National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Fremanezumab for preventing migraine

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Teva UK Limited	Yes, it is considered appropriate to refer this topic to NICE for appraisal	Comment noted
	The Migraine Trust	Yes. It is appropriate to refer this topic to NICE for appraisal.	Comment noted
	Novartis Pharmaceuticals UK Ltd	We consider the proposed appraisal appropriate.	Comment noted
	Association of British Neurologist	Yes. It is appropriate to refer this topic to NICE for appraisal.	Comment noted
	British Association for the Study of Headache	Yes	Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Teva UK Limited	To appraise the clinical and cost effectiveness of fremanezumab within its marketing authorisation for the prevention of episodic and chronic migraine in adults Proposed licence indication: [redacted]	Comment noted
	The Migraine Trust	Yes. The wording of the remit reflects the issues of clinical and cost effectiveness about the technology or technologies that NICE should consider.	Comment noted
	Association of British Neurologist	Yes	Comment noted
	Barts Health NHS Trust and UKCPA	Should prophylaxis against migraine – be used instead of preventing migraine (to tie I n with language used below)	Comment noted. The current wording is correct and consistent with previous NICE scopes. No change was made to the scope.
	British Association for the Study of Headache	Yes	Comment noted
Timing Issues	Teva UK Limited	Fremanezumab is intended to prevent episodic and chronic migraine in adults, a disease with currently a high unmet need. Therefore, we believe it should be assessed at the earliest opportunity.	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.

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	The Migraine Trust	This is an extremely urgent matter. Migraine is highly prevalent and can be very disabling. There are currently no preventative drug treatment options that are specifically designed to reduce the frequency and severity of attacks. There is a NICE technology appraisal [ID1188] currently underway for another Calcitonin-related gene peptide (CGRP) erenumab that works in a similar manner as Fremanzemab.	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.
	Barts Health NHS Trust and UKCPA	No timescale indicated	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.
	Association of British Neurologist	The appraisal should be considered in a timely manner alongside NICE appraisal for Erenumab. These treatments may be a step change in treatment for migraine with a lesser side effect profile, better adherence profile and equivalent or better efficacy data compared to current therapies for the commonest UK neurological disorder i.e. migraine	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.
	British Association for the Study of Headache	As NICE is already doing TAG for Erenumab, it is important for this to be considered at the same time, if not soon after.	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Teva UK Limited	Suggest amending the following sentence, to include the words photophobia and phonophobia for additional clarification of the symptoms (between brackets): "It is often accompanied by nausea, sometimes vomiting, sensitivity to light *(photophobia)*, sensitivity to sound *(phonophobia),* and/or other sensory stimuli. Suggest removing the sentence: *"It can also include medications, which are generally considered for people who have at least 2 attacks a month, whose attacks are increasing in frequency, whose attacks are increasing in frequency, whose attacks cause significant disability despite abortive treatment, or who cannot take abortive treatment for migraine attacks."* We suggest removing this sentence as neither the NICE clinical guideline nor the NICE technology appraisal guidance 260 refer to these medications.	Comment noted. The background section of scope has been amended. The background section of the scope is only intended to give a brief overview of the condition, its epidemiology and the treatment pathway.
	The Migraine Trust	The sentence 'Factors that can trigger attacks in people susceptible to migraines ..*include but are not limited to hunger, changes of routine travel …'* People with migraine are three time more likely to also have depression. Anxiety is also often co-morbid with migraine. Migraine can be classed as a disability and have a negative impact on a person's quality of life and ability to work.	Comment noted. The background section of the scope is only intended to give a brief overview of the condition, its epidemiology and the treatment pathway.
	Association of British Neurologist	Prophylactic mediation is considered not just on migraine frequency but on headache burden i.e. number of days of headache x severity of attacks. In the UK prophylaxis in general terms is considered if individuals experience 4 or 6 days per month of troublesome migraine/headache per month.	Comment noted. The background section of the scope has been revised.

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	Barts Health NHS Trust and UKCPA	ICHD-3 – instead of International Headache Society - definitions of migraine should be used	Comment noted. The background section of the scope has been revised.
	British Association for the Study of Headache	Prophylaxis is offered based on the disease burden and not just the attack frequency. The burden can be measured through validated scores such as HIT6 MIDAS and EQ5D that takes into account severity and frequency of the attacks and measure days with headache and migraine. Lifestyle measures and trigger management is important but lack of specialist headache nurses in the UK makes this aspect of management difficult considering there are very few headache specialist who are not able to address such issues in the consultation time.	Comment noted. The background section of the scope has been revised.

