years accrue in the model

The company's model includes health states which are defined by MMDs, where each MMD health state is associated with specific utility value. The distribution of MMDs is separately modelled for responders and non-responders. Therefore, migraine frequency and treatment response rates drive the accumulation of QALYs in the economic model. The company modelled differential on and off treatment utility values, therefore the accrual of QALYs is also affected by whether people receive fremanezumab, onabotulinumtoxin A or BSC in the company's model.

2. Summary of the technical report

After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below.

2.1 In summary, the technical team considered the following:

- A positive treatment stopping rule is not realistic (issue 1)
- A lifetime model time horizon is preferred to 10 years (issue 2)
- Additional on treatment utility benefit should not be modelled (issue 3)

- Administration costs should be applied for 10% of people receiving fremanezumab (issue 5)
- Fremanezumab and onabotulinumtoxin A assumed to have equal efficacy [applies to chronic migraine only] (issue 6)

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- No long-term evidence is available
- No evidence available for people for whom 4 or more preventative treatments have failed
- There are no head-to-head trials comparing fremanezumab with onabotulinumtoxin A in chronic migraine.

2.3 Taking these aspects into account, the technical team's preferred assumptions result in incremental cost-effectiveness ratios (ICERs) for fremanezumab of above 30k per QALY gained compared with BSC in episodic migraine, between £20k and £30k per QALY gained compared with BSC in chronic migraine and above £30k per QALY gained compared with onabotulinumtoxin A in chronic migraine.

2.4 Additional consideration of the innovative nature of technology is not necessary (see table 3).

2.5 The company, clinical and patient groups highlighted that migraine can be classed as a disability under the Equality Act (2010) and is a condition that is more common in women who may face further inequity and disadvantage in the workplace. In addition, there may be unequal access to specialist headache clinics in England. The technical team concluded that these are not issues that can be addressed by NICE guidance on fremanezumab (see table 3).

3. Key issues for consideration

Issue 1 – Treatment stopping rules

Questions for engagement	1. Is treatment stopped when people respond positively to treatment and migraine frequency decreases? 2. Annually, what proportion of people on therapy will stop treatment because of a positive response? 3. Will the treatment effect be maintained indefinitely after treatment is stopped? If not, how long would you expect treatment effect to continue following treatment stopping (after a positive response)? 4. Will treatment be restarted if treatment effect diminishes after stopping treatment? If yes, by how much would treatment effect have to diminish before treatment is restarted? 5. Will treatment be stopped if people do not respond to treatment? What proportion of people do you expect to stop treatment following a negative treatment response?
Background/description of issue	**The company** To reflect the fact that a proportion of people who respond to treatment will discontinue (no longer take it), the company applied a positive stopping rule in its base case analysis. The positive stopping rule is applied by assuming there is an assessment period at 52 weeks after initial assessment where all people have a 12-week treatment break to assess response. After this assessment point 20% of responders discontinue treatment, a proportion based on clinical expert opinion. This rule is then applied every 52 weeks for the rest of the model time horizon. The company noted that the European Headache Federation (EHF) recommends a similar approach stopping anti-CGRPs. The guideline states "treatment can be stopped if migraine is considered too infrequent to justify preventive treatment." Because there is no evidence to suggest that the treatment effect would

	wane, treatment benefit is assumed to be maintained indefinitely (at zero cost) for people who discontinue because of the positive stopping rule. In a scenario analyses the company explored the effect of applying the positive stopping rule to 10% of responders and another in which no positive stopping rule is applied. Reducing the proportion of people to which the positive stopping applies increases the ICER. **The ERG** The ERG highlighted that the pattern of long-term fremanezumab use is unclear and because of this it is uncertain whether the company's positive stopping rule is reflective of clinical practice. Further to this, the ERG noted that it could be optimistic to assume full prophylactic effect after stopping treatment without treatment cost. The ERG noted that the assumptions relating to the positive stopping should have be subject to further testing in a two-way sensitivity analysis (with model time horizon), stating that without this exploration the company's conclusion of ICER stability was overly optimistic. The ERG ran a two-way sensitivity analysis, varying the proportion of people stopping treatment following positive assessment and the model time horizon. In this analysis the ICERs were sensitive to both variables and in some instances were higher above the acceptable ICER threshold for cost-effectiveness. The ERG consulted clinical experts to consider the plausibility of a continued treatment effect after stopping treatment following positive assessment. Based on expert advice the ERG considered an appropriate approach was to apply a waning of the treatment effect (to baseline) over 5 years, while also modelling the re-starting of preventative therapy when treatment effect has declined to half of the full benefit. **Clinical expert advice** • The proportion of people who discontinue treatment after a positive response is not known. The proportion depends on time on treatment and the definition of response. More people may respond if on treatment longer (e.g. 12 months), however it is not clear if extended use is justified.

	• A continued treatment effect for positive treatment responders is not expected. Some responders may stop treatment, but the condition may be triggered again in those who stop. • It would be rational to restart treatment if treatment effectiveness diminishes after stopping. • People who do not respond to treatment would be stopped. Depending on how response is defined, up to 50% may not respond to treatment. • More non-responders expected in the high-frequency chronic migraine group.
Why this issue is important	Assuming continued treatment benefit after stopping without cost affects the accrual of QALYs and costs in the model and drives the ICER.
Technical team preliminary judgement and rationale	• Despite a lack of available evidence on the long-term efficacy and usage of fremanezumab, it is plausible that treatment may be continued until relapse, it is also plausible that people restart treatment after stopping following a positive response because their symptoms return. Therefore, assuming all treatment responders stop treatment indefinitely is unrealistic. • A range of ICERs should be provided including scenarios where no positive stopping rule is applied, and where a positive stopping rule applies but treatment is restarted after treatment effect diminishes by 50%. • Where a person's migraines do not respond to treatment (at least a 50% reduction in MMDs for EM and at least a 30% reduction in MMDs for CM), treatment should be stopped (negative stopping rule).
Summary of comments	**Company** • Assuming that 20% of people stop fremanezumab following a positive response is conservative • Expert opinion suggested that fremanezumab should reduce migraines, and, once migraine frequency is reduced, improvements are expected to be maintained • It is plausible that people will restart treatment if there is a deterioration in a person's condition • If a person's condition does not respond to treatment it would be stopped **Allergan** • Treatment is stopped if migraine frequency improves from chronic to episodic (less than 15 MHDs, of which 8 have characteristics of migraine) • Assuming fremanezumab effectiveness is continued indefinitely after stopping treatment (at zero cost) is highly optimistic and underestimates the ICER

