NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from GlaxoSmithKline:**
   a. Main response
   b. Response to queries from NICE technical team
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   e. Letter to NICE with updated PAS

3. **Consultee and commentator comments on the Appraisal Consultation Document from:**
   a. Lupus UK
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5. **Evidence Review Group critique of company comments on the ACD:**
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6. **Expert personal perspective** from:
   a. Abbie Thomas – patient expert, nominated by Lupus UK

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Belimumab for treating active autoantibody-positive systemic lupus erythematosus

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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 number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	GlaxoSmithKline (GSK)	Since embarking on seeking NHS access for baseline commissioning of belimumab in 2011, GSK remains as equally as committed to ensuring belimumab continues to offer a clinically proven treatment option for systemic lupus erythematosus (SLE) patients with high disease activity in England and Wales. We offer a revised PAS to share the risk of outstanding uncertainty but believe our base case remains the most appropriate for decision making. Whilst the volume and duration of outcome data captured from the BILAG-Biologics Registry (BILAG-BR) for patients commencing on belimumab was limited, we are pleased that a revised population, HDA-2 (a requirement of a SELENA-SLEDAI [SS] score ≥ 10 and only one serological biomarker) has been accepted by the Committee as appropriate for decision making. We agree with the Committee that the long-term extension (LTE) studies do not provide long-term comparative effectiveness evidence for belimumab versus standard therapy (ST) alone. However, this is no different to clinical trial programs for other chronic diseases; it would simply not be ethical to run such studies. In the absence of long-term comparative effectiveness, we do not believe it is a reasonable nor a fair assessment to dismiss in its entirety, the comparative evidence presented from the Propensity Score (PS)-Matched analysis between belimumab and ST on a highly clinically relevant end point, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). The dismissal of the PS-matched study is also a disservice to those SLE patients in need. It is well documented that an increasing SDI score is linked to worse long-term outcomes and an increased risk of morbidity and mortality in SLE patients. In addition, we do not believe that the Committee's assessment that the results from the PS-matched analysis are biased in favour of belimumab is accurate, based on the matching-exercise and the withdrawal data from the LTEs (details presented later). Irrespective of an HTA assessment, such degree of bias towards an intervention, if of concern, would question the robustness and reliability of the study which has never been the case working with Canadian Lupus Experts and indeed the independent peer review of the resultant publications. A robust PS-matched comparative analysis serves as the most appropriate and robust alternative to address the evidence gap. The key driver of the presented base case cost-effectiveness analyses is the additional benefit experienced by belimumab responders in terms of slower organ damage progression compared with ST, which is implemented via a derived calibration factor, the results for the 5-year change in SDI from the PS-matched analysis. Disappointingly, the Committee Meeting focused on the size of the calibration factor (0.491) applied to belimumab responders to 6 years in the model, and not the assumed incremental absolute SDI benefit which would have allowed clinical expert inclusion in the discussion. This is critically important to reassure the Committee that belimumab does offer additional benefit in terms of slowing down the rate of organ damage progression over a long period	Comments noted. The committee considered the consultation response, new evidence and revised commercial offer from the company. Please see individual responses below: <u>Propensity score-matched analysis</u> The committee discussed the propensity score-matched analysis comparing organ damage progression in people having treatment with belimumab or standard therapy with 5 or more years of follow-up. It considered that the results of the propensity score-matched analysis may not be relevant to NHS clinical practice and were likely biased in favour of belimumab. See FAD sections 3.8 to 3.9. <u>Calibration factor</u> The committee understood why organ damage progression had been adjusted in the original model to reflect the observed long-term data now available for belimumab but had concerns about how this had been implemented. It concluded that the calibration factor was not appropriate for decision making. See FAD sections 3.11 to 3.12.

