National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (review of TA397) [ID1591]

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	GlaxoSmithKline	GSK would like the remit to read: To appraise the clinical and cost effectiveness of belimumab within its licensed indication for the treatment of active autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (HDA).	Comment noted. The remit notes that belimumab will be appraised "within its licensed indication". The scope table has been revised to clarify this.
	British Society of Rheumatology	Yes	Comment noted.
	Lupus UK	No comment	Comment noted.
	NHS England Specialised Rheumatology Clinical Reference	Yes	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Group		
	Renal Association	The wording is fine.	Comment noted.
Timing Issues	GlaxoSmithKline	There remains a significant unmet need for more patients with SLE, who continue to have HDA despite standard therapy, to have access to a licensed and effective therapy. Currently, belimumab powder for concentrate for solution for infusion [intravenous (IV) formulation] is only recommended in a small proportion of SLE patients with HDA (TA397) and therefore there continues to be a significant proportion of patients who fall outside of this criteria who remain under-treated. During the COVID-19 pandemic, patients with SLE receiving belimumab intravenously were deemed to be at a high-risk for infection and required to self-isolate +/- shield (NHS April 2020, Publications approval reference: 001559). Therefore, GSK has temporarily made available belimumab 200 mg solution for injection in pre-filled pen to allow treatment continuation through self-administration at home, demonstrating the importance of having an alternative administration route available for such circumstances. In the future, the pre-filled pen will also enable eligible patients who are not geographically positioned near a specialist centre, have difficulty taking time off work, or prefer to self-administer their medication, to have access to an appropriate treatment option in a non-hospital setting. Therefore, GSK believes the timing of this appraisal should be considered with relative urgency to ensure patients with SLE, who continue to have high disease activity despite standard therapy, gain access to an alternative treatment option with two available formulations to suit the patient's individual	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.

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		circumstances and needs.	
	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. At present few patients are able to access Belimumab due to stringent criteria for usage put in place in the UK. Even for those meeting criteria the current 'managed access' requirements including a clause that patients may be withdrawn from therapy based on future appraisals even if effective for individual patients. There is therefore some urgency to resolve this uncertainty for patients.	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.
	Lupus UK	It is very important that this appraisal is completed prior to the end of the existing Managed Access Agreement. We hope that eligible patients in need of this treatment will be able to access it, without any gaps in provision.	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.
	NHS England Specialised Rheumatology Clinical Reference Group	Patients can currently access use of IV belimumab through the managed access agreement provided they meet the current stringent criteria, namely that they have positive double stranded DNA antibodies, low complement and a SLEDAI of 10 or more. In light of the COVID-19 pandemic patients who are established on IV belimumab can now use s/c belimumab for a minimum of 3 months. Patients would like ongoing access to this route of administration of belimumab.	Comment noted. The appraisal has been scheduled into the Technology Appraisal programme.
	Renal Association	Depends! If there is a plan to stop the current funding mechanism then very urgent. But I would argue that this is exactly the wrong time to do this appraisal. The BLISS-LN trial of belimumab in lupus nephritis has just reported positive results that suggest the licence will be extended to include renal disease. MUCH more sensible to do this appraisal when that licence is	Comment noted. The appraisal has been scheduled into the Technology Appraisal

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		granted (likely Q1 2021 latest?)	programme.
Additional comments on the draft remit	GlaxoSmithKline	None.	Comment noted.
	British Society of Rheumatology	The remit should be explicitly specify that it will address use of belimumab in childrena dn adolescents as well as adults.	Comment noted. The remit notes that belimumab will be appraised “within its licensed indication”. The scope table indicates that the relevant population is “people aged 5 years or more”.
	Lupus UK	No additional comments	Comment noted.
	NHS England Specialised Rheumatology Clinical Reference Group	-	-
	Renal Association	Not sure if comes in the remit or the scope but the marketing authorisation is as an add-on therapy in people aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (for example, positive anti-dsDNA and low complement) despite standard therapy. However, NICE / NHSE have taken a more stringent view of when to use Belimumab – positive dsDNA, low complement and SLEDAI of 10 despite standard therapy. There are many patients who don’t meet all three requirements who would likely benefit (we believe) but	Comment noted. The remit notes that belimumab will be appraised “within its licensed indication”.

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		who don't have access – the key part of the remit should be to assess against the marketing authorisation rather than the funding strategy which aimed to limit use.	