	• If there is a loss of efficacy after stopping treatment, there may be a need to restart **Novartis** • Positive discontinuation scenarios were considered inappropriate in the appraisal of erenumab • Evidence demonstrating the maintenance of treatment effect after positive stopping has not been provided **Professional groups** • Treatment is stopped after negative response OR when MMDs drop below 8 or 10 • 'Drug holidays' are recommended to determine if continued treatment is necessary • There is limited data on those who stop treatment following a positive response • Fremanezumab would be restarted if effect diminishes with people treated for a further 6 to 12 months **NHS England** • At a minimum people should be reviewed 3 months after initiating treatment and treatment should be stopped in non-responders **ERG comments** • The decision to continue treatment will likely follow a similar rule to OBA where people who respond to treatment after 12 weeks will remain on treatment and have their response assessed annually. • Given current clinical practice and experience is reasonable to assume there will be an assessment period of 3 months to monitor migraine frequency, and, a proportion with continued treatment effect after stopping treatment. • The approach used by the company to estimate the proportion (20%) stopping treatment follow each year follow a positive response is satisfactory. However, this figure is still uncertain. • It is highly uncertain whether treatment effect will continue after treatment is stopped. • It is reasonable to use the response rates from FOCUS to implement a stopping rule for people who do not respond to treatment.

Technical team judgement after engagement	• Assuming continued treatment effectiveness after stopping treatment is not supported by trial evidence. • Assuming continued effectiveness at zero cost is optimistic and underestimates the ICER, and therefore, should not be assumed.

Issue 2 – The model time horizon

Questions for engagement	6. Will all the costs and benefits of fremanezumab be captured over 10 years? 7. Is a lifetime model time horizon more appropriate than 10 years?
Background/description of issue	**The company** In its economic model, the company used a time horizon of 10 years because it expected all meaningful differences in costs and QALYs between treatments to be captured by within this time horizon. The company noted that people are not expected to remain on treatment indefinitely. It further noted that the lack of long-term natural history data made modelling natural variations in migraine over time (such as, menopause) challenging, and because of this the use of a longer time horizon could lead to considerable uncertainties in the economic model. Therefore, the company considered the use of a time horizon of longer than 10 years, such as lifetime, inappropriate. **The ERG** The ERG considered that setting a 10-year time horizon is problematic for the prediction of long-term safety and effectiveness outputs. However, it noted that a 10-year time horizon was a reasonable compromise because most of the expected differences in costs and outcomes between treatments will be captured within this time horizon and beyond this point there is increasing uncertainty in terms of the extrapolation of short-term evidence. Further to this, the ERG noted that the sensitivity of the ICERs to variations in the model time horizon and positive stopping rule (see issue 1) were not tested sufficiently.
Why this issue is important	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Therefore, restricting the length of the modelled time horizon has implications for

	the prediction of long-term costs and efficacy outcomes. Arbitrarily capping the model time horizon can increases uncertainty in the model and resulting estimates.
Technical team preliminary judgement and rationale	• Extending the model time horizon introduces uncertainty into the analysis because the model does not capture all of the natural history of migraine. • In the ongoing appraisal of erenumab [ID1188], the committee considered a 10-year time horizon arbitrary and preferred a lifetime time horizon, in line with the NICE reference case. Therefore, to ensure that all costs and benefits are adequately captured a lifetime model time-horizon is preferred.
Summary of comments	**Company** • All meaningful benefits and costs are sufficiently captured using a 10-year time horizon • Because data is not available to allow the accurate modelling of the natural history of migraine, extending the model time horizon increases uncertainty • ERG scenario analysis assuming people who respond to treatment could revert to baseline MMDs after stopping treatment is clinically implausible. The alternative ERG scenario where

	people reverted to BSC MMDs after stopping treatment and a proportion then revert to baseline MMDs after not responding to BSC is a more reasonable and justifiable approach. **Allergan** • A lifetime model time horizon less appropriate given the uncertainty in key model assumptions. A shorter time horizon would result in more robust estimates. **Novartis** • It was felt a lifetime time horizon fully capture the costs and benefits associated with treatment in the appraisal of erenumab. A consistent approach should be used. **Professional groups** • A lifetime time horizon is preferable, however, because of difficulties modelling the natural history of migraine using a shorter time horizon (5 years) is reasonable. **NHS England** • A lifetime horizon is reasonable. **ERG comment** • A 10-year time horizon is reasonable timeframe to capture most costs and benefits. • As longer time horizons require extrapolation of short-term data, extending the time horizon exacerbates uncertainty in the model and the degree of uncertainty around the ICERs.
Technical team judgement after engagement	• Lifetime time horizon is preferred to ensure the costs and benefits associated with fremanezumab are fully captured and to align with the NICE reference case.

