National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Erenumab for preventing migraine ID1188

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	ABN	The draft remit appears appropriate.	Comment noted. No action required.
	Migraine Action	Yes. First treatment designed exclusively for migraine for many years.	Comment noted. No action required.
	The Migraine Trust	Yes. It is appropriate to refer this topic to NICE for appraisal.	Comment noted. No action required.
	National Migraine Centre	It is appropriate to refer this topic for appraisal. Migraine causes a substantial disease burden and more effective treatments are required. This new treatment offers potential for major benefit to migraine sufferers who have not benefited from existing approaches	Comment noted. No action required.
	Novartis Pharmaceuticals	We consider it appropriate to refer this topic to NICE for appraisal	Comment noted. No action required.
Wording	The Migraine Trust	Yes. The wording of the remit reflects the issues of clinical and cost effectiveness about this technology or technologies that NICE should consider	Comment noted. No action required.

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	National Migraine Centre	It addresses some of the relevant issues. However, the remit only considers treatment for episodic migraine, in line with the published phase 3 data. The most severe morbidity associated with migraine is however seen patients with chronic migraine	Comment noted. The remit refers to migraine without specifying 'episodic' or 'chronic'. No action required.
	Novartis Pharmaceuticals	The licence wording is currently anticipated to be: [redacted] Therefore, we consider the wording of the remit to be appropriate.	Comment noted. No action required.
Timing Issues	ABN	This appraisal is a potentially important milestone for the treatment of migraine within the NHS. The appraisal will assess the first of potentially 4 new preventative therapies based on CGRP blockade that has been developed solely and specifically for the treatment of migraine (as opposed to adopting their use from another disorder). The appraisal may make available a new treatment for patients 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, affecting patients in the UK.	Comment noted. No action required.
	The Migraine Trust	This is a highly urgent matter. Migraine is highly prevalent and can be extremely disabling. There are currently no preventative drug treatment options which are specifically designed to reduce the frequency and severity of migraine attacks.	Comment noted. No action required.
	National Migraine Centre	It should be considered as urgent in view of the relative lack of effective and well-tolerated treatments for a substantial proportion of patients.	Comment noted. No action required.

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	Novartis Pharmaceuticals	Erenumab offers a novel mechanism of action and is a step change in the prophylaxis of migraine, an area of high unmet need. We therefore believe that timely NICE guidance for erenumab would be valuable to the NHS	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	ABN	We disagree with the last 2 sentences of paragraph 2, Page 1 of the Background session relating to the definition of Chronic migraine. There are established criteria for its recognition which are used operationally in clinical practice by many Neurologists The current preventative treatment groups mentioned are correct (end of Page 1-start Page 2) There is less evidence to support their usage in chronic migraine. Topiramate and Botulinum toxin type A has most data in this area. It is possible that one of these treatments would be displaced if the appraisal data is satisfactory. The background information does not give sufficient information about what proportion of UK migraine sufferers currently use or need preventative medication from one of the subgroups. What proportion use 1, 2 or 3 preventatives without benefit i.e. No background data on the possible migraine population that might be targeted as appropriate to receive this new therapy? It is possible that the background information in the last paragraph on page 1 about the use of prophylactic chronic migraine (CM) medications considered for people who have 2 attacks /month is incorrect and does not make sense and needs clarification & correction.	Comments noted. The background section is only intended to provide a brief description of the disease and current management options. It has been amended to make the distinction between episodic and chronic migraine clearer.