Comment 2: the draft scope

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Background information	GlaxoSmithKline	• GSK proposes replacing the following wording 'Active SLE involves frequent flares and more severe symptoms compared with inactive disease which is when the disease is in remission' with 'Active SLE involves frequent flares and more severe symptoms compared with inactive disease or when the disease is in remission.' • GSK would like to add in 'mucocutaneous disease' to the list of conditions that can occur as a result of SLE i.e. 'SLE can lead to mucocutaneous disease, arthritis, kidney failure, heart and lung inflammation, central nervous abnormalities and blood disorders.' • Update spelling of 'arthralgia'. • According to the 2019 update on the joint EULAR-EDTA guidelines on management of lupus nephritis, 40% of SLE patients develop renal disease (Fanouriakis 2020). Furthermore, the prevalence of lupus nephritis varies across ethnicities ranging from 14-23% in white patients to 33-55% in Black, Asian and Hispanic populations (Parikh, 2020). GSK proposes updating the % of patients who develop renal disease to 'Up to 55%' (Parikh, 2020). • GSK proposes the statement on *'Long-term damage accrues as a result of persistent disease activity and also due to cumulative effects of steroids'* is amended to '*Persistent disease activity and side-effects from cumulative dose of corticosteroids contribute significantly to the accrual of irreversible long-term organ damage'* (Fanouriakis 2019). • GSK proposes updating the information regarding incidence and	Comment noted. The background section of the scope has been revised. The background section of the scope is only intended to give a brief overview of the condition, its epidemiology and the treatment pathway.

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		prevalence to '*The incidence for 1999–2012 was 4.91 per 100 000 person-years (95% CI 4.73 to 5.09) and the prevalence in 2012 was 97.04 per 100 000 people (95% CI 94.19 to 99.94). Data suggest that although the prevalence is increasing, the incidence is decreasing (Rees, 2016).* • The female predominance can vary but it is generally thought to be 9 times more common in women than in men (Weckerle 2011). • GSK would also like to add that SLE predominantly affects women of child-bearing age. • GSK agrees that NSAIDs should be listed under standard therapy but suggests updating this to 'short-term use of NSAIDs' as the UK lupus community is moving away from use of NSAIDS due to toxicity. • GSK would like to highlight that whilst oral prednisolone is frequently prescribed for mild-moderate disease, IV methylprednisolone is generally reserved for organ or life-threatening disease.	
	British Society of Rheumatology	Broadly speaking this is complete. It is important to highlight that everyone's lupus is different with different organ systems being involved and with differing responses to available medications. Some patients will have very mild disease but a significant number will have severe refractory disease that requires strong immunosuppression to control their disease. Sometimes we struggle to control disease activity in these unfortunate patients and they experience significant morbidity and mortality. A specific question for consultation was whether childhood SLE was adequately described. There are various academic references that could be selected, although the current reference to the Lupus UK website does link to a reasonable 'lay' summary. I would add that evidence points to a higher *mortality* in this age group as well as the economic impact of developing disease-related damage at a younger age. Educational attainment is also adversely affected in this age group.	Comment noted. The background section of the scope has been revised.

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		Minor point page 2 Appendix B - 'erythematosus' is missing from Safety of Estrogen in Lupus Erythematosus National Assessment	
	Lupus UK	The background suggests that SLE is "7 times more common in women than men", however the vast majority of literature indicates that SLE is 9 times more common in women than men. The background states "The aim of current treatments is to control and ease symptoms, and prevent organ damage and long-term complications". We feel it may be helpful to include examples of long-term complications, such as cardiovascular or pulmonary disease.	Comment noted. The background section of the scope has been revised.
	NHS England Specialised Rheumatology Clinical Reference Group	It is important to highlight that everyone's lupus is different with different organ systems being involved and with differing responses to available medications. Some patients will have very mild disease but a significant number will have severe refractory disease that requires strong immunosuppression to control their disease. Sometimes we struggle to control disease activity in these unfortunate patients and they experience significant morbidity and mortality. Considerable outcome data have been published regarding juvenile SLE, including some data related to therapeutic interventions including those from the UK Juvenile SLE Cohort Study but we agree there are fewer papers compared with outcomes and treatments in adults as the disease is rarer in the paediatric population. As stated, children often have more severe disease. Minor point page 2 Appendix B - 'erythematosus' is missing from Safety of Estrogen in Lupus Erythematosus National Assessment	Comment noted. The background section of the scope has been revised.
	Renal Association	It's pretty accurate. I think it should say that for the moment belimumab is not licenced for renal or neurological lupus. DMARDs for non renal, non neurological lupus relatively rarely include cyclophosphamide but it is used. It is much more common to use azathioprine, methotrexate or mycophenolate	Comment noted. The background section of the scope has been revised.