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			and that we are not in any way double counting projected model-derived benefit. We believe the benefits seen on organ damage progression are clinically plausible given the impact belimumab has on reducing disease activity and because patients controlled with belimumab will be able to reduce their exposure to oral steroids; both of these (steroid use and disease activity) lead to organ damage accrual. We suggest that clinical experts are invited to comment at the next ACM on the impact of organ damage to patients with SLE and the clinical plausibility of PS-matched analysis. In the uncalibrated model, the 5-year SDI increase (between years 1.5 and 6.5) was projected at 0.568 units and the application of the calibration factor reduced this change to 0.283 units. GSK acknowledges the uncertainty of the application of the PS-matched analysis results to the economic model. Therefore, our approach was that by applying the benefit conservatively i.e., by applying to belimumab responders only and not making any adjustment to the ST arm, to 6 years of a lifetime model, and assuming the same level of benefit from an ITT population to a HDA-2 population, that this would in effect underwrite the uncertainty. We do not agree with a complete dismissal of some implementation of benefit for belimumab responder patients; this is not an appropriately, evidence-based decision. Because of the complexity of the model structure, offering an alternative modelling approach is not feasible. We recognise that our conservative approach to implementation is not deemed adequate by the Committee at this stage in sharing the risk of decision error with the NHS. We therefore offer a revised PAS comprising a [redacted] discount on the list price across both formulations, bringing the base case cost-effectiveness analysis to £25,042 and £24,952 per QALY gained for the SC and IV models respectively.	
2	Consultee (company)	GSK	**GSK welcomes the acceptance of the updated sub-group (HDA-2 population) as being relevant for decision making** • The acceptance of the HDA-2 population will allow better identification of appropriate patients who could potentially benefit from belimumab. • Please note typo of “HAD-1” at bottom of page 6.	Comments noted. Please note that the typographical error has been corrected in the FAD.
3	Consultee (company)	GSK	**GSK acknowledges that if belimumab was not available, a small proportion of overlapping patients could potentially receive rituximab** • In accordance with the NHSE clinical commissioning policy for rituximab, patients are only eligible for rituximab if they have failed one or more immunosuppressants, one of which must be mycophenolate or cyclophosphamide. This is not the case for those receiving belimumab in the clinical trials and clinical practice. Cyclophosphamide and mycophenolate are usually prescribed to patients with lupus nephritis or CNS involvement, which falls outside of the scope of this appraisal. • Belimumab is an ongoing maintenance treatment to achieve a long-term sustained response and therefore reserved for patients with ongoing active disease uncontrolled by standard therapy. Rituximab, however, is not prescribed in a similar manner (i.e., on-going	Comments noted**.** The committee discussed the appropriate comparators for the population being considered in this appraisal. It concluded that rituximab is a relevant comparator. See section 3.4 of the FAD.

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			maintenance) and therefore a proportion of patients can experience re-population of their B-cells following initial B-cell depletion with rituximab. In essence, these drugs are prescribed very differently in clinical practice and under different circumstances. • GSK recognises that if belimumab was not available, a small proportion of overlapping patients could potentially receive rituximab. This reflects the unmet need in the absence of licensed effective treatments. • It is worth noting that the 'NHSE interim clinical commissioning policy statement for rituximab for treatment of SLE in adults' was published in 2013 when belimumab was not available. At this time, clinicians had no choice than to use rituximab in patients who were not responding to standard therapies. As the treatment landscape has since evolved, the 2020 published 'NHS England clinical commissioning policy for rituximab for refractory SLE' now recommends consideration of belimumab, an effective, well studied licensed treatment, prior to the use of rituximab. Therefore, a proportion of the current prescribing of rituximab in patients with SLE is likely to be habitual and from previous experience acquired prior to the availability of belimumab in 2016 and does not necessarily translate into rituximab being an appropriate comparator.	
4	Consultee (company)	GSK	**Information only: belimumab improves SRI4 response rate in the new HDA-2 subpopulation** • The results from the HDA-2 subgroup analysis of BLISS IV (52/76) and SC trials have now been published and no longer need to be marked as confidential (http://lupus.bmj.com/cgi/content/full/8/1/e000459).	Comments noted. The results for the HDA-2 subgroup have now been included in section 3.5 of the FAD.
5	Consultee (company)	GSK	**Long-term effectiveness evidence for belimumab compared with standard therapy** • GSK would like to highlight that the 52 and 76-week follow up periods in the Phase 3 studies are in line with EMA guidance and other comparative trials in SLE. • At the time of the last appraisal (TA397), there was limited long-term data for belimumab, and the Committee were uncertain whether the treatment effect seen with belimumab in the clinical trials would be maintained over time. Therefore, as part of this appraisal, we provided additional published data to demonstrate the long-term efficacy and safety of belimumab. Whilst this is not direct comparative data to ST alone, the wealth of long-term evidence in belimumab is extremely relevant to understanding the impact of belimumab on organ damage accrual and therefore, should not be disregarded. It is well documented in guidelines that the aim of treatment is remission of disease symptoms and signs, prevention of damage accrual and minimisation of drug side effects. The data presented demonstrates this and provides clinicians with the reassurance on the safety and tolerability of belimumab up to 13 years, as well as evidence of a sustained treatment response and low damage accrual. Furthermore, GSK would like to point out this is a large dataset to have available for any biological drug being appraised by NICE. • GSK would like to reiterate that it is not feasible to conduct a long-term placebo-controlled study in patients with SLE comparing belimumab plus ST to ST alone, as this would be highly unethical in a patient group who are at an increased risk of morbidity and mortality, particularly where the pivotal trials demonstrated significant benefit on treatment with	Comments noted. The committee discussed the BLISS long-term extension studies which were newly presented in this appraisal. It considered that because the studies did not have comparator arms, they did not provide long-term effectiveness evidence for belimumab compared with standard therapy. See section 3.6 of the FAD. Please note that the factual inaccuracies have been corrected in the FAD.