Issue 3 – Utility values used in the economic model

Questions for engagement	8. Is the Migraine-Specific Quality of Life Questionnaire (MSQoL) used to measure the quality of life of people with migraine in clinical practice? If not, what alternative measure(s) are used? 9. The NICE reference case and current position statement on the EQ-5D-5L, state a preference for the use of EQ-5D-3L for base-case analyses. Is the EQ-5D-3L insensitive to changes in quality of life caused by migraine attacks? 10. Are utility values mapped from the MSQoL to EQ-5D-3L more appropriate than those mapped from EQ-5D-5L to EQ-5D-3L? 11. Are utility values estimated from the full FOCUS trial population (≥2 prior preventative therapies) generalisable to the population of interest (≥3 prior preventative therapies)? 12. Do preventative therapies result in quality of life improvements beyond those achieved by reducing the frequency of migraine days?
Background/description of issue	**The company** Health-related Quality of Life (HRQoL) data was collected in the FOCUS trial using the EQ-5D-5L. The company highlighted that because EQ-5D-5L data collected in the FOCUS trial was measured during clinic visits, utility decrements from migraine attacks could be missed. It noted that a more appropriate quality of life measure was the Migraine-Specific Quality of Life Questionnaire (MSQoL) because it included a 4-week recall period. In its base case, the company used EQ-5D-3L utility values which were mapped from MSQoL subgroup scores using the Gillard et al. 2012 algorithm. Due to data limitations a more detailed mapping algorithm including patient characteristics could not be used. To map from MSQoL to EQ-5D-3L, the company used the full FOCUS trial population, then split the EQ-5D utility values into “on treatment” and “off treatment” groups. Off treatment health state utility values were estimated using baseline (week 0) MSQoL data, on treatment utility values were estimated from the week 4 and week 12 MSQoL data. Off-treatment utility values were applied to BSC and on-treatment utility values were used for fremanezumab and onabotulinumtoxin A strategies until people stop treatment. The company highlighted that on treatment utility benefits have been demonstrated for people with migraine and noted that the application of treatment specific utility values is consistent with previous migraine appraisals (TA260 and ID1188 [ongoing]).

	Figure redacted - AIC Source: generated using data from table 52 company submission **The ERG** The ERG highlighted that the model used HRQoL data collected from the full FOCUS trial population (≥2 prior preventative therapies), which does not align to the population of interest (≥3 prior preventative therapies). Therefore, there is a population inconsistency for utility and effectiveness estimates; however, the ERG considered this inconsistency would not have a significant effect on the final results.

	The ERG explained that utility estimates based on 3 data collections points (week 0, 4 and 12) were used to model utility for the duration of the model time horizon (10 years) because the company had assumed monthly migraine day (MMD) health state utility would remain constant. The ERG considered this was a simplification as the condition may evolve if people have had migraines long-term. This limitation together with use of a simplified mapping algorithm which failed to account for other patient characteristics means there is an uncertain level of bias associated with the model utility values. The ERG noted that the company had not provided evidence to support its claim that on treatment utility benefits have been demonstrated for people with migraine. It also highlighted that in one of the appraisals (TA360; onabotulinumtoxin A for migraine) which the company used to further justify its approach to modelling differential utility values, the appraisal committee considered that "there was still considerable uncertainty around the degree to which differential [on/off treatment] utilities existed within each health state". For episodic migraine, the ERG noted differences in baseline on and off treatment utility values, stating this was inappropriate as at baseline people will not have received treatment. For chronic migraine it highlighted that there were differences between responder and non-responder baseline utility values for the on treatment and off treatment groups. Considering all the above, the ERG was concerned that the health state utility values were underestimated, particularly for chronic migraine. **Clinical expert advice** • MSQoL is a reasonable tool to assess QoL in migraine but it is not routinely used in clinical practice in the UK. MSQoL is primarily used in clinical trials. • The Headache Impact Test 6-item (HIT-6) and Migraine Disability Assessment (MIDAS) are both used in clinical practice but have limitations. • A recently published review of QoL tools used to assess migraine has been published in cephalalgia. • There is anecdotal evidence to suggest treatment improves quality of life beyond that achieved from reducing monthly migraine days (e.g. reduces nausea and improves recovery time). It is

	challenging to capture or measure broader quality of life benefits in a trial setting. Patient narrative would be valuable here.
Why this issue is important	Utility values will have a direct influence of the cost-effectiveness estimates. Uncertainty in the utility estimates is carried into the cost-effectiveness estimates.
Technical team preliminary judgement and rationale	• In the ongoing appraisal of erenumab [ID1188] EQ-5D-3L utility values were also estimated from a population broader than the target population and mapped from MSQoL. The committee agreed that the rationale for using MSQoL - that is to capture the quality of life effect of migraine attacks which would otherwise be missed by EQ-5D - was plausible. However, clinical experts explained that HIT6 and MIDAS tools were more regularly used in clinical practice than MSQoL and suggested that the MSQoL may not be the best available measure of quality of life in this population. • On balance, similar concerns regarding the utility values were considered in the ongoing appraisal of erenumab, and although the committee noted concerns about the reliability of the utility values the committee agreed they may be reasonable. • As outlined in the current position statement, because of concerns regarding the validity of the EQ-5D-5L valuation set, data collected using EQ-5D-5L should be mapped onto the EQ-5D-3L valuation set. As such, alternative analyses using EQ-5D-5L data mapped to EQ-5D-3L should be provided for consideration. • The company's base-case EQ-5D-3L utility values (mapped from MSQoL) should be re-analysed to account for base-line characteristics, with analyses using these utility values being provided. • There is no evidence to suggest people on treatment (fremanezumab or onabotulinumtoxin A) would achieve an additional utility benefit beyond that from reducing migraine days. Equivalent on/off treatment health state utility values should be applied in the economic model.
Summary of comments	**Company** • Because of their simplicity HIT-6 and MIDAS are used in practice. The MSQoL is a more detailed measure which includes additional domains and should therefore be considered the most appropriate measure for assessing QoL in people with migraine.