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		mofetil (MMF)	
The technology/ intervention	GlaxoSmithKline	We propose the intervention section is expanded to: Belimumab 10 mg/kg by intravenous infusion or Belimumab 200 mg by subcutaneous injection as add on to standard therapy	Comment noted. Both subcutaneous and intravenous infusion routes of administration are included in the scope. The scope does not include any detailed information on dosing but will be considered in the appraisal.
	British Society of Rheumatology	Yes	Comment noted.
	Lupus UK	It describes one of the methods for administration of belimumab as “sub-cutaneous injection”. However, this method of administration is not typically available to patients in the UK and has only been made available during the COVID-19 pandemic to prevent long hospital infusions. Does the inclusion of sub-cutaneous injections of belimumab within the scope indicate that this method for administration will be more widely available for patients moving forward?	Comment noted. Both subcutaneous and intravenous infusion routes of administration are included in the scope.
	NHS England Specialised Rheumatology Clinical Reference	Yes; IV and s/c should be considered. A subcutaneous preparation is now available.	Comment noted. Both subcutaneous and intravenous infusion routes of administration are included in the

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	Group		scope.
	Renal Association	Rightly says route of administration is IV or subcutaneous – however, hasn't been marketed as sc in England until the covid pandemic (so as to avoid hospital admissions). This is an important route of administration and should be evaluated for longer term use.	Comment noted. Both subcutaneous and intravenous infusion routes of administration are included in the scope.
Population	GlaxoSmithKline	GSK accepts the population wording of the draft scope. As stated under 'The Technology' belimumab is available for intravenous or subcutaneous injection. Whilst belimumab for IV administration is indicated as an add-on therapy in patients aged 5 years and older, belimumab for SC administration is indicated as add-on therapy only in adults.	Comment noted. The difference in the availability of both formulations has been noted in the scope.
	British Society of Rheumatology	Yes. Dosing and usage in children/adolescents may need a separate section. Clinical trial evidence suggests belimumab may be more effective for particular disease manifestations, for example cutaneous disease. It may be worth examining usage for specific manifestations as well as for globally active disease. NICE should consider the rationale for approving of Belimumab only in patients with both positive dsDNA antibodies and low complement. Many patients with highly active disease will only manifest one or the other of these biomarkers (or none), but may nonetheless have clinically active disease and may benefit from treatment.	Comment noted. The background section of the scope has been revised.

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	Lupus UK	No comment	Comment noted.
	NHS England Specialised Rheumatology Clinical Reference Group	Yes The license states that belimumab is for use in patients with high disease activity e.g. ds DNA positivity and low complement but it is not mandatory for patients to have (both) these specific criteria. Currently the TA stipulates that patients have to be dsDNA autoantibody positive and have low complement but this sometimes excludes relevant patients e.g. patients with active refractory disease who have failed conventional DMARDs and who are positive for other lupus related autoantibodies e.g. RNP, Smith, and Ro. This combination of criteria was previously chosen because of cost effectiveness and identified patients who would be most likely to respond but patients with these other autoantibodies are also more likely to respond. Patients with cutaneous SLE manifestations (belimumab trials showed effectiveness for this manifestation) do not always have low complements so again this group of patients with high disease activity who have failed conventional DMARDs are excluded from trying this drug. Data regarding the effectiveness of belimumab In glomerulonephritis has recently been published in abstract form and presumably a paper has been submitted for peer review. The use of belimumab in patients with glomerulonephritis should also be considered.	Comment noted. The remit notes that belimumab will be appraised “within its licensed indication”.
	Renal Association	Yes appropriate. Some might want children evaluated separately.	Comment noted.
Comparators	GlaxoSmithKline	GSK believes that standard therapy alone is the most clinically relevant comparator in this appraisal. Rituximab, although mainly reserved for patients with lupus nephritis or CNS lupus, is also prescribed in a small number of refractory SLE patients with high disease activity, who would also be eligible for belimumab.	Comment noted. As per Section 2.2.4 of the 2013 TA methods guide, “The scope identifies all potentially

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		Rituximab may be considered an additional comparator in this appraisal if the BILAG-Biologics Registry shows that a sufficient number of belimumab eligible patients have been prescribed rituximab. GSK does not believe IV cyclophosphamide plus standard therapy is an appropriate comparator. Cyclophosphamide is usually reserved for the treatment of severe disease such as CNS or renal lupus i.e. lupus nephritis, although now rarely used due to toxicity. This is not the population under consideration in this appraisal. It was also stated in Section 4.3 of TA 397 that clinical experts use cyclophosphamide infrequently due to side effects.	relevant comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator. At this stage of the appraisal, identification of comparators should be inclusive." Clinical experts indicated that rituximab and cyclophosphamide can be used to treat moderate-severe refractory lupus. The background section of the scope has been revised to indicate cyclophosphamide is not frequently used because of its side effects.
	British Society of Rheumatology	There is no single comparator appropriate for comparison with belimumab as different manifestations of lupus are typically managed using different drugs. There are no clinical trials comparing belimumab with single treatment options. Standard therapy, as much as it can be defined, would generally consist of a combination of a conventional oral immunosuppressant (DMARD) combined with hydroxychloroquine and corticosteroid. Topical therapies could be added	Comment noted.