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		In the UK prophylaxis in general terms is considered if individuals experience 4 or 6 days per month of troublesome migraine/headache per month. The definition of CM needs at least 15 days headache per months for > 3 months this need rewriting and revision to make more clear.	
	Migraine Action	Para 3 would include WHO Global Burden of disease study ranking migraine as 5th in UK. Would add that evidence for existing prophylactic treatments is sparse, and that issues with side effects can lead to limited patient compliance.	Comment noted. The background section is only intended to provide a brief description of the disease and current management options. No action required.
	The Migraine Trust	To include in the Background information that amongst others, menstruation is an important migraine trigger factor, and is thought to be the reason, at least in part, why more women than men suffer migraine attacks. Depression and anxiety are co-morbid with migraine, and it is known that many people with migraine do not fulfil their potential in education or career. Migraine can thus have an important and cumulative impact on the quality of life.	Comment noted. The background section has been amended to include menstruation as a trigger factor, and emphasise the impact of migraine on quality of life.
	National Migraine Centre	Additional points to mention 1. Hormonal influences in triggering migraine 2. Better describe episodic vs chronic migraine. 3. Sentence beginning "to fulfil the criteria ..." is slightly inaccurate. It should state five attacks fulfilling criteria for migraine with or without aura. 4. In treatment section suggest change " the antidepressant amitryptiline" to "tricyclics antidepressants such as amitryptiline"	Comments noted. The background section has been amended to include menstruation as a trigger factor and to make the distinction between episodic and

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		5. Suggest add to second paragraph wording to reflect that there is also no clear consensus as to timing or type of treatment for chronic migraine. 5. There is a section on the treatment that begins with "there are 3 broad approaches…" This section is about treatment of chronic migraine but instead seems to describe treatment of episodic migraine. The proposed appraisal is about episodic migraine and not chronic migraine	chronic migraine clearer. The inaccuracy identified under point 3 has been corrected. The paragraph on the management of migraine has been updated in line with NICE clinical guideline 150.
	Novartis Pharmaceuticals	The background information currently focuses on chronic migraine. However, it should also include information about episodic migraine as this is within the remit of 'preventing migraine' and the anticipated marketing authorisation for erenumab. In this respect, it is also important to note that migraine is on a continuum and it is possible for people to move between episodic and chronic migraine.	Comments noted. The background section has been amended to make the distinction between episodic and chronic migraine clearer.
	Novartis Pharmaceuticals	The definition for chronic migraine with aura should be included in the chronic migraine definition.	Comment noted. This inaccuracy has been corrected.
	Novartis Pharmaceuticals	The significant impact of migraine on health-related quality of life and work productivity are important aspects of this condition that are not covered in the background section. Migraine is the seventh most disabling disorder amongst all disease and the leading cause of disability among all neurological disorders1,2 and represents a significant burden to the NHS and UK society.	Comment noted. The background section has been amended to emphasise the impact of migraine on quality of life.

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	Novartis Pharmaceuticals	Current NICE Clinical Guidelines do not recommend treatment with calcium channel-blockers or serotoninergic modulators.3-4	Comment noted. The paragraph on the management of migraine has been updated in line with NICE clinical guideline 150.
The technology/ intervention	ABN	Yes	Comment noted. No action required.
	The Migraine Trust	Yes. The description of the technology is accurate based on the current available information.	Comment noted. No action required.
	National Migraine Centre	The description seems accurate. Suggest the first sentence is altered to read "…the action of calcitonin…" rather than "…the activity of calcitonin	Comment noted. The scope has been amended to reflect this comment.
	Novartis Pharmaceuticals	The population studied within the erenumab clinical trial programme includes both chronic and episodic migraine. Therefore, the information in this section should also explicitly reference erenumab being investigated in chronic migraine. Data in chronic migraine has recently been published[5]. This large phase II study meets all methodological standards for a phase III study for regulatory purposes. Information on the efficacy and safety of erenumab in chronic and episodic migraine has been included in the European regulatory submission and the licence is not anticipated to differentiate between episodic and chronic migraine wording. It is anticipated to state: [redacted]	Comments noted. The scope has been amended to reflect this comment.