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The technology/ intervention	Teva UK Limited	Fremanezumab is a fully humanised monoclonal antibody which potently and selectively binds the calcitonin gene-related peptide (CGRP) ligand, a peptide directly involved in the pathophysiology of migraine. Fremanezumab has been and is currently studied in three randomized, placebo-controlled, double-blind, multicenter clinical trials, in episodic and chronic migraine patients: - **HALO trial Episodic Migraine** (NCT02629861) is comparing the efficacy and safety of 2 dose regimens of fremanezumab versus placebo for the preventive treatment of episodic migraine - **HALO trial Chronic Migraine (**NCT02621931) is comparing the efficacy and safety of 2 dose regimens of fremanezumab versus placebo for the preventive treatment of chronic migraine - **FOCUS trial Episodic and Chronic Migraine (**NCT03308968) is evaluating the efficacy, safety, and tolerability of 2 dose regimens of fremanezumab vs. placebo in patients with chronic migraine (CM) or episodic migraine (EM) who have responded inadequately to 2 to 4 classes of prior preventive treatments The FOCUS trial is a phase IIIb clinical study that is currently ongoing and estimated to be finished in Q1 2019.	Comment noted. The technology section of the scope is intended to provide a brief overview of the technology and its clinical trials. The description of the mechanism of action and trial populations has been revised.
	The Migraine Trust	Yes. The description of the technology is a accurate and based on the current available information.	Comment noted.
	Novartis Pharmaceuticals UK Ltd	The following sentence should be updated: *Fremanezumab (brand name unknown, 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*.	Comment noted. The technology section of the scope has been revised.

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	Association of British Neurologist	Yes	Comment noted.
Population	Teva UK Limited	The population is appropriate, to be in line with our submitted licence wording.	Comment noted.
	The Migraine Trust	Yes. The population is defined appropriately. There are no specific groups within this population that should be considered separately.	Comment noted.
	Barts Health NHS Trust and UKCPA	The population only mentions adults with chronic or episodic migraine. For such a new technology, episodic migraine should be considered in terms of high frequency (>10 days/ month) and low frequency (<9 days per month) migraine. The population should consider patients who have failed 3 or more prophylactic treatments in line with NICE TA 260	Comments noted. Subgroups according to frequency of episodic migraine and number of previous prophylactic treatments are included in the 'other considerations section of the scope. No change was made to the scope.
	British Association for the Study of Headache	Episodic Migraine (1-14 days) can be further divided into those with high frequency (8-14 days) that has the same disability as that of chronic migraine.	Comments noted. Subgroups according to frequency of episodic migraine and number of previous prophylactic treatments are included in the 'other considerations section of the scope.

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	Barts Health NHS Trust and UKCPA	Should adults and children over the age of 16 be used?	Comment noted. Fremanezumab will be appraised within its marketing authorisation. No change was made to the scope.
Comparators	Teva UK Limited	The comparators should be "established clinical management for episodic and chronic migraine prophylaxis without fremanezumab, excluding invasive procedures." Exclusion of invasive procedures is in line with the scope of a previous technology appraisal in migraine prophylaxis. Comparators will depend on the patient population and place in therapy for fremanezumab. For episodic migraine patients who have failed on prior oral prophylactics or are intolerant or contra-indicated to oral prophylactics, an appropriate comparison would be fremanezumab plus best supportive care (e.g. acute migraine treatments) vs. best supportive care. It also depends on whether erenumab will be considered as established clinical management by the time of the fremanezumab appraisal. For chronic migraine patients who have not responded to at least 3 prior pharmacological prophylaxis therapies, an appropriate comparison would be fremanezumab plus best supportive care vs. Botulinum toxin type A plus best supportive care. Again, it also depends on whether erenumab will be considered as established clinical management by the time of the fremanezumab appraisal.	Comment noted. Established clinical management should be defined in the company's evidence submission and validated by clinical experts. Best supportive care is listed as a comparator in the scope. Erenumab is listed as a comparator "subject to ongoing NICE appraisal".
	The Migraine Trust	The comparator is the standard treatments currently used in the NHS with which the technology should be compared. • Beta blockers – propranolol, metaprolol, atenolol, nadaolo, timolol	Comment noted. The comparators listed are covered in the scope

