National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Anifrolumab for treating active autoantibody-positive systemic lupus erythematosus ID3804

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	AstraZeneca	It is appropriate for this topic to be referred to NICE	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	Yes [appropriate]	Comment noted. No changes to the draft scope required.
	LUPUS UK	Yes, it is very appropriate to refer this topic to NICE for appraisal. Anifrolumab is a new medication for people with systemic lupus erythematosus (SLE) which would increase the range of available treatment options for the management of this chronic and often debilitating disease. Approximately 10 to 15% of people with SLE continue to have high disease activity despite standard therapy and therefore additional treatment options are needed.	Comments noted. No changes to the draft scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	We believe it is appropriate to refer this topic for appraisal.	Comment noted. No changes to the draft scope required.
Wording	AstraZeneca	Yes the wording is appropriate	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	Yes [appropriate]	Comment noted. No changes to the draft scope required.
	LUPUS UK	No comment.	Comment noted. No changes to the draft scope required.
	NHS England	We believe that the wording of the remit does reflect the issues that NICE should consider.	Comment noted. No changes to the draft scope required.
Timing Issues	AstraZeneca	We consider this appraisal to be urgent for the following reasons: 1.Anifrolumab will provide substantial health benefits to relevant patients. 2. Given the relative paucity of available treatment options for patients with SLE it would be of great benefit to them to have anifrolumab available as soon as possible	Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society of Rheumatology	There remains no definitive treatment for lupus, which causes considerable morbidity and is potentially life-threatening. There is much reliance on corticosteroid treatment which is associated with unacceptable iatrogenic complications such as infection, cardiovascular disease and osteoporosis. Access to current biological therapies for lupus (Belimumab and Rituximab) is highly restricted and access to additional clinically effective treatments is still required.	Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.
	LUPUS UK	No comment.	Comment noted. No changes to draft scope required.
	NHS England	While not urgent we believe this appraisal is an important one for consideration	Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	Accurate and appropriate	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	Broadly speaking this is complete.	Comment noted. No changes to the draft scope required.
	LUPUS UK	The background information inaccurately includes “biological DMARDs such as rituximab and belimumab” as standard therapies. The background information does not include cyclophosphamide as a standard therapy. This needs to be included. This is especially relevant because a significant proportion of SLE cases are young women and cyclophosphamide can potentially reduce fertility. The background information does not currently state the average age of disease onset. This is typically between the ages of 15-55 and is relevant because most people are of working age when initially diagnosed. As a result, lupus can have a significant impact on the education and employment of patients. In a recent LUPUS UK online survey, approximately 58% of respondents indicated that they found maintaining employment ‘difficult’ or ‘very difficult’. RAIRDA’s 2018 report “Reduce, Improve, Empower” showed that 25% of respondents to their survey indicated that either they or their partner/carer had reduced working hours as a result of their condition. A further 20% reported that either they or a partner/carer had been forced to give up working due to their condition.	Comments noted. Rituximab and belimumab have been removed as ‘standard therapies’ in the background. The draft scope also states that “*Approximately 10 to 15% of people with systemic lupus erythematosus continue to have high disease activity despite standard therapy and are treated with rituximab or belimumab”.* Cyclophosphamide is listed as a treatment option in the scope under conventional