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		The following sentence should be changed to: It has been studied in clinical trials, compared with placebo, in adults with both episodic and chronic migraine. The trials excluded people who had no therapeutic response with more than 2 (in episodic) or 3 (in chronic migraine) prophylactic treatments. The following sentence should be changed to state: Erenumab works by binding to the CGRP receptor that is believed to transmit signals that can cause severe pain. [redacted] 5. Tepper, S. et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol, 2017 Jun;16(6):425-434	
Population	ABN	The population only appears to mention episodic migraine. It does not mention patients with currently defined “chronic migraine”. The technology has been studied in both groups. The appraisal should look at “all migraine “groups and not just lower frequency. The population mentions only patients who have failed 2 or more prophylactic treatments. There are 5 evidence based treatments for episodic migraine and NICE TA 260 looks at non-response to at least 3 types of prophylactic agents. Thus there needs to be some justification or consideration around its effect in these different treatment response populations to reflect real word clinical practice.	Comments noted. The population in the scope has been broadened to include both episodic and chronic migraine, and wording amended to describe the populations included in the clinical trials.

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	The Migraine Trust	Yes. The population is defined appropriately. There are no specific groups within this population which should be considered separately.	Comment noted. The population in the scope has been broadened to include both episodic and chronic migraine.
	National Migraine Centre	Population is defined appropriately through should add note on diagnosis on HIS criteria	Comment noted. The population in the scope has been broadened to include both episodic and chronic migraine.
	Novartis Pharmaceuticals	The population is incorrectly defined. It should align with the remit of the appraisal for prevention of migraine in adults. The wording in this section should state either: 'Adults with migraine' or 'Adults with episodic or chronic migraine', and the phrase 'history of' should be omitted to align with the anticipated licence wording. Please also see our response to 'the technology/intervention' above for supporting rationale.	Comments noted. The population in the scope has been broadened to include both episodic and chronic migraine.
Comparators	ABN	The comparator is currently suggested as "established clinical management without Erunumab" is appropriate It would be additionally useful to consider /compare "established clinical management with the addition of Erunumab" to current therapies.	Comments noted. Erenumab would be appraised, within its marketing authorisation, in line with how it would be used in clinical

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			practice. No action required.
	Migraine Action	Prophylaxis should include Candesartan	Comment noted. Established clinical management without erenumab is expected to include treatments used to manage migraine in the NHS. The committee will consider the appropriateness of the treatments included as established clinical management based on the available evidence. No action required.
	The Migraine Trust	Yes. The comparator is the standard treatments currently used in the NHS with which the technology should be compared. There are currently no preventative drug treatment options which are specifically designed to reduce the frequency and severity of migraine attacks.	Comment noted. No action required.
	National Migraine Centre	Yes. A number of standard alternative treatments are not described in the existing NICE guidance CG150	Comment noted. No action required.
	Novartis Pharmaceuticals	The comparators should be 'established clinical management for migraine prophylaxis without erenumab, excluding invasive procedures' Exclusion of invasive procedures is in line with the scope of a previous technology appraisal in migraine prophylaxis.[6]	Comments noted. The comparator in the scope has been amended to

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		Comparators may vary according to patient population and place in therapy. For people who have failed on prior oral prophylactics or are intolerant to oral prophylactics, an appropriate comparison would be erenumab plus best supportive care (e.g. acute migraine treatments) versus best supportive care alone.	'established clinical management for migraine prophylaxis without erenumab'. Consultees are expected to define what they consider to represent established clinical management in their evidence submission. Erenumab would be appraised, within its marketing authorisation, in line with how it would be used in clinical practice.
Outcomes	ABN	The outcomes are fairly standard outcomes. It would be useful to ensure that Health related QoL change is due to change in the suggested parameters and not any other reason. 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	Comments noted. If the evidence allows, subgroups defined by the frequency of episodic migraine will be considered.
	Migraine Action	Reduction of frequency of attacks & subsequent effectiveness of rescue medication and reduction in use of rescue medication	Comment noted. These additional outcomes are covered by the outcomes listed in the