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		• Anti 5-HT – pitzotifen, methysergide • Tricyclib antidepressants – amitriptyline, dosulepinm notriptyline • Anti-convulsants – sodium valproate, topiramate, gabapentin • Non-steroidal anti-inflammatory drugs – naproxen • Calcium channel blockers – flunarizine • Angiotensin II blockers – candestartan. There are currently no preventative drug treatment options which are specifically designed to reduce the frequency and severity of migraine attacks. However there is a preventative treatment, another CGRP (erenumab) currently further ahead in the NICE technology appraisal process. How will NICE consider erenumab if outcome of its technology appraisal recommendation is positive, ahead of completion of frenuzamab's technology appraisal?	under "oral preventative treatments". Erenumab is listed as a comparator "subject to ongoing NICE appraisal". Fremanezumab will be appraised in comparison with what is being used in clinical practice at the time of the appraisal. This would include erenumab if it is considered to be established practice at the time of appraising fremanezumab.
	Novartis Pharmaceuticals UK Ltd	The comparison with botulinum toxin type A should state 'Botulinum toxin type A for chronic migraine that has not responded to at least 3 prior pharmacological prophylaxis therapies' as per TA 260. It should be noted that galcanezumab was filed with the EMA prior to fremanezumab in December 2017 and therefore this may also be an appropriate comparator subject to NICE appraisal.	Comment noted. Botulinum toxin type A will be considered an appropriate comparator in line with the committee's recommendation in TA260. Fremanezumab will be appraised in comparison with what is being used in clinical

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			practice at the time of the appraisal.
	Association of British Neurologist	Botulinum toxin A is licenced only for chronic migraine not episodic migraine A number of other standard alternative treatments are not described in the existing NICE guidance CG150 e.g candersartan, There is currently no head-to-head comparison between these options for care to describe which is 'best': overall benefit is based on both efficacy and lack of adverse effects.	Comment noted. Candersartan is covered in the scope under "oral preventative treatments". Details of available evidence to enable a direct and indirect comparison of fremanezumab and comparators will be covered in the company's evidence submission.
	Barts Health NHS Trust and UKCPA	Flunarizine could also be considered as a preventative comparator	Comment noted. Flunarizine is covered in the scope under "oral preventative treatments".
	British Association for the Study of Headache	Oral treatments also include Candesartan that are recommended by other guidelines (SIGN 155). Onabotulinumtoxin is only licensed for chronic migraine There is lack of consensus on what is the best supportive care for patients with migraine.	Comment noted. It is noted that best supportive care could cover a range of treatments and care. It

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			is anticipated that the best supportive care in clinical practice in England would be determined during the appraisal and therefore it is not defined in the scope.
Outcomes	Teva UK Limited	The following outcome should be removed: - Number of cumulative hours of headache or migraine on headache or migraine days. This is not included as a clinical endpoint in the fremanezumab clinical trials. The following outcome should be added: Change in patient depression status. The reason is that depression is an important comorbidity of migraine and should be considered as a meaningful outcome.	Comment noted. 'Change in patient depression status' will be captured in health-related quality of life. The list of outcomes represent a broad range of possible outcomes that have been identified in previous scopes. Any exclusions or inclusions should be appropriately justified in the company's evidence submission.
	Novartis Pharmaceuticals UK Ltd	Yes. These outcomes will capture the most important health related benefits and harms of the technology.	Comment noted.

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	Association of British Neurologist	The subgroup with higher frequency episodic migraine and chronic migraine have historically greater Health related QoL impairment and may see a more clinically effective and cost effective outcomes compared with episodic migraine. It is important that a QoL looking at function, e.g. absenteeism from work, is also considered.	Comments noted. If the evidence allows, subgroups defined by type of migraine and frequency of episodic migraine will be considered. These subgroups are included in the 'other considerations' section of the scope.
	Barts Health NHS Trust and UKCPA	Reduction in most disabling migraine symptom (which may not always be headache) Clear differentiating between what is meant by headache day and migraine day	Comment noted. More specific outcomes can be considered under the broad scope outcomes, as part of the full appraisal.
	British Association for the Study of Headache	No of patients with 30%, 50%, 75% and 100% response rate. 30% for chronic migraine as TA260 use this outcome.	Comment noted. The outcomes listed in the scope do not normally refer to specific measures. The response rates would be captured under frequency of migraine/headache days.