Section	Consultee/ Commentator	Comments [sic]	Action
			disease-modifying anti-rheumatic drugs (DMARDs). The background section is intended to give a brief summary and therefore no changes are required to the description of the condition. NICE committee will consider all relevant impacts of the new technology within its marketing authorisation.
	NHS England	We consider this to be accurate and complete.	Comment noted. No changes to the draft scope required.
The technology/ intervention	AstraZeneca	Accurate and appropriate	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	Yes [accurate]	Comment noted. No changes to the draft scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	LUPUS UK	No comment.	Comment noted. No changes to the draft scope required.
	NHS England	Yes [accurate]	Comment noted. No changes to the draft scope required.
Population	AstraZeneca	Yes, this reflects the anticipated licence population for the technology	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	Yes [appropriate]	Comment noted. No changes to the draft scope required.
	LUPUS UK	The population within the draft scope only includes adults with “active autoantibody positive” SLE. It does not state which autoantibodies would be required within the population. Will this be defined as positive anti-double-stranded DNA, to match similar guidance for belimumab and rituximab in treating adults with SLE? Approximately 80% of SLE patients with active, untreated disease have positive tests for anti-double-stranded DNA. In many cases patients will already be receiving standard therapy and therefore the prevalence of those who are antibody positive will be lower than 80%. The population within the draft scope will therefore exclude a group of patients with active disease.	Comments noted. NICE will appraise anifrolumab within the population outlined in its marketing authorisation. No changes to the draft scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	Yes [population is appropriate]. No [no subgroups within this population that should be considered separately].	Comment noted. No changes to the draft scope required.
Comparators	AstraZeneca	Accurate and appropriate	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	There is no single drug comparator appropriate for comparison with anifrolumab as different manifestations of lupus are typically managed using different drugs. Standard therapy, as much as it can be defined, would generally consist of a combination of a conventional oral immunosuppressant (typically mycophenolate mofetil, azathioprine or methotrexate) combined with hydroxychloroquine and corticosteroid. Cyclophosphamide is still used for severe disease as standard of care, although a number of serious treatment-related issues mean this is far from an ideal treatment (including potential affect on fertility which is relevant given most patients with lupus are young women; possible increased cancer risk with higher cumulative doses). Topical therapies could be added for patients with cutaneous disease. All the above options were permissible as ‘standard care’ in the key phase III anifrolumab clinical trial). Biologic treatments for lupus (Rituximab and Belimumab) are approved for more severe refractory lupus providing certain criteria are met. There will be no data to specifically support comparisons between anifrolumab and belimumab or rituximab at this stage.	Comments noted. The description of standard care in the scope is in line with the comment. The NICE committee will look at all relevant clinical evidence. No changes to the draft scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	LUPUS UK	"Standard therapy with belimumab" has been listed as a comparator, but it should be noted that this treatment is undergoing a NICE technology appraisal and has only been available for patients in England through the Managed Access Agreement or other clinical trials at specialist centres. "Standard therapy with rituximab" has been listed as a comparator, but it should be noted that this is an unlicensed treatment for lupus and is only available for patients with active, auto-antibody positive SLE which is refractory. It is also worth noting that rituximab is recognised as a treatment which can reduce the efficacy of vaccinations. With the advent of COVID-19, it is entirely possible that people with SLE will require more frequent vaccinations and booster jabs, especially when combined with programmes for other circulating viruses such as influenza. If the frequency of essential vaccinations continues to increase it will reduce the viability of rituximab. Due to the varied presentation and response to treatment in lupus, there is not a particular therapy that could be described as 'best' at present.	Comments noted. The draft scope has been updated to note that belimumab is available via a managed access agreement and that the technology is subject to an ongoing NICE appraisal. The draft scope states that "*Approximately 10 to 15% of people with systemic lupus erythematosus continue to have high disease activity despite standard therapy and are treated with rituximab or belimumab*". The NICE committee will consider all relevant comparators and clinical evidence for this appraisal.
	NHS England	Yes, these are the standard treatments currently.	Comment noted. No changes to the draft scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Outcomes	AstraZeneca	Yes. The outcomes are appropriate and will capture the most important benefits of the technology	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	Yes – a focus on steroid reduction is important. Although possibly captured by the outcome 'corticosteroid use' it may be appropriate to actually specify a 'low-corticosteroid remission' (British Society of Rheumatology (NICE approved) specifically recommend a target dose of Corticosteroid ≤ 7.5 mg Prednisolone. NICE should also be aware of the possibility different elements of the disease may respond better than others, but clinical trials may be underpowered to elucidate this in detail and it may get 'lost' when looking at composite endpoints. The key anifrolumab phase 3 trial for example suggests that cutaneous lupus may respond particularly well. Cutaneous outcomes are worth adding specifically.	Comment noted. The outcomes in the draft scope are not intended to be an exhaustive list. The NICE committee will consider relevant outcomes and disease subgroups. No changes to the draft scope required.
	LUPUS UK	Health-related quality of life (HRQoL) should be an outcome measure, but the way it is measured needs to be appropriate for lupus patients. A study has indicated that not all HRQoL measures are as sensitive to changes in disease or treatment. In particular, EQ-5D is noted as lacking sensitivity or failing to capture important aspects of health in SLE. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6178935/#b20-prom-9-339 The outcome measures in the draft scope do not appear to take into account the impact upon carers and/or close family of changes to the patient's condition from their medication.	Comments noted. The NICE committee will consider the appropriateness of outcome measures used to capture HR-QoL in this condition. The NICE committee can consider health-related quality of life impacts on carers as stated in the NICE methods guide. No

Section	Consultee/ Commentator	Comments [sic]	Action
			changes to the draft scope required.
	NHS England	Yes [appropriate].	Comment noted. No changes to the draft scope required.
Economic analysis	AstraZeneca	The time horizon for the economic analysis will be a lifetime perspective	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	Important to consider UK data The scope stipulates a 'long' horizon which we would agree with. No specific timeframe is suggested, but lupus is a relapsing and remitting disease and the true value of treatments may take a long time to understand. We would note specific scenarios in which the economic impact of lupus may be particularly important – for example meeting the costs of renal replacement therapy/transplantation in patients developing end-stage kidney disease due to lupus nephritis (currently about 10% of nephritis patients – 2-4% of lupus in total). Similarly 'standard of care' cyclophosphamide can be associated with infertility of this population of predominantly young women – marked costs in infertility care.	Comments noted. The NICE committee will consider relevant characteristics of the condition and the impact of the new technology in its decision-making. No changes to the draft scope required.
	LUPUS UK	It is important to use an appropriate measure for "quality-adjusted life year". As mentioned in our comments in the 'outcomes' section, some measures for quality of life are not necessarily sensitive enough for lupus patients.	Comments noted. The NICE committee will consider the appropriateness of outcome measures used to capture HR-QoL in this condition.