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		for patients with cutaneous disease. it would seem appropriate to consider belimumab in a treatment pathway after failure one of one standard therapy rather than as a 'last-ditch' option after all else fails.	
	Lupus UK	No comment	Comment noted.
	NHS England Specialised Rheumatology Clinical Reference Group	Yes; belimumab is considered when patients have active SLE and have failed a combination of conventional DMARDs +/- requiring unacceptably high doses of oral corticosteroids to control their disease. Current established clinical practice includes a combination of hydroxychloroquine, mepacrine, methotrexate, azathioprine, mycophenolate mofetil with oral prednisolone if required. Topical corticosteroids are also added to treat cutaneous manifestations. Patients who have resistant /refractory disease would then be considered for belimumab, rituximab and/or cyclophosphamide according to their manifestations, autoantibody profile, complement results and level of disease activity. Some patients develop secondary nonresponse to rituximab or can not tolerate it so other antiCD20 drugs are used e.g. obinutuzumab. Use of belimumab should be considered in patients with moderate/severe disease who either can not reduce oral prednisolone below 7.5mg once daily or who have active disease despite 2 DMARDs (in addition to corticosteroids). This is in line with the use of rituximab in SLE (off label) as per the recently published NHSE clinical commissioning policy. Other comparators are on the horizon and being tested in RCTs such as JAK inhibitors, anti-IL17.	Comment noted.
	Renal Association	• No – for non-renal non neurological lupus the comparators should be rituximab, methotrexate (MTX), azathioprine and Mycophenolate mofetil (MMF) as well as cyclophosphamide – the latter is used relatively rarely in non renal non neuro lupus. • Rituximab, MTX and MMF are not licensed for use and whilst	Comment noted.

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		azathioprine, MTX and MMF are relatively widely available, the use of rituximab is strictly limited by some trusts due to cost. I'm not entirely sure what standard therapy other than these would be.	
Outcomes	GlaxoSmithKline	GSK does not consider the rate and duration of remission as suitable outcomes in this submission and these outcomes were not included within the belimumab pivotal trials.	Comment noted. The scope should include outcomes that are important to patients or carers (which may differ from the outcomes measured in the relevant clinical studies and the aspects of health included in generic measures of health-related quality of life).
	British Society of Rheumatology	Yes appropriate outcomes are selected. The importance of steroid minimisation as a key outcome in addition to disease activity should be emphasised. In most patients disease activity can be suppressed in the short term to a greater or lesser extent with excessive corticosteroid doses, but this comes at a considerably cost in relation to drug-related morbidity. A composite outcome based on disease activity and steroid minimisation seems most appropriate. Whether to focus on composite measures of disease activity or to separately evaluate specific manifestations remains a complex issue in lupus.	Comment noted. The outcomes section of the scoping table has been updated.
	Lupus UK	The outcome measures fail to measure the impact on the family/household. This may be especially relevant in childhood SLE where caring needs may be higher and result in lost income for parents or other family members.	Comment noted. Evidence submission from patient and carer groups may provide

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			perspectives from patients and carers on outcomes that are important to patients or carers (which may differ from the outcomes measured in the relevant clinical studies and the aspects of health included in generic measures of health-related quality of life).
	NHS England Specialised Rheumatology Clinical Reference Group	Yes The corticosteroid sparing effect is important as long term use of corticosteroids leads to damage. In light of the recent renal data and potential use for belimumab in SLE patients with glomerulonephritis, renal involvement and end stage renal disease should also be included.	Comment noted.
	Renal Association	• The challenge will be how disease activity is measured? Which tools? Worth adding Low Disease activity (LDA) as an outcome measure. • Need to look at specific flares – e.g. prevention of renal flares very important and perhaps should be weighted more strongly than prevention of a skin flare in terms of long term impact. Even more important given the recent trial data suggesting effectiveness of belimumab in combination specifically with MMF for improved maintenance of remission of lupus nephritis – hugely important for preservation of renal function in the long term. • Steroid minimisation hugely important outcome from a long term morbidity and risk analysis especially given the high representation of patients from	Comment noted.