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Economic analysis	Association of British Neurologist	The time horizon for episodic migraine is likely to be different from the time horizon for chronic migraine (CM). The time horizon for episodic migraine should include at least 1-2 years in contrast to CM where the time horizon should be longer and at least 3-5 years	Comment noted. Details of the time horizon will be included in the evidence submission and considered as part of the full appraisal.
	Barts Health NHS Trust and UKCPA	Will consideration be given to the fact that many of the comparator medications are unlicensed and prices can vary widely (with some being imported specially)	Comment noted. Fremanezumab will be appraised in comparison with what is being used in clinical practice at the time of the appraisal. This may include unlicensed and off-label medicines.
	British Association for the Study of Headache	Migraine is a life-long condition. Around 5% patients with episodic migraine become chronic and vice versa per year. Hence the impact on QoL over a long term period is more appropriate (3-5 years).	Comment noted. The reference case defined in the NICE guide to the methods of technology appraisal 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.

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Equality and Diversity	Association of British Neurologist	No issues	Comment noted.
	Barts Health NHS Trust and UKCPA	No mention of treating children	Comment noted. Fremanezumab will be appraised within its marketing authorisation.
	British Association for the Study of Headache	Migraine is more common in women (22% versus 8% in men). Most of the migraine sufferers are in the working age group. The indirect cost of migraine to the economy in general is far higher than the direct cost to the NHS.	Comment noted. Only direct costs should be included, as specified in the reference case defined in the NICE guide to the methods of technology appraisal.
Other considerations	Teva UK Limited	Fremanezumab is a CGRP antibody with a novel mechanism of action, to be used in prevention of migraine in patients with both episodic and chronic migraine, offering a rapid, significant reduction in the frequency of migraine attacks and headaches. Fremanezumab is designed to selectively and potently bind to CGRP, a peptide directly involved in the pathophysiology of migraine. With two dose regimens (monthly and quarterly) of fremanezumab, this technology provides flexibility for patients and physicians in real world. Migraine mostly affects the adult working population (as it is typically occurring in people 20 – 40 years old) and it is more common in females than males. There will be indirect benefits of treatments (e.g. work productivity, school productivity, and ability to care for other household members) that will not be included in the QALY calculation. The HALO trials and FOCUS trial	Comment noted. The mechanism of action, innovation, dosage and any potential significant and substantial health-related benefits not included in the model will be considered during the appraisal.

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		capture work and activity benefits via the Work Productivity and Activity Impairment (WPAI) questionnaire.	
	Association of British Neurologist	Looking at the efficacy in medication overuse headache	Comments noted. If evidence allows, other subgroups not listed in the scope should be presented in the evidence submissions for the committee to consider.
	British Association for the Study of Headache	Those migraine sufferers that are refractory to more than 4 treatments need to be estimated to evaluate the burden of the disease.	Comments noted. If evidence allows, other subgroups not listed in the scope should be presented in the evidence submissions for the committee to consider.
Innovation	The Migraine Trust	Yes. The technology is innovative in its potential to make a significant and substantial impact on the health-related benefits for people living with migraine. It would help improve the way they current need is met. There are currently no preventative drug treatment options which are specifically designed to reduce the frequency and severity of migraine attacks	Comments noted. Innovation will be considered in more detail as part of the full appraisal.
	Association of British Neurologist	Yes – This could be step change in the management of the condition for the following reasons: 1. Better tolerated treatment compared with currently prescribed oral agents for migraine 2. Attractive adherence potential and	Comments noted. Innovation will be considered in more