Section	Consultee/ Commentator	Comments [sic]	Action
			No changes to draft scope required.
	NHS England	No appropriate time horizon was provided in the scope but we agree with the following statement: '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'	Comment noted. No changes to the draft scope required.
Equality and Diversity	AstraZeneca	No equality measures are identified	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	All patients with any autoantibody-positive lupus should have access to anifrolumab.	Comment noted. NICE will appraise the technology within its marketing authorisation. No changes to the draft scope required.
	LUPUS UK	SLE affects people of all ethnic groups but is more prevalent in people of African, Caribbean and Asian heritage. People from these ethnic groups are also more likely to experience severe disease and higher rates of premature mortality. There are some important considerations that must be made for these groups of patients: • Double-stranded-DNA antibodies are less common in patients of African descent, so it could be perceived as discriminatory to stipulate dsDNA antibody positivity as a criterion and not consider other lupus-related antibodies.	Comments noted. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. NICE will appraise anifrolumab within its marketing

Section	Consultee/ Commentator	Comments [sic]	Action
		• People from these ethnic groups are already at a high risk of developing diabetes and hypertension. If anifrolumab is a steroid-sparing treatment it could have additional advantages over standard treatments by reducing some adverse effects and risks of comorbidities. At present, the other biologic treatments used within this population are only made available through specialist centres. A Rare Disease UK study (https://www.rarediseasе.org.uk/media/1601/centres-of-excellence.pdf) has previously shown that only 27% of patients with rare diseases are cared for in specialist centres. This presents a barrier to access for some patients who may live a considerable distance from a specialist centre or have difficulty travelling due to their ill-health and/or disability. As such, those living in more remote parts of the country or with mobility issues may be less likely to benefit from a treatment if it continues to be administered only at specialist centres by IV infusion. Treatments that are administration by IV infusion at specialist centres may also present a barrier to access for some patients of working age. The frequency and duration of infusions (with additional travelling time) can incur a considerable amount of time away from the workplace. Many lupus patients are of working age and may choose not to access this treatment if they fear their employment may be put at risk by regular absences.	authorisation. No changes to the draft scope required.
	NHS England	SLE disproportionately affects women rather than men, and it is more common in black and Asian women. Access to effective treatments is therefore important in addressing health inequalities faced by these groups. Some immunosuppressants work better in certain ethnic groups compared with others, hence the importance of having options available for different cohorts.	Comments noted. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider

Section	Consultee/ Commentator	Comments [sic]	Action
			population. No changes to the draft scope required.
Other considerations	AstraZeneca	None	Comment noted. No changes to the draft scope required.
	British Society of Rheumatology	Clinical trial evidence suggests Anifrolumab may be more effective (but not exclusively effective) in patients displaying a high 'interferon signature'. 'Interferon signature' testing remains a research tool rather than a 'standard of care' test. Whether use of this test should be accredited and be more widely available in clinical practice could perhaps be considered in the scope of this appraisal.	Comment noted. The committee will consider all relevant evidence submitted. No changes to the draft scope required.
	LUPUS UK	No comment.	Comment noted. No changes to the draft scope required.
	NHS England	We have no additional suggestions.	Comment noted. No changes to the draft scope required.
Innovation	AstraZeneca	Yes. Anifrolumab is innovative; and represents a step-change both in its potential to make a significant impact on health-related benefits; and its potential to improve how the current need is met for SLE patients	Comment noted. The innovative nature of the technology will be considered by the committee based on evidence presented to it. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society of Rheumatology	Yes this is innovative; QALY calculation/comparison with standard therapy will not incorporate the long term consequences of adverse events from increased corticosteroids that will develop increasingly over many years as a consequence of high dose corticosteroids during active lupus disease and from chronic moderate dose use over many years that may be reduced by this new therapy. There is extensive data about the risk of accumulating damage from long term corticosteroid usage in lupus patients and there is data supporting the steroid-sparing properties of anifrolumab.	Comment noted. The innovative nature of the technology will be considered by the committee based on evidence presented to it. No action required.
	LUPUS UK	This medication does appear to be innovative in its approach to treating SLE in adults. Previous biologic treatments approved for use in lupus have targeted B-cells or their receptors, but this is a novel approach which will hopefully present a new hope for people with refractory lupus which has not responded to standard therapy or who cannot tolerate some treatments. There have been very few new treatments made available for people with lupus, with anifrolumab joining belimumab as the only medications specifically licensed for the disease in approximately 60 years. This medication represents hope to lupus patients that new treatments can be developed. The impact of an appraisal on the lupus drugs market needs to be carefully considered. To decline a treatment that is working for patients could result in a reduction of investment in new therapies and innovation that could further disadvantage this patient group.	Comment noted. The innovative nature of the technology will be considered by the committee based on evidence presented to it. No action required.
	NHS England	Yes. Some patients do not respond to conventional Disease-modifying antirheumatic drugs (DMARDs), and/or rituximab and belimumab and so continue to require treatment with high doses of prednisolone (and experience the consequent drug toxicity) and accrue irreversible organ damage.	Comment noted. The innovative nature of the technology will be considered by the committee based on