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			scope. No action required.
	The Migraine Trust	Yes. These outcomes will capture the most important health related benefits (and harms) of the technology.	Comments noted. No action required.
	National Migraine Centre	Suggest include specific headache measures such as Hit-6 scores	Comment noted. The outcomes do not normally refer to specific measures. No action required.
	Novartis Pharmaceuticals	We consider the specified outcome measures to be appropriate. An additional outcome measure is response to treatment	Comment noted. This outcome is covered by the outcomes listed in the scope. No action required.
Economic analysis	ABN	Migraine is a lifelong condition most prevalent between adolescence and the 5th -6th decades of life. Approx. 3% of population into the 7-8th decade 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. The baseline data from the multiple studies of CM could be used to give a median or mean estimate of the duration such patients live with active chronic migraine to help with defining an appropriate time horizon.	Comment noted. The company would be expected to choose a time horizon long enough to reflect any differences in costs or outcomes between the technologies being compared. No action required.
Equality and Diversity	ABN	No obvious issue	Comment noted. No action required.

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	Novartis Pharmaceuticals	Limiting the population to adults with episodic migraine and not including people with a chronic migraine (see comments on 'population') could lead to equality issues. Data in chronic migraine has recently been published5 and this large phase II study meets all methodological standards for a pivotal study for regulatory requirements. The chronic migraine population will be included in the anticipated erenumab licence and these patients have significant disease burden and unmet need.	Comment noted. The population in the scope has been broadened to include both episodic and chronic migraine.
Innovation	ABN	Yes – This could be step change in the management of the condition for the following reasons: 1. First treatment studied on the basis of an understood biological mechanism in migraine. 2. Best tolerated treatment compared with currently prescribed oral agents for migraine 3. Attractive adherence potential and rapid onset of action compared with historical preventative treatments. Clinical trial data will give some of this information. There needs to be comparison with data on the other agents to compare efficacy vs. adherence vs. outcome to help try to answer this question.	Comment noted. Consultees are encouraged to describe the innovative nature of erenumab in their evidence submission to NICE. No action required.
	Migraine Action	Possibly yes. It may be that a sub group of responders have excellent results where others could be compared to standard treatments. May be a possibility to see quickly whether an individual is a "super responder"	Comment noted. Consultees are encouraged to describe the innovative nature of erenumab in their evidence submission to

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			NICE. No action required.
	The Migraine Trust	Yes. The technology is 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. There are currently no preventative drug treatment options which are specifically designed to reduce the frequency and severity of migraine attacks.	Comment noted. Consultees are encouraged to describe the innovative nature of erenumab in their evidence submission to NICE. No action required.
	National Migraine Centre	Yes	Comment noted. Consultees are encouraged to describe the innovative nature of erenumab in their evidence submission to NICE. No action required.
	Novartis Pharmaceuticals	Erenumab offers a novel targeted mechanism of action and is a step change in the prophylaxis of migraine, an area of high unmet need. It binds to the Calcitonin-Gene-Related-Peptide (CGRP) receptor, thereby inhibiting its activation by CGRP. Through its receptor, CGRP is thought to be pivotal in the genesis of migraine. Existing prophylactic treatments have been repurposed from other indications whereas erenumab is the first molecule to have been specifically developed and investigated for migraine prophylaxis.	Comment noted. Consultees are encouraged to describe the innovative nature of erenumab in their evidence submission to NICE. No action required.

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		Migraine typically affects younger people, with onset typically occurring in 20-40 year olds and it is more common in females than males. As such there are likely to be indirect benefits of treatment (such as work productivity and ability to care for other household members) that will not be included in the QALY calculation. The erenumab clinical trial programme captured work productivity benefits via the WPAI-GH (Work productivity and Activity Impairment General Health).	
Other considerations	ABN	Need to ensure that chronic migraine as well as episodic migraine is covered by the appraisal given there is data on Erunumab in both episodic and chronic migraine. Need to look at whether Erunumab therapy in migraine is affected my analgesic medication overuse or not and evaluate whether this needs to be addressed (similar to Botox) or not given this is a major issue and was mentioned in NICE CG150 and in NICE TA 260	Comment noted. The population in the scope has been broadened to include both episodic and chronic migraine.
	Migraine Action	Subgroups – those with chronic migraine followed by high frequency/impact episodic. NICE pathway? Depends on price/efficacy/AE data. Presumably after failure of 2/3 standard preventative medications	Comment noted. If the evidence allows, subgroups defined by the frequency of episodic migraine will be considered.
Questions for consultation	ABN	The place of Erunumab in the NICE pathway is difficult to predict. On initial data assessment the efficacy in low frequency episodic migraine appears similar to oral prevention and the Responder rate data in chronic migraine appears as good if not better that oral prevention but similar to Botulinum toxin type A. The adherence is much better. I would this envisage Erunumab as being ascend line agent similar to Botulinum toxin type A after initial oral	Comment noted. No action required.