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		BAME communities and their concomitant high risk of hypertension and diabetes. From patient perspective – Health related quality of life clearly critical, but from the SONG initiative (standardised outcomes in nephrology - https://songinitiative.org) it is clear that assessing “Life participation” is very important to patients with chronic conditions such as lupus.	
Economic analysis	GlaxoSmithKline	GSK has no further comment.	Comment noted.
	British Society of Rheumatology	Important to consider UK data. The scope stipulates a 'long' horizon which I would agree with. No specific timeframe is suggested, but lupus is a relapsing an remitting disease and the true value of treatments may take a long time to understand. I would note some specific scenarios in which the economic impact of lupus may vastly exceed a typical QALY analysis. For example meeting the consts or renal replacement therapy/transplantation in a patient develping end-stage kidney disease due to lupus nephritis (currently about 10% or nephritis patients - 2-4% of lupus in total). Similarly 'standard of care' cyclophosphamide can be associated with infertility in this population of predominantly young women - marked costs in infertility care. Current authorisation in UK is for intravenous belimumab, although subcutaneous belimumab is available (self administered at home). The economic costs of time off work when receiving i.v. rather than s.c. need to be considered.	Comment noted. The costs of administration and the costs and health consequences of developing complications and organ damage should be accounted for in the model.
	Lupus UK	No comment	Comment noted.
	NHS England	None but just to highlight that organ damage can accrue over many years.	Comment noted. The

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	Specialised Rheumatology Clinical Reference Group	Our aim is to treat active inflammation in any organ system early with the aim of achieving complete suppression of inflammation and thus preventing damage.	costs and health consequences of developing complications and organ damage should be accounted for in the model.
	Renal Association	• It is critical to take a suitably long view to include the impact of minimising steroids (see above), hospital admissions for flares etc. • Also need to evaluate the costs of subcutaneous administration over IV. Also need to build in (especially with IV administration) the known adherence vs the high rates of non adherence with oral medications and resultant flare rates (will be picked up in outcomes one would hope).	Comment noted. The costs of administration and the costs and health consequences of developing complications and organ damage should be accounted for in the model.
Equality and Diversity	GlaxoSmithKline	GSK believes the proposed remit and scope is appropriate.	Comment noted.
	British Society of Rheumatology	All patients with any autoantibodies associated with lupus should have access to belimumab, including those that do not have anti-dsDNA antibodies but have serological evidence of active lupus with low complement. Current policy specifically excludes patients with severe disease and that may have permanent disabilities from lupus that have previously been treated with cyclophosphamide or rituximab if they no longer have anti-dsDNA antibodies but still have evidence of severe active lupus clinically with low complement supporting the activity of the disease. SLE affects all ethnic groups. SLE is more prevalent in people of African Caribbean and Asian heritage and often they have more severe disease. Some ethnic groups respond better to some drugs compared with others.	Comment noted. This has been included in the equality impact assessment form for consideration by the committee.

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		These ethnic groups need to be considered separately. 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 include the other lupus-related antibodies.	
	Lupus UK	We do not believe the proposed remit and scope would exclude from full consideration any people protected by the equality legislation.	Comment noted.
	NHS England Specialised Rheumatology Clinical Reference Group	Patients have only been able to access IV belimumab administered at specialised centres so this has prevented some patients choosing to start this drug e.g. if they live a considerable distance from the specialised centre and have transport problems. Patients who are at work are also not choosing this drug option when eligible because the IV infusions occur 4 weekly and last an hour so with travelling time included incur a considerable amount of time off work. Lupus patients are often of working age and we want to help to keep them at work but sometimes their employment is threatened if they are unavailable for work on a regular basis. They would use it if they could access s/c as this would involve fewer hospital attendances and self- administration of the drug at home. The availability of subcutaneous belimumab would resolve these two inequalities. SLE affects all ethnic groups. SLE is more prevalent in people of African Caribbean and Asian heritage and often they have more severe disease. Some ethnic groups respond better to some drugs compared with others. These ethnic groups need to be considered separately. 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 include the other lupus-related antibodies. Cyclophosphamide is still used to treat major organ involvement but is not always appropriate in women of child bearing age. Women wishing to	Comment noted. This has been included in the equality impact assessment form for consideration by the committee.