Section	Consultee/ Commentator	Comments [sic]	Action
			evidence presented to it. No action required.
Questions for consultation	AstraZeneca	**Do you consider that the use of anifrolumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** There is significant use of oral corticosteroids (OCS) within SLE, which cause significant long term adverse events. While we will endeavour to model this to the best of our ability, it is likely that some of these adverse events will be unquantified and therefore will underestimate the benefit of anifrolumab on reducing the need for and use of OCS	Comments noted. No changes to the draft scope required.
	British Society of Rheumatology	Questions for consultation that have not been answered above are: 1) *Are people with active SLE clinically identifiable and distinguishable* – yes they are. The SLEDAI and BILAG disease activity indices can be used to define active SLE (BILAG index probably preferable in clinical practice as it captures a much wider range of disease features and forms the basis of the outcome measure in the positive anifrolumab clinical trial). 2) *Where would anifrolumab fit in to existing NICE pathway* – the challenge as always is that clinical studies focus on front-line use, alongside standard of care for a relatively treatment naïve population, whereas experience suggests that to be cost effective NICE may wish to apply more stringent criteria. Pragmatically it would seem reasonable to position anifrolumab as 'add-on' therapy to patients with persistent lupus disease activity following a reasonable trial (say 6 months) of standard of care therapy. Based on current evidence it would not be appropriate to recommend Anifrolumab for patients with renal or neurological disease. Rituximab would remain a preferred	Comments noted. No changes to the draft scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		first-line biologic for renal disease. Anifrolumab would therefore position as an alternative to belimumab for non-renal, non-neurological lupus and further clinical experience/trial evidence would have to determine order of usage. Currently Belimumab usage guidelines stipulate positivity for both positive dsDNA antibodies and low complement levels. There seems no rationale for doing this with anifrolumab as the trials did not segregate patients like this. There is evidence of greater efficacy of anifrolumab in patients with a high 'interferon signature', but currently testing this is not a standard clinical lab test – whether it should be is a point for discussion.	
	LUPUS UK	All questions we can answer have been discussed within the appropriate topic headers above.	Comment noted. No changes to the draft scope required.
	NHS England	Is cyclophosphamide used to treat active autoantibody positive SLE in clinical practice in the NHS? Yes IV cyclophosphamide is still used to treat severe active SLE particularly patients with severe glomerulonephritis and cerebral lupus. Which treatments are considered to be established clinical practice in the NHS for active autoantibody positive SLE? A combination of the following are used hydroxychloroquine, mepacrine, prednisolone/IV methylprednisolone/topical steroids/intra-articular steroids and intramuscular steroids, mycophenolate, methotrexate, azathioprine, ciclosporin, IV cyclophosphamide, rituximab and belimumab. The treatment chosen depends upon severity of disease activity, the organ involved and previous treatments that have been tried and the previous response.	Comment noted. No changes to the draft scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are people with active SLE clinically identifiable and distinguishable? What are the clinical criteria for active SLE? Disease activity tools are used such as the BILAG disease activity index and SLEDAI to record disease activity in different organ systems to provide an overview of whether a patient's disease is improving, stable or deteriorating. ESR, dsDNA antibodies , C3 and C4 are also checked to look for disease activity. Patients can have mild, moderate or severe flares. Active disease is implied if a patients has one or more B scores on the BILAG or SLEDAI of 4 or more. Where do you consider anifrolumab will fit into the existing NICE pathway, systemic connective tissue conditions? As an alternative to belimumab and rituximab. It may depend upon the patient's interferon signature.	
Additional comments on the draft scope	NHS England	1. Regarding related NHSE clinical commissioning policies it should be 'Rituximab for refractory SLE in adults and post pubescent children [200402P] which was published on 9th July 2020 and not 2014.	Comment noted. This error has now been corrected.

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

GlaxoSmithKline (GSK)