	• EQ-5D is not sensitive to QoL changes caused by migraine attacks. • Utility values were estimated from the whole FOCUS population to ensure reliability and robustness. There is evidence of consistency across the full population and the population in which 3 or more treatments have failed. • There is evidence of an addition on treatment utility benefit from FOCUS. This benefit was also supported by comments from clinical experts. **Allergan** • MSQoL is reliable and valid, however, mapping has limitations and direct elicitation from a sensitive measure is preferred. • HIT-6 and MIDAS are recommended as useful efficacy endpoints in migraine by the International Headache Society Clinical Trials Subcommittee Guidelines. • The impact of estimating utility values from the full trial population is unknown. • For people receiving OBA there is evidence of improvements in QoL beyond that achieved by reducing MMDs. **Professional groups** • HIT-6 and MIDAS are preferred to MSQoL in clinical practice. • EQ-5D is less used than other tools in clinical practice. • There are QoL improvements from preventative therapies resulting from the reduced the severity and duration of migraines. • Basing QoL on changes in MMDs will not capture symptoms which have a substantial impact on QoL such as pain and nausea. • The population used to estimate utility values are easier to manage than those who have failed 3 or more preventative therapies. **NHS England** • A consistent approach with previous appraisals would be reasonable. **ERG comments** • For use in the population of interest the MSQoL is a more appropriate measure than either HIT-6 or MIDAS.

	• The choice to use EQ-5D-3L utility values mapped from MSQoL instead of directly observed EQ-5D-5L utility values is reasonable. • The lack of adjustment for baseline characteristics when mapping from MSQoL to EQ-5D-3L, is a potential source of bias. • Inconsistencies between the overall trial population and the population in which 3 or more preventative therapies have failed is not likely to have a substantial effect on the utility values. • It is uncertain whether it is reasonable to assume that HRQoL benefits beyond those achieved by reducing MMDs are not adequately captured by the MSQoL.
Technical team judgement after engagement	• HIT-6 and MIDAS are more commonly used QoL measures than MSQoL, however, no utility data from these measures is available. • There is contradictory evidence regarding whether treatment leads to additional improvements in quality of life beyond those achieved by reducing MDDs.

Issue 4 – The high-frequency episodic migraine subgroup

Questions for engagement	13. Is the high-frequency episodic migraine (HFEM) subgroup recognised in clinical practice? 14. If yes, what definition of "high-frequency" is used in clinical practice?
Background/description of issue	**The company** In its submission the company explained that not everyone who fit the episodic migraine category could be considered equivalent, highlighting that there was a subgroup of people who have a high frequency of episodic migraines (HFEM) who have more disability. It noted that because of this the HFEM subgroup should be considered separately considered. It defined the HFEM subgroup as people who have episodic migraines with between 8 and 14 headache days per month. It highlighted that the HFEM subgroup have limited treatment options because they are not eligible to receive onabotulinumtoxin A, as such there is a particularly high unmet need for treatment. It further noted that the adverse effect of the condition on people in the HFEM subgroup is similar to that experienced by people who have chronic migraines.

	The company recognised that a clear definition of HFEM has not been accepted in the literature and acknowledged that ICHD-3 guidelines do not define HFEM. **The ERG** The ERG consulted a clinical expert for guidance relating to the high-frequency episodic subgroup. The expert stated that although people with HFEM have higher disability, they are biologically distinct from people who have chronic migraines. They further explained that it is more clinically relevant to classify episodic migraine into low and high frequency. The ERG noted that the company based their HFEM definition (8 to 14 monthly headache days) on a reference which defined HFEM as 10 to 14 monthly headache days. The expert to the ERG considered a definition of 10 to 14 monthly headache days more clinically relevant than the company's, and noted that they defined HFEM as 11 to 14 monthly headache days. Therefore, the ERG noted that although a consensus regarding the definition of HFEM has not been reached, the company's definition deviates from that included in the literature presented. The ERG explored the effect of using a 10 to 14 monthly headache day definition in the analysis of HFEM and noted that the results were very similar to those reported for the company's HFEM analysis using the wider HFEM definition. **Clinical expert advice** • HFEM is a recognised subgroup in clinical practice. • There is no consensus on the definition of HFEM. People having 2 headaches or more a week are considered to be at risk of headache frequency increasing. • HFEM has not been clearly defined, but it is a useful clinical concept. In the UK 10 to14 monthly migraine days is considered HFEM. • A single migraine attack per week or less is considered 'low-frequency'. • People who have 4 to 8 monthly migraine days and do not always need preventative treatment may be considered low frequency. • If aggressively managed with bursts of preventative therapies or more consistent rescue therapy, HFEM could be returned to episodic migraine (<10 monthly migraine days).