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		preserve fertility need to be considered separately.	
	Renal Association	• People affected by severe lupus are much more likely to come from BAME communities in whom the risk of developing diabetes and hypertension are already high – therapies which don't minimise steroids may be as effective and cheaper but could have a serious adverse impact on these patients and that needs to be factored in when considering indications and use. The vast majority of patients with lupus are women, mostly of child bearing age. Impact on fertility and pregnancy need to be considered.	Comment noted. This has been included in the equality impact assessment form for consideration by the committee.
Other considerations	GlaxoSmithKline	-	-
	British Society of Rheumatology	It will be important to review evidence for benefit of belimumab in patients with autoantibody positive lupus and significant clinical activity patients who are anti-dsDNA positive or have low complement (C3/C4). It should be possible for patients to have belimumab with either of these serological options in addition to clinically active disease, rather than asking for both positive anti-dsDNA antibodies and low complement at the same time in addition to clinical disease activity and this is within the license. The original analyses from the phase 3 BLISS trials showed that these were independent predictors of belimumab response and both together was not greatly better than either alone in addition to the other criteria. However the current guidance on needing both serological items excludes patients that meet all the other criteria but have only one of these serological abnormalities , have failed other therapies and who would likely benefit from belimumab. At present these patients end up having more corticosteroids and repeating drug therapies that they have already failed with substantial increased risk of adverse events and low probability of response. Given that lupus is common in women of reproductive age the scope should	Comment noted. The remit notes that belimumab will be appraised "within its licensed indication".

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		comment on whether belimumab can be used in pregnancy.	
	Lupus UK	No comments	Comment noted.
	NHS England Specialised Rheumatology Clinical Reference Group	The management of patients with SLE is complex and requires experienced centres.	Comment noted.
	Renal Association	For the kidney community, the key question is the use of belimumab in lupus nephritis – given the recent positive results of BLISS-LN, it would seem prudent to wait on market authorisation for LN and address in the round.	Comment noted. The remit notes that belimumab will be appraised "within its licensed indication".
Innovation	GlaxoSmithKline	GSK considers belimumab is an innovative treatment option for patients who continue to have high degree of disease activity despite standard of care. Whilst other therapies may provide treatment of near-term symptoms, a recent propensity score matching study has demonstrated the value of belimumab in reducing long-term organ damage (Urowitz, 2019). Furthermore, it is the only approved medicine (and B Lymphocyte Stimulator [BLyS] antagonist) to treat patients suffering with SLE. While patients with other autoimmune conditions, such as rheumatoid arthritis, have seen a substantial growth in the number of treatment options and experienced their associated clinical and QoL benefits, this has not been the case for patients with SLE. Despite the significant long-term investment in research to identify and develop new treatments for SLE in the past 50 years, all except belimumab, have failed to demonstrate a significant clinical benefit	Comment noted. The evidence submissions can expand on the innovative nature of the technology, which will be taken into account by the appraisal committee

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		and gain approval. Therefore, the mainstay of treatment for these patients is limited to older, non-specific therapies to treat their disease. The heterogeneity of SLE, various disease mechanisms and trial design has made it challenging to develop drugs to treat this debilitating autoimmune disease (Touma and Gladman 2017). Over the last decade, GSK has generated a wealth of robust clinical trial and real-world evidence (Collins, 2019) that has demonstrated belimumab's effectiveness in managing this complex disease with an established and acceptable safety profile. This has also been demonstrated in independent real-world datasets. Since 2011, GSK has remained committed to bringing effective treatment options for patients with lupus, hence the subsequent approval of belimumab for subcutaneous administration as a pre-filled pen in November 2017. This alternative route of administration will allow patients to self-administer at home minimising the need to take time off work and travel to attend hospital appointments, thus increasing capacity in outpatient infusion clinics. Therefore, GSK believes that belimumab addresses a substantial unmet need in a debilitating disease, that if not controlled, can lead to irreversible organ damage with increased risk of morbidity and mortality.	
	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 due to inability to reduce disease activity without this new therapy belimumab. 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	Comment noted. The evidence submissions can expand on the innovative nature of the technology, which will be taken into account by the appraisal