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		rapid onset of action compared with historical preventative treatments. Clinical trial data will give some of this information. The QALY calculation may not reflect a possible sub-group of 'super-responders' who have excellent results e.g. 75-100% headache response	detail as part of the full appraisal. If evidence allows, other subgroups not listed in the scope should be presented in the evidence submissions for the committee to consider.
	British Association for the Study of Headache	The treatment is innovative as it involves a novel mechanism of action. This is the first ever migraine-specific treatment for prevention (including Erenumab already being appraised by NICE). The side effect profile is comparable to placebo and is well tolerated. The treatment involves once a month subcutaneous injection that can be self-administered that would save considerable time and cost to the patient and healthcare provider. The treatment is likely to have a better compliance than existing treatments.	Comments noted. Innovation will be considered in more detail as part of the full appraisal.
Questions for consultation	Teva UK Limited	**How is fremanezumab expected to be used in clinical practice? Would it be used upfront as an alternative to oral preventive treatments or when there is an inadequate response to oral preventive treatments?** No, fremanezumab is expected not to replace oral preventive treatment, but only to be used following failure to respond to prior oral prophylactic treatments or if these are not tolerated or contra-indicated; no displacement would occur. **Have all relevant comparators for fremanezumab been included in the scope?**	Comment noted. The place in therapy will be considered in more detail as part of the full appraisal. Comment noted. Established clinical

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		The comparators should be “established clinical management for episodic and chronic migraine prophylaxis without fremanezumab, excluding invasive procedures.” Comparators will depend on the patient population and place in therapy for fremanezumab. For episodic migraine patients who have failed on prior oral prophylactics or are intolerant or contra-indicated to oral prophylactics, an appropriate comparison would be fremanezumab plus best supportive care (e.g. acute migraine treatments) vs. best supportive care. It also depends on whether erenumab will be considered as established clinical management by the time of the fremanezumab appraisal. For chronic migraine patients who have not responded to at least 3 prior pharmacological prophylaxis therapies, an appropriate comparison would be fremanezumab plus best supportive care vs. Botulinum toxin type A plus best supportive care. Again, it also depends on whether erenumab will be considered as established clinical management by the time of the fremanezumab appraisal. **Which treatments are considered to be established clinical practice in the NHS for preventing chronic and episodic migraine?** NICE Headache Guidelines (CG150, 2015) recommend offering topiramate or propranolol for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. The ‘Management of Migraine (with or without aura)’ section of the NICE Headache Pathway also states to consider amitriptyline for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse.	management should be defined in the company’s evidence submission and validated by clinical experts. Best supportive care is listed as a comparator in the scope. Erenumab is listed as a comparator “subject to ongoing NICE appraisal” Comments noted. The suggested comparators have been listed in the ‘comparators’ section of the scope.

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		British Association for the Study of Headache (BASH) Guideline recommends various prophylactic treatment options. However, this guideline has not been updated since 2010 and is currently under review. References: • NICE Clinical Guideline. Headaches in over 12s: diagnosis and Management (CG150), September 2012 https://www.nice.org.uk/guidance/cg150 • NICE Pathway, 'Management of Migraine (with or without aura)' https://pathways.nice.org.uk/pathways/headaches/management-of-migraine-with-or-without-aura • BASH - Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine Tension-Type Headache Cluster Headache Medication-Overuse Headache. 3rd edition (1st revision) 2010 http://www.bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf **Are the outcomes listed appropriate?** The following outcome should be removed: - Number of cumulative hours of headache or migraine on headache or migraine days. This is not included as a clinical endpoint in the fremanezumab clinical trials. The following outcome should be added: - Change in patient depression status. The reason is that depression is an important comorbidity of migraine and should be considered as a meaningful outcome.	'Change in patient depression status' will be captured in health-related quality of life. The list of outcomes represent a broad range of possible outcomes that have been identified in previous scopes. Any exclusions or inclusions should be appropriately justified in

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			the company's evidence submission.
		Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom fremanezumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? The subgroups suggested are appropriate. Further sub-group analysis is currently being explored.	No comment
		Where do you consider fremanezumab will fit into the existing NICE pathway, Headaches? Pending the outcome of this appraisal we would envisage that fremanezumab will fit within the "migraine prophylaxis" section of the "Headache" pathway.	Comment noted. The pathway will be agreed by the digital team at NICE.
		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology in practice? If yes, please describe briefly. No barriers to adoption are expected in practice.	Comment noted.
		NICE intends to appraise this technology through its Single Technology Appraisal (STA) process. We welcome comments on the appropriateness of appraising this topic through this process. We agree that STA is the most appropriate process to appraise fremanezumab.	The appraisal has been scheduled into the Technology Appraisal programme.
		Cost comparison: Would it be appropriate to use the cost comparison methodology for this topic? It depends on what is considered the right place of fremanezumab in the treatment pathway and the comparators accordingly. In principle we consider it appropriate to use the cost comparison methodology for this topic.	The appraisal has been scheduled into the