Why this issue is important	Recommendations should only be made for clinically relevant and distinct subgroups. If HFEM is not recognised in clinical practice it should not be separately considered.
Technical team preliminary judgement and rationale	• There is no consensus regarding the appropriate definition of HFEM. • The HFEM group in FOCUS is a post-hoc subgroup of the episodic population. • HFEM is not a clinically distinct subgroup and does not need to be considered separately.
Summary of comments	**Company** • The opinion of headache specialists is that the HFEM subgroup is a recognised and clinically distinct subgroup. • The lack of an internationally agreed definition should not prevent the consideration of HFEM. • The most commonly used definitions of HFEM range from 8-14 to 10-14 MHDs. • HFEM has a substantial effect on QoL and there are limited treatment options available, therefore, this subgroup has a high unmet need. **Allergan** • There is no internationally agreed definition for HFEM. • HFEM has been defined in the literature as between 8-14, 9-14 and 10-14 MHDs for a minimum of 3 months. **Novartis** • A consistent approach with the erenumab appraisal should be taken. HFEM should not be separately considered. **Professional groups** • HFEM is recognised in clinical practice (10 to 14 MHDs) and is challenging to treat • HFEM is recognised in clinical practice and is believed to cause similar disability to CM. • Clinicians define HFEM as 8-14 to 10-14 MHDs. **NHS England** • Clinicians define HFEM as 10 or more MMDs. **ERG comments** • The HFEM subgroup is clinically relevant and biologically distinct from CM • The most comment definition in the literature is 10-14 MHDs

Technical team judgement after engagement	• There is no agreed definition of HFEM and it should not be separately considered.

Issue 5 –Resource use and costs

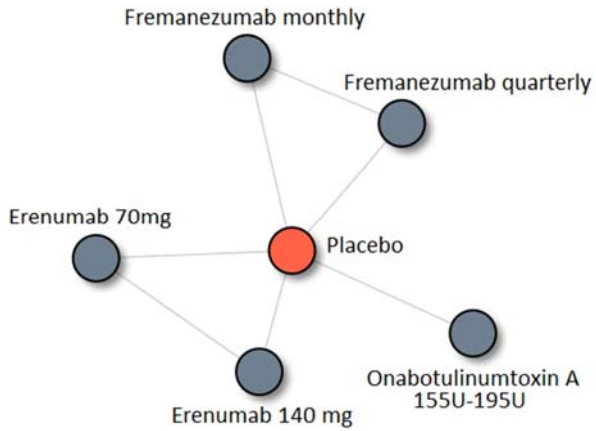
Questions for engagement	15. Will everyone be capable of self-administering fremanezumab? If not, what proportion do you expect will need their treatment administered for them?
Background/description of issue	**The company** The company's modelled 2 fremanezumab doses; a single monthly injection (225 mg) or 3 injections every 3 months (675 mg). The company assumed that fremanezumab could be self-administered by subcutaneous injections. It also assumed that resource use would be equivalent for both dosing schedules. The company noted that onabotulinumtoxin A cannot be self-administered, so fremanezumab administration represents an innovation which offers convenience to people with migraine and reduces the burden to NHS migraine services. Because the company assumed fremanezumab is self-administered in all scenarios, a zero cost for treatment administration is applied in the economic model. The company noted that, although the majority of people will be capable of self-administering treatment, some may not. In a scenario analysis, the company explored the effect of applying a treatment administration cost for 10% of patients, assuming treatment would be administered by a hospital-based nurse. **The ERG** The ERG noted that the company assumed equivalent resource use for both fremanezumab dosing schedules, it highlighted that this could be a conservative assumption as quarterly administration is likely to be less resource intensive. The ERG also highlighted that the company's assumption that all people would be able to self-administer fremanezumab was unrealistic but noted that there was only a marginal increase in the ICER when administration costs (for 10%) were modelled. **Clinical expert advice** • One expert noted all people would be able to self-administer fremanezumab, another suggested not all, but most will be able to self-administer.

	• People with physical or mental disabilities, the elderly and those who have a phobia of needles may not be able to self-administer. Approximately 5% would need their treatment administered for them. • Consultations are needed when initiating treatment (1 to 2 consults) and during the assessment period (phone consultations over 6 to 12 month period) • Additional services may be needed for delivery or homecare services for training on how to administer treatment. • An online video may be made available to give guidance on self-administration.
Why this issue is important	The estimation resource use and costs feed into the economic model and cost-effectiveness analyses. Misrepresenting costs in the economic model will affect the ICER.
Technical team preliminary judgement and rationale	• It is unrealistic to assume that all people receiving fremanezumab will be capable of self-administering treatment. Therefore, it is appropriate to assume that a proportion (10%) of people receiving fremanezumab will have their treatment administered by a healthcare professional.
Summary of comments	**Company** • Assuming a proportion of people will need their treatment administered for them is reasonable. • The proportion needing their treatment administered is likely to be lower than 10%. In line with clinical expert estimates, a proportion of 5% should be considered. • Changing this assumption has a negligible impact on the ICER **Allergan** • Assuming 100% of people could self-administer treatment (zero administration cost) is highly optimistic. • It is more realistic to assume that, people won't self-administered from the treatment initiation, some will need treatment administering for them and compliance and response will be monitored by specialists. • It is recommended that OBA response is assessed every 3 months. The cost of any response assessments should be accounted for in the model. • People with physical or mental disabilities or those who are needle phobic may not be able to self-administer.

	Novartis • Administration requires patients injecting 3 pre-filled syringes at alternate injection sites (recommended) which could be practically challenging for some people. • There could be difficulties administering for people with needle phobias as the needle is visible in the pre-filled syringes. • In the clinical trials, fremanezumab was administered in a clinical setting, therefore self-administration is not demonstrated. • Fremanezumab needs to be used within 24 hours after it is removed from a refrigerator, therefore, people need to have appropriate storage for self-administration. **Professional groups** • 5% to 10% may need their treatment administered. • Vast majority will self-administer treatment, over 95%. **NHS England** • It is reasonable to assume that some will not be able or willing to self-administer. The exact proportion needing assistance with administration is unknown. • Previous appraisals could inform the estimated proportion requiring self-administration. **ERG comment** • Scenarios provided where an administration cost was applied to either 5% or 10% of those in the fremanezumab group. • Another scenario was provided where an average weighted cost for oral and injectable triptans was included in the economic model.
Technical team judgement after engagement	• Administration costs for 10% should be modelled. • Changing this assumption has a negligible impact on the ICER. • Appropriate triptan costs should be captured and modelled.