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		belimumab.	committee
	Lupus UK	We believe belimumab is an innovative treatment which can provide significant improvements to quality of life for some people living with lupus who may not adequately respond to, or be unable to tolerate, standard therapy or other available alternatives.	Comment noted. The evidence submissions can expand on the innovative nature of the technology, which will be taken into account by the appraisal committee
	NHS England Specialised Rheumatology Clinical Reference Group	Yes – it has the potential to make a significant impact.	Comment noted. The evidence submissions can expand on the innovative nature of the technology, which will be taken into account by the appraisal committee
	Renal Association	• Yes – it is the ONLY new drug licenced for use in lupus in 50+ years so undoubtedly a step change but the current restrictions on use in England make it available to relatively few patients. • Yes – to date the safety of belimumab has been excellent and it is very well tolerated by patients. If made generally available by the sub cutaneous route (so could be self administered) it would substantially free up patients from hospital attendances – if well could simply have regular blood and urine tests (less frequently than say for azathioprine, MTX or MMF where need to monitor liver function (aza and MTX) and white cells for safety) to monitor disease activity and consultations for any breakthrough symptoms. Highly important in the era of Covid-19 but also liberates patients for better life participation (see earlier in outcomes).	Comment noted. The evidence submissions can expand on the innovative nature of the technology, which will be taken into account by the appraisal committee

Section	Consultee/ Commentator	Comments [sic]	Action
		• Long term data from other countries (e.g. Germany) where much more liberal use. • For the reduced attendance at hospital could also compare to e.g. use of sub cut anti TNF in rheumatoid arthritis and the resultant improvement in QoL.	
Questions for consultation	GlaxoSmithKline	• Is the burden of childhood SLE adequately described? GSK propose additional information to describe the burden of childhood SLE. The incidence and prevalence of SLE is significantly lower than in adults. Paediatric patients who develop SLE in childhood experience a more aggressive course of disease and generally present with a higher degree of organ damage than patients who have disease onset in adulthood, particularly renal and neurological systems. Despite the limited evidence to support the treatment of paediatric SLE patients, current treatment approaches largely involve the off-label use of drugs used in adults, including corticosteroid, anti-malarials, immunosuppressants and biologics. Given the lack of evidence on the use of current therapies in paediatric patients and their adverse effects, there remains an unmet need for a treatment that targets the underlying disease in paediatric patients that is supported by safety and efficacy data. • Which treatments are considered to be established clinical practice in the NHS for SLE (for both paediatric and adult population)? According to the 2018 British Society of Rheumatology guideline for the	• Comment noted. The background section of the scope has been revised.

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		management of systemic lupus erythematosus in adults, the mainstay of treatment for active lupus is NSAIDs, corticosteroids, antimalarials and immunosuppressants, although not all of these are licensed specifically for lupus. Similarly, these treatments are also used to managed paediatric patients with SLE. In addition, a proportion of patients who continue to have high disease activity despite standard therapy may be considered for treatment with a biologic. The treatment for patients with severe lupus nephritis and CNS lupus differs and is not within scope of this TA. • Are there any subgroups of people in whom belimumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? In June 2016 NICE recommended the use of belimumab as add-on to standard therapy in an adult SLE population with evidence for serological disease activity (defined as positive anti-double-stranded DNA AND low complement) and a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI [SS]) score of greater than or equal to 10 despite standard treatment. This represented a sub-population of the licensed population (based on BLISS-52 and BLISS-76) where belimumab demonstrated a greater benefit than the Intent-To-Treat (ITT) population. This is the subgroup on which data have been collected in the BILAG registry as part of the TA397 Managed Access Agreement. During the MAA data collection period clinical experts highlighted problems with identifying patients satisfying all three reimbursement criteria. As patients were already exhibiting HDA due to having an SS score of ≥10, it was considered unnecessary for patients to also have both low complement and positive dsDNA, and that having just one of these is considered	

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		sufficient. Therefore, GSK is seeking reimbursement for a slightly broader subgroup of HDA patients defined as having a baseline SS score ≥10 despite standard treatment, with at least one of low complement and positive dsDNA. • Where do you consider belimumab will fit into the current standard care pathway? Belimumab should be considered as add-on therapy for moderate to severe lupus with persistent disease activity despite standard therapy. • Do you consider that the use of belimumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? GSK believes that the use of belimumab results in potential significant and substantial health-related benefits that are unlikely to be fully accounted for in the QALY calculation. This is partially due to the QALY calculation being based on utility scores derived from the EQ-5D instrument in the pivotal trials. This instrument lacks sensitivity in certain relevant dimensions of health such as chronic fatigue and sensory impairment. In addition, other aspects of the disease, such as flares, may also be underestimated due to the complexity of including the impact of these in the health economic modelling. • Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. The secondary end points from the pivotal trials BLISS-52, BLISS-76 and BLISS-SC, including those that involve the FACIT-Fatigue instrument will be presented. • NICE intends to appraise this technology through its Single Technology	