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		Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? Analyses are currently ongoing to explore the comparative clinical efficacy and safety of fremanezumab vs. the comparators after correcting major confounding factors e.g. different definitions of clinical endpoints, different timing of evaluate the clinical endpoints, etc. **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Yes **Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?** As mentioned in the "Technology/intervention" section, the FOCUS trial is ongoing for fremanezumab and results are to be expected in Q1, 2019.	Technology Appraisal programme. This will be assessed in detail as part of the full appraisal. Comment noted. Comment noted.
	The Migraine Trust	The Migraine Trust considers that the following factors may act as barriers to adoption of this technology into practice: **Data:** There is no national prevalence and incidence data recorded for migraine or other neurological conditions in England. This data is essential for CCGs to be able to understand the disease impact of migraine locally and allocate sufficient resources accordingly. The existing Neurology Intelligence Network and local RightCare data sets are inadequate to provide commissioners with a true picture and understanding of the cost migraine locally. *Recommendation: NHS England and the Department of Health should work with the Neurology Intelligence Network (NIN) and the voluntary sector to produce reliable prevalence data for migraine and other neurological*	Comment noted. The remit for this appraisal is to assess the clinical and cost-effectiveness of fremanezumab within its marketing authorisation.

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		conditions. Robust and measurable migraine indicators should be developed for inclusion in key incentive and accountability mechanisms within the NHS. **Commissioner Disengagement**: A 2016 Freedom of Information audit of Clinical Commissioning Groups (CCGs) by the Neurological Alliance clearly shows that the majority are largely disengaged from neurology services and in no position to deliver improved pathways of care - Only 13.9% of CCGs have assessed local costs relating to the provision of neurology services - Only 19.1% have assessed the prevalence of neurological conditions within their area - Only 20.1% of CCGs have made an assessment of the number of people using neurology services locally *Recommendation: NHS England should better engage with CCGs to ensure that they understand their commissioning responsibilities relating to migraine and other neurological conditions.* **Lack of clarity on neurology commissioning:** Specialised commissioned services for neurology have been subject to unacceptable confusion arising from inconsistent statements in the current Manual for Prescribed Specialised Services and the Adult Neurosciences Service Specification. The latter in particular has been misinterpreted by CCGs to mean that they have no neurological commissioning responsibilities, leading to situations where neither CCGs nor NHS England are willing to take responsibility for commissioning certain services, allowing people in need to go without treatment and support. *Recommendation: The Neurosciences Service Specification must ensure clarity of commissioning responsibilities for non-specialised as well as specialised treatments.*	Issues around commissioning and prevalence/incidence data cannot be resolved within the context of a technology appraisal. These issues would need to be directed to the Adoption and Impact team at NICE for further consideration. As part of the evidence submission, the company is expected to

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		Cost: It is anticipated that this monoclonal antibody will be relatively expensive for the NHS and therefore CCGs may be reluctant to fund the treatment for the vast numbers of patients who may benefit from them. The confusion regarding commissioning and the lack of data to determine disease impact locally will exacerbate this. *Recommendations: NHS England and the pharmaceutical company marketing the technology to engage in negotiations regarding cost from the earliest possible opportunity to achieve the best possible deal.*	carry out a budget impact assessment which will be reviewed by NICE with input from NHS England as required.
	Novartis Pharmaceuticals UK Ltd	**How is fremanezumab expected to be used in clinical practice?** *No comment* **Would it be used upfront as an alternative to oral preventive treatments or when there is an inadequate response to oral preventive treatments?** *No comment* **Have all relevant comparators for fremanezumab been included in the scope?** *Please see the comment above in the 'Comparators' section regarding the potential for addition of galcanezumab as an appropriate comparator.* **Which treatments are considered to be established clinical practice in the NHS for preventing chronic and episodic migraine?** *NICE Headache Guidelines (CG150, 2015) recommend offering topiramate or propranolol for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events[1]. The 'Management of Migraine (with or without aura)' section of the NICE Headache Pathway also*	Comment noted. Comment noted. Fremanezumab will be assessed in comparison with what is being used in clinical practice at the time of the appraisal. Comments noted. The suggested comparators have been listed in the 'comparators' section of the scope.