Issue 6 – Network meta-analysis for chronic migraine

Questions for engagement	16. Is fremanezumab more effective at preventing migraines than onabotulinumtoxin A?

	17. Is it reasonable to assume monthly headache days will be equivalent to monthly migraine days?
Background/description of issue	**The company** There is no head-to-head trial evidence for fremanezumab compared with onabotulinumtoxin A. To indirectly compare relevant treatments in people who have failed three or more prior migraine preventive therapies, the company did a network meta-analysis (NMA). *Episodic migraine:* An NMA for episodic migraine was not possible because no relevant comparators with appropriate efficacy data were available. *Chronic migraine:* The network diagram for chronic migraine can be seen below:  Source: figure 5 company submission. The results from the NMA for chronic migraine are as follows: *Reductions in monthly migraine days* Results suggest a higher probability of a greater reduction in monthly migraine days with fremanezumab than onabotulinumtoxin A. Fremanezumab (monthly) had a numerically greater

	treatment effect compared to onabotulinumtoxin A [redacted] *People with at least 50% reduction in monthly average number of migraine days* Results suggest a higher probability of response with fremanezumab than onabotulinumtoxin A. Fremanezumab had a numerically greater treatment effect compared to onabotulinumtoxin A [redacted] The company highlighted the following assumptions and uncertainties with the NMA: *Assumptions:* • Onabotulinumtoxin A results reported at 24 weeks but fremanezumab at 12 weeks – equivalent efficacy is assumed between the 2 timepoints • Onabotulinumtoxin A response (decrease in monthly headache days) assumed equivalent to fremanezumab (decrease in monthly migraine days) • Sample sizes and time points assumed consistent for all outcomes in the results for erenumab *Uncertainties:* • All comparisons are made through the placebo arms • No trials focused on the population of interest (previously failed 3 or more prior migraine preventive therapies); all data was from the post-hoc subgroup analysis • No direct comparison between results in model and real-life data on comparative efficacy **The ERG** *Methodology* One of the ERG's main concerns regarding the NMA was the exclusion of outcomes in the FOCUS trial from the comparison. It noted that the company did not give a justification for its choice of outcomes, highlighting that it missed informative outcomes such as mean monthly days of use of any acute headache medication and 75% reduction in MMD.

	The ERG also noted the following concerns or errors relating to the company's NMA. Firstly, the company claimed that the inclusion of erenumab in the network would strengthen (improve) the analysis; however, as erenumab is only connected to the network by the placebo node it's unclear how its inclusion would strengthen it. Secondly, the ERG raised concerns regarding the company's searches for clinical effectiveness evidence, noting that studies could have been missed as a result of the company's search strategy. However, further searches from the ERG did not identify any additional studies. *Results* • The company's NMA results are accurate as verified by the ERG • The lack of available evidence to populate the network is a major weakness • Using data from a subgroup analysis in the NMA and assuming equivalent efficacy across different measurement time points (24 week assessment in the onabotulinumtoxin A trial and 12 week assessment in FOCUS) weakens confidence in the estimates • It was not possible to test the similarity of individual characteristics of subgroups in the NMA as the evidence network was too sparse **Clinical expert advice** • It is not reasonable to assume equivalence between migraine and headache days. Headache days compared to migraine days are often less impactful for patients. • Assuming equivalence between migraine and headache days may minimise or flatten the response.
Why this issue is important	A lack of direct comparative evidence means the comparison of effectiveness between fremanezumab and onabotulinumtoxin A for people with chronic migraine has to be estimated. Issues with the NMA means estimates of response rates and effect size estimates in the comparison of fremanezumab and onabotulinumtoxin A may not be robust. This uncertainty is carried through the model and into the cost-effectiveness estimates.

Technical team preliminary judgement and rationale	• NMA results for chronic migraine suggest an improvement in outcomes with fremanezumab compared to onabotulinumtoxin A; however, the differences in treatment effect are not statistically significant meaning the possibility of no comparative benefit cannot be ruled out • It is appropriate to consider a scenario in which fremanezumab and onabotulinumtoxin A have the same efficacy. ICERs should be provided where equal efficacy is assumed. • The exclusion of other outcomes from FOCUS in the NMA limits the value the of comparison. NMA results should be provided for all available trial outcomes, also including, mean monthly days of use of any acute headache medication and mean change from baseline in monthly average number of headache hours. • There are notable concerns regarding the similarity of the evidence used in the NMA. The trials included in the NMA had differences in population, assessment timepoints and outcomes, which all contribute to the uncertainty in the comparison. The lack of quality evidence in the NMA for chronic migraine means the estimates produced from the analysis are highly uncertain and this uncertainty is carried into the cost-effectiveness estimates. A placebo-adjusted analysis would address some of the concerns relating to between trial differences. Therefore, placebo-adjusted NMA results and accompanying cost-effectiveness analyses should be provided.
Summary of comments	**Company** • In the absence of a head to head comparison the NMA represents the best evidence available comparing of fremanezumab with onabotulinumtoxin A. • The placebo-adjusted analysis requested by NICE was considered infeasible by the ERG because of limitations with the available evidence. • NMA shows additional benefit for fremanezumab compared to onabotulinumtoxin A across all endpoints. • Different assessment timepoints (12 week [FOCUS] and 24 week [onabotulinumtoxin A trial]) and outcomes (reduction in MMDs [FOCUS] and reduction in MHDs [onabotulinumtoxin A trial]) in the fremanezumab and onabotulinumtoxin A trials favour onabotulinumtoxin A. Therefore, the