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		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). GSK considers that the Single Technology Appraisal (STA) Process is an appropriate route for the consideration of belimumab IV and belimumab SC.	
	British Society of Rheumatology	The questions for consultation include a query on available data. In addition to full published trial data I am aware that there is advanced data presented in abstract form specifically in relation to lupus nephritis. I am also aware of a UK trial specifically looking at Belimumab/Rituximab in combination. I am not aware of when these trials will publish in full. Presumably GSK will be able to inform you regarding the lupus nephritis study. I am sure NICE are also aware of the collection of 'real world' outcome date within the University of Manchester sponsored BILAG biologics registry and will be using this to inform their decision as well.	Comment noted.
	Lupus UK	Is the burden of childhood SLE adequately described? Whilst the background accurately captures the increased prevalence of severe disease manifestations in childhood SLE, it fails to reflect the burden on quality of life for the child and their family. The onset of SLE during childhood can have a significant impact on a child's education and future prospects and introduce significant caring requirements for parents, potentially resulting in lost income from forgone employment. The emotional wellbeing of all family members can be affected. Have all relevant comparators for belimumab been included in the scope? Yes Which treatments are considered to be established clinical practice in the NHS for SLE (for both paediatric and adult population)? No comment	Comment noted. The background section of the scope has been revised.

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		Are the outcomes listed appropriate? The outcome measurements that are listed are appropriate. However, they fail to include the impact upon the family/household as a whole. This can be significant if the lupus patient requires additional care. Are there any subgroups of people in whom belimumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? No comment Where do you consider belimumab will fit into the current standard care pathway? Belimumab will be considered as an option for eligible patients who do not improve with, or cannot tolerate standard therapy.	
	NHS England Specialised Rheumatology Clinical Reference Group	-	-
	Renal Association	• *Is the burden of childhood SLE adequately described?* – Doesn't really capture the relapsing remitting nature of the disease and the risk of permanent damage especially in relation to steroid use, the risk of infertility from cyclophosphamide and the teratogenicity of cyclophosphamide, MTX and MMF – all hugely important given that the average patient is a woman of child bearing age. Also that it is so important to have treatments which are more specific to the disease process, and which minimise the overall burden of long term immunosuppression vis a vis increased risk of infections and cancer.	Comment noted. The background section of the scope has been revised.

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		• *Are the outcomes listed appropriate*? Would stress need to consider specific outcomes e.g. renal flares as more adverse than some others. Not just because can lead to much more severe long term consequences but also the need for increased immunosuppression and the subsequent increased risks of infections and cancer. • *Are there any subgroups of people in whom belimumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?* Addressed above re children. Additionally, There is an argument for specifically considering those at risk of low adherence (who undoubtedly have worse long term outcomes) such as adolescents, those with mental health issues, those with challenging social conditions who find taking tablets regularly difficult. • *Where do you consider belimumab will fit into the current standard care pathway?* I think it will increasingly become standard of care for those with active severe non renal lupus – as a steroid sparing agent and possibly to avoid oral medications altogether (much as we choose to use rituximab – unlicensed- in some patients) especially if able to have the subcut preparation. It should be allowed according to the market authorisation (severe antibody +ve disease) and not have to have low complement and a minimum sledai. Reasonable to say have to evaluate after 6 months for effectiveness. If this appraisal is delayed until the renal licence is granted, then it will undoubtedly rapidly be used to improve outcomes in renal lupus in addition to MMF and steroids. T*o 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.* The main barrier will be cost – there is growing confidence in its use (slow uptake at the beginning given it was a completely new drug with “no history” in other conditions), its safety profile and low frequency of adverse reactions. Patients like it.	

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Additional comments on the draft scope	GlaxoSmithKline	-	-
	British Society of Rheumatology	Additional references on the management of lupus including complications that can occur should be considered such as EULAR recommendations over the last 10 years, the most recent and comprehensive is : Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, Cervera R, Doria A, Gordon C, Govoni M, Houssiau F, Jayne D, Kouloumas M, Kuhn A, Larsen JL, Lerstrom K, Moroni G, Mosca M, Schneider M, Smolen JS, Svenungsson E, Tesar V, Tincani A, Troldborg A, van VR, Wenzel J, Bertsias G, Boumpas DT: 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78:736-745.	Comment noted.
	Lupus UK	No additional comments.	Comment noted.
	NHS England Specialised Rheumatology Clinical Reference Group	-	-
	Renal Association	It doesn't really address the added benefit of an intermittent parenteral drug (that can be given subcutaneously – licenced to be given via this route through the Covid pandemic) as a preferential choice both for adherence and convenience. Nor the possibility of reducing oral DMARDs. It appears to give no weight to the fact that all the DMARDs are not licenced whereas belimumab is.	Comment noted.

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

Pfizer Ltd