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		therapy. It`s place in Medication overuse headache management also will need consideration The order is which they suggested deserve discussion and data review.	
	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 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	Comments noted. Consultees are encouraged to include any factors that may affect the adoption and implementation for this technology in their evidence submission for the appraisal committee's consideration.

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		- 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. 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.	

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	Novartis Pharmaceuticals	<u>Which treatments are considered to be established clinical practice in the NHS for treating migraine?</u> 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[3]. The 'Management of Migraine (with or without aura)' section of the NICE Headache Pathway also states to consider amitriptyline[4] 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. British Association for the Study of Headache (BASH) Guideline recommends various prophylactic treatment options[7]. However this guideline has not been updated since 2010 and is currently under review. 3. NICE Clinical Guideline. Headaches in over 12s: diagnosis and Management (CG150), September 2012 https://www.nice.org.uk/guidance/cg150 4. NICE Pathway, 'Management of Migraine (with or without aura)' https://pathways.nice.org.uk/pathways/headaches/management-of-migraine-with-or-without-aura 7. 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 <u>Are there any treatments that would be displaced if erenumab was recommended?</u>	Comments noted. The background section of the scope reflects the current management of migraine described in this comment. If the evidence allows, subgroups defined by the number of previous prophylactic treatments will be considered. Consultees are encouraged to describe the innovative nature of erenumab in their evidence submission to NICE.

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		This depends on the populations or place in therapy at which erenumab is considered for use. At earlier treatment steps, some of the treatments described in the guidelines mentioned above could be displaced. However, after prior oral prophylactic treatments, or if oral prophylactic treatments are not appropriate e.g. due to contraindications or safety concerns, no displacement would occur (see also comments on 'Comparators'). <u>Are the outcomes listed appropriate?</u> Please see the 'Outcomes' section of our response. <u>Are there any subgroups of people for whom erenumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?</u> This is currently being explored. It is expected that subgroups relating to the number of prior oral prophylactic treatments will be analysed. Final study results are currently being analysed which may identify relevant sub-groups. <u>Where do you consider erenumab will fit into the existing NICE pathway?</u> Pending the outcome of this appraisal we would envisage that erenumab will fit within the 'migraine prophylaxis' section of the 'Headache' pathway. See also our comments on the earlier question regarding which treatments would be displaced if erenumab was recommended. <u>Do you consider erenumab to be innovative in its potential to make a significant impact of 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?</u>	

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		Erenumab will be a step-change in the management of migraine. Existing preventive therapies have been repurposed from other indications and are often associated with poor tolerability and lack of efficacy, which lead to increasing discontinuation rates and dissatisfaction among patients. Erenumab is expected to be the first preventative therapy specifically designed to block the CGRP receptor, which is a critical target in the pathophysiology of migraine. It is anticipated to have rapid onset of efficacy and an improved safety and tolerability profile compared to the current standard of care that will lead to a better potential to sustain efficacy in this chronic disorder. <u>Do you consider that the use or erenumab can results in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?</u> Migraine is most common in the 20-40 year age group. As such, there will be health-related indirect benefits of treatment (such as work productivity) that will not be included in the QALY calculation. Please also see our comments on 'Innovation'. <u>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.</u> The STA process is the appropriate route for the appraisal of erenumab.	
Additional comments on the draft scope	Royal College of Physicians	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the ABN.	Comment noted. No action required.

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

None.