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		states to consider amitriptyline[2] for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Botulinum toxin type A is also recommended as an option for the prophylaxis of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse[3]. British Association for the Study of Headache (BASH) Guideline recommends various prophylactic treatment options[4]. 1. NICE Clinical Guideline. Headaches in over 12s: diagnosis and Management (CG150), September 2012 https://www.nice.org.uk/guidance/cg150 2. NICE Pathway, 'Management of Migraine (with or without aura)' https://pathways.nice.org.uk/pathways/headaches/management-of-migraine-with-or-without-aura 3. NICE TA 260 https://www.nice.org.uk/guidance/ta260 4. BASH - Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine Tension-Type Headache Cluster Headache Medication-Overuse Headache. 3rd edition (1st revision) 2010 http://www.bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf ***Are the outcomes listed appropriate?*** No comments. ***Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom fremanezumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** No comments. ***Where do you consider fremanezumab will fit into the existing NICE pathway, Headaches?*** Pending the outcome of this appraisal we would	Comment noted. Comment noted. Comment noted. The pathway will be agreed

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		envisage that fremanezumab will fit within the 'migraine prophylaxis' section of the 'Headache' pathway.	by the digital team at NICE.
		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope. No comments.	Comment noted.
		Do you consider fremanezumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? No comments.	Comment noted.
		Do you consider that the use of fremanezumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation*?* No comments.	Comment noted.
		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. No comments.	Comment noted.
		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). We consider an STA to be the appropriate NICE assessment route.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. • ***Would it be appropriate to use the cost comparison methodology for this topic?*** A cost comparison methodology would only be appropriate if fremanezumab has similar health effects and similar costs to a NICE approved comparator, and could therefore be recommended for use in the same patient population as that comparator. As we are not the manufacturer of this technology, we cannot comment on whether this is expected to be the case. • ***Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?*** As we are not the manufacturer of this technology, we cannot comment on whether this is expected to be the case. • ***Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?*** No comment • ***Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?*** As mentioned in the comparators section Galcanezumab was filed with the EMA for the prophylaxis of migraine in December 2017 prior to fremanezumab in February 2018.	Comments noted. Fremanezumab will be appraised in comparison with what is being used in clinical practice at the time of the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Neurologist	It is anticipated that such a new technology will be used in secondary care for patients with disabling chronic migraine who have tried at least 3 standard preventative medications. It may be used as an alternative to botulinum toxin treatment, although the anticipated higher cost of fremanezumab may place it to be used after a trial of botulinum toxin. It is not yet known whether fremanezumab will be effective in patients with medication overuse headache but standard practice and other NICE guidelines eg CG150 recommend that patients are appropriately managed for mediation overuse headache before escalating prophylactic treatment options. The question of MOH should be addressed in a NICE appraisal of the treatment. The currently available published randomised placebo controlled phase 3 trial has focussed on chronic migraine (Sildestein et al NEJM 2017: 377 2113); such data is currently lacking for episodic migraine. The outcomes listed are appropriate but 'health-related quality of life' should include reference to the functional impact and the huge economic burden from migraine to the UK economy in terms of absenteeism and reduced productivity at work. Migraine specific questionnaires such as MIDAS reflect these issues to an extent	Comment noted. Subgroups according to number of previous prophylactic treatments are included in the scope. If evidence allows, the appraisal committee will consider other subgroups not included in the scope. The appraisal committee will consider all the available evidence on how fremanezumab will be used in clinical practice, including submissions and testimonies from clinical experts. All aspects of health-related quality of life should be included in the evidence submissions for the committee to consider.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Association for the Study of Headache	We only have data on chronic migraine published by Silberstein et al NEJM 2017;377:3113). Data on episodic migraine is yet to be published. The questions to be answered are: 1. Responder rates (30% in Chronic Migraine) 2. Where this should be placed as the likely cost of the technology may limit its use to those refractory to at least three conventional prophylactics. 3. Whether this should be used before or after Botox. Impact on the QoL scores measured through validated questionnaires such as MIDAS HIT 6	Comment noted. These questions are expected to be addressed in the evidence submissions and in the committee's discussions.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None