	effect estimate from the NMA is likely underestimated, and because of this, assuming equal efficacy is not reasonable. • NMA effect estimates which were not statistically significant have been accepted in previous appraisals. • Including people who had prior onabotulinumtoxin A use in the NMA has a minimal effect on the results. • Although differences in MHDs and MMDs are acknowledged, they were assumed equivalent because of data limitations. This assumption could underestimate relative benefit of frem compared to onabotulinumtoxin A because MHD reductions are easier to achieve than MMD reductions. **Allergan** • There is no robust evidence demonstrating that fremanezumab is more clinically effective than onabotulinumtoxin A. • Data limitations prevent a robust indirect comparison. **Novartis** • Numerical, but not statistically significant, benefits estimated from the NMA comparing erenumab with onabotulinumtoxin A were not accepted in the appraisal of erenumab. • There is no robust evidence of a treatment benefit for fremanezumab beyond that achieved with onabotulinumtoxin A. **Professional groups** • The relative effectiveness of fremanezumab and onabotulinumtoxin A is unknown because there is no direct head to head comparison of the treatments. • Assuming equivalence of MHDs and MMDs is unreasonable because headache and migraine days are of a different severity. • There is no evidence that there is a relative benefit for people on fremanezumab compared with onabotulinumtoxin A, however patients may prefer fremanezumab administration to onabotulinumtoxin A injections.

	ERG comment • The relative effectiveness of fremanezumab compared to onabotulinumtoxin A appears to be reduced for people who were previously treated with onabotulinumtoxin A. • It is reasonable to assume MHDs are equivalent to MMDs. • Scenario provided where equal effectiveness of fremanezumab and onabotulinumtoxin A is assumed.
Technical team judgement after engagement	• There is no robust evidence suggesting that fremanezumab leads to a relative clinical benefit compared with OBA.

Issue 7 – Use of fremanezumab after onabotulinumtoxin A (added after technical engagement)

Questions for engagement	18. Would fremanezumab be considered as an option once onabotulinumtoxin A has failed, is not considered to be appropriate or has not been tolerated?
Background/description of issue	**The company** In its submission, the company positioned fremanezumab as a treatment option after 3 or more failed preventative therapies It suggested that this position would allow fremanezumab treatment to be focussed on patients who do not respond sufficiently to other preventive therapies and would therefore match the positioning in chronic migraine where OBA has been approved by NICE (TA260). The FOCUS trial was conducted internationally and therefore included patients who had previously received OBA at various lines of treatment that may not be available in England. At technical engagement, the company provided further subgroup analyses based on the FOCUS trial in patients with chronic migraine who have failed three or more classes of preventive therapy. The results

	showed that in patients with prior OBA use, fremanezumab had a similar efficacy compared to the overall trial results. **The ERG** In further subgroup analysis presented by the company (prior use of OBA), the ERG noted a substantial difference for the fremanezumab monthly group in the monthly migraine days reduction versus placebo, compared with no prior use of OBA. The efficacy appeared reduced for participants who have had prior OBA treatment in the fremanezumab monthly group.
Why this issue is important	Providing there is evidence to suggest that fremanezumab is clinically and cost-effective, it may be appropriate to consider fremanezumab as an option for a subgroup of people who have chronic migraine, where previous OBA has failed, not considered to be appropriate, or has not been tolerated.
Technical team preliminary judgement and rationale	• There is some clinical evidence (albeit small numbers and uncertainty relating to how many preventative treatments those with prior-OBA exposure have failed) to suggest that there may be a reduction in monthly migraine days when fremanezumab is used after OBA on a monthly basis. • The company did not provide clinical effectiveness evidence for fremanezumab when OBA is not considered to be appropriate or has not been tolerated. • The company did not submit cost-effectiveness evidence for fremanezumab and therefore its cost-effectiveness in this position cannot be determined.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1a: Technical team preferred assumptions and impact on the cost-effectiveness estimate (episodic migraine)

Alteration	Technical team rationale	ICER	Δ from base case
Company base case	Comparison of fremanezumab with BSC	£13,954	-
ERG fixes	The ERG corrections are acceptable	£13,535	-£419
No positive stopping rule	There is insufficient evidence to support a positive stopping rule (see issue 1).	£20,214	£6,260
Lifetime model time horizon (after discontinuation) Scenario A (frem reverts to baseline MMDs and BSC linearly wanes to baseline over 5 years) Scenario B (revert to BSC MMDs and apply BSC response rates [non-responders revert to baseline])	A lifetime model time horizon is preferred to ensure all costs and benefits are adequately captured (see issue 2). Scenario A is preferred because a treatment effect is not expected in fremanezumab non-responders and the duration and magnitude of BSC effect is expected to be limited.	A: £25,957 B: £8,933	£12,003 -£5,021
No additional on treatment utility benefit	There is contradictory evidence regarding whether an additional on treatment utility benefit is plausible. Therefore, in the absence of robust evidence, no additional on treatment utility benefit should be modelled (see issue 3).	£16,435	£2,481
Administration cost for 10% in frem group	It's unrealistic to assume 100% of people could self-administer treatment (see issue 5).	£14,022	£68
Cumulative impact of the assumptions on the cost-effectiveness estimate (scenario A)		£53,309	£39,355
Cumulative impact of the assumptions on the cost-effectiveness estimate (scenario B)	–	£16,902	£2,948

Table 1b: Technical team preferred assumptions and impact on the cost-effectiveness estimate (chronic migraine [BSC comparison])

Alteration	Technical team rationale	ICER	Δ from base case
Company base case	Comparison of fremanezumab with BSC	£11,825	-
ERG fixes	The ERG corrections are acceptable	£11,487	-£338
No positive stopping rule	There is insufficient evidence to support a positive stopping rule (see issue 1).	£16,951	£5,126
Lifetime model time horizon (after discontinuation) Scenario A (frem reverts to baseline MMDs and BSC linearly wanes to baseline over 5 years) Scenario B (revert to BSC MMDs and apply BSC response rates [non-responders revert to baseline])	A lifetime model time horizon is preferred to ensure all costs and benefits are adequately captured (see issue 2). Scenario A is preferred because a treatment effect is not expected in fremanezumab non-responders and the duration and magnitude of BSC effect is expected to be limited.	A: £12,078 B: £23,464	£253 £11,639
No additional on treatment utility benefit	There is contradictory evidence regarding whether an additional on treatment utility benefit is plausible. Therefore, in the absence of robust evidence, no additional on treatment utility benefit should be modelled (see issue 3).	£13,363	£1,538
Administration cost for 10% in frem group	It's unrealistic to assume 100% of people could self-administer treatment (see issue 5).	£11,881	£56
Cumulative impact of the assumptions on the cost-effectiveness estimate (scenario A)		£21,529	£9,704
Cumulative impact of the assumptions on the cost-effectiveness estimate (scenario B)	–	£43,754	£31,929

Table 1c: Technical team preferred assumptions and impact on the cost-effectiveness estimate (chronic migraine [onabotulinumtoxin A comparison])

Alteration	Technical team rationale	ICER	Δ from base case
Company base case	Comparison of fremanezumab with BSC	£16,227	-
ERG fixes	The ERG corrections are acceptable	£16,118	-£109
No positive stopping rule	There is insufficient evidence to support a positive stopping rule (see issue 1).	£24,756	£8,529
Lifetime model time horizon (after discontinuation) Scenario A (frem reverts to baseline MMDs and BSC linearly wanes to baseline over 5 years) Scenario B (revert to BSC MMDs and apply BSC response rates [non-responders revert to baseline])	A lifetime model time horizon is preferred to ensure all costs and benefits are adequately captured (see issue 2). Scenario A is preferred because a treatment effect is not expected in fremanezumab non-responders and the duration and magnitude of BSC effect is expected to be limited.	A: £17,905 B: £18,700	£1,678 £2,473
No additional on treatment utility benefit	There is contradictory evidence regarding whether an additional on treatment utility benefit is plausible. Therefore, in the absence of robust evidence, no additional on treatment utility benefit should be modelled (see issue 3).	£20,681	£4,454
Administration cost for 10% in frem group	It's unrealistic to assume 100% of people could self-administer treatment (see issue 5).	£16,332	£105
Equal effectiveness of frem and OBA	There is no robust evidence to suggest frem is more effective than OBA (see issue 6).	Dominated	N/A
Cumulative impact of the assumptions on the cost-effectiveness estimate (scenario A)		Dominated	N/A

Alteration	Technical team rationale	ICER	Δ from base case
Cumulative impact of the assumptions on the cost-effectiveness estimate (scenario B)	**–**	Dominated	N/A

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Long-term treatment effectiveness	There is no long-term clinical effectiveness data, therefore relative effectiveness estimates have to be extrapolated beyond what was observed in the FOCUS trial at 12 weeks. The extrapolation of long-term effectiveness is uncertain because there is no data which can be used for external validation.	Assuming fremanezumab effectiveness is maintained long-term may lead to an underestimation of the ICERs.
The relative effectiveness of fremanezumab compared with onabotulinumtoxin A	There is no head-to-head trial evidence for the comparison of fremanezumab with onabotulinumtoxin A in people with chronic migraine. Therefore, the relative effectiveness has to be estimated. This adds a degree of uncertainty in the assessment of clinical effectiveness.	Unknown impact on the ICER.
No evidence available for people who have failed 4 or more preventative treatments	Without any evidence covering this portion of the population, the effectiveness of fremanezumab in this group is unknown.	This is a small part of the overall population of interest, and it may be responsible to assume similar response as those who have not responded to 3-4 medicines. The impact on the ICER is not expected to be substantial.

Table 3: Other issues for information

Issue	Comments
The structure of the company's economic model	The structure of the company's economic model did not allow for the modelling of the natural history of migraine. This restriction may oversimplify the modelling of migraine. However, the model structure is similar to that in previous (TA260) and ongoing (ID1188) migraine appraisals.
Coding and implementation errors in the economic model	The ERG corrected for 2 errors in the company's economic model: (i) correction of coding for averaging of cycle level utility; and (ii) correction of assessment period length and alignment with 24-week treatment cycles to produce a 48-week treatment year.
Resource use estimates	The company based its resource use on estimates from a European study of migraine burden by Vo et al (2018). It noted limitations, including estimates based on monthly headache days, not migraine days, could underestimate the migraine cost burden. The ERG considered that the company's estimate of resource was an underestimate. It also noted that resource use rates were not specific to the population of interest (after 3 failed preventative therapies) but based on the general migraine population, because of this it is unclear whether the estimates are reflective of the resource used by the model population. However, these estimates are consistent with those used in the ongoing NICE technology appraisal of erenumab (ID1188) and therefore can be considered.
Adverse event costs	Because adverse events relating to the treatment and comparators are expected to be uncommon, no cost for adverse events were included in the model.
Innovation	The company considers the novel treatment class (anti-CGRP) and administration of fremanezumab to represent a step-change in the management of migraine. However, the technical team considers that these aspects have been adequately captured in the economic model. Therefore, the technical team believes further consideration of the innovative nature of fremanezumab is not needed.
Equality considerations	The company noted that migraine prevalence is higher in women than men, meaning a restriction of access will be a greater disadvantage to women. The technical team considered that this was not an equality issue which could be addressed in its recommendations.

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