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			belimumab plus ST compared to ST alone. Therefore, a robust and well-designed propensity-score matched comparative analysis between patients receiving belimumab in the BLISS-US long-term extension study compared with a real-world cohort of patients with SLE (Toronto Lupus Cohort [TLC]), serves as the most appropriate and reasonable alternative. • GSK would like to correct the information provided regarding the BLISS-76 US long-term extension study. The primary outcome of this trial was to measure long-term safety of belimumab, frequency of adverse events [AEs] and damage assessed using the SDI, not the SRI 4 response as per the Phase 3 BLISS-76 trial. • GSK would also like to correct the information provided regarding the BLISS-SC extension study. The outcomes measured in the extension study included safety and efficacy, and changes in biomarker and B cell levels. The ACD states 61.4% of patients achieved an SRI 4 response in the total population at 6 months This is incorrect and should say 'At week 24, a SRI4 response was achieved in 16.1% of patients in the placebo-to-belimumab group and 76.3% patients in the belimumab group.' It was in the BLISS-SC pivotal trial that 61.4% of patients receiving belimumab achieved a SRI4 response, but this was at week 52.	
6	Consultee (company)	GSK	**Indirect treatment comparison between belimumab and rituximab in the relevant population remains challenging** • Whilst the Committee would have preferred to have seen an indirect treatment comparison between belimumab and rituximab, this is not possible in the relevant population i.e., HDA-2 as the BILAG-BR collected data for the HDA-1 population only. • GSK would like to reiterate due to the lack of positive and robust randomised controlled trial and long-term effectiveness data for rituximab in patients with SLE, GSK does not believe that a reliable robust indirect treatment comparison can be conducted. The ERG acknowledged the associated methodological challenges (which too, were also acknowledged by the previous ERG in TA397).	Comments noted. The committee considered that because rituximab is a relevant comparator, it would have preferred to see an indirect treatment comparison between belimumab and rituximab based on the data collected from the BILAG-BR substudy. It concluded that in the absence of this comparison, the uncertainty about the relative clinical and cost effectiveness of belimumab and rituximab remains. See FAD sections 3.4 and 3.7.
7	Consultee (company)	GSK	**Results of the propensity score-matched analysis is not biased in favour of belimumab** • GSK disagrees with the Committee's conclusion that the PS-matched analysis is biased in favour of belimumab. • GSK does not agree that important variables were not matched on. The most clinically relevant variables, as identified by a systemic literature review and validated by non-GSK clinical experts, were matched on in the primary analysis of the study, including baseline disease activity and baseline SDI. However, it is not suitable to match on variables such as disease progression and disease activity over time (as suggested in the ACD) as they would be considered as potential confounders in the analysis. GSK acknowledges that a social deprivation (SD) index was not available to use as a matching variable in the PS-matched study, however household income and educational attainment were matched variables and will in some way act as a proxy for SD.	Comments noted. The committee discussed the propensity score-matched analysis comparing organ damage progression in people having treatment with belimumab or standard therapy with 5 or more years of follow-up. It considered that the results of the propensity score-matched analysis may not be relevant to NHS clinical practice and were likely biased in favour of belimumab. See FAD sections 3.8 to 3.9.

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			• GSK acknowledges that there were some differences in the baseline characteristics between the two cohorts compared in the analysis (the US LTE study cohort and the TLC) pre- and post-matching. However, study arms were tested for statistically significant differences in patient baseline characteristics (using Welch's t-test) and the standardised mean difference was also determined for each covariate. GSK agrees that smoking can affect outcomes in patients with SLE and whilst prior to the propensity score matching, the cohort samples were not well balanced, once PS-matched, the samples of 99 LTE and 99 TLC patients were well balanced with a bias of less than 5% for nine of the seventeen variables, and less than 10% for all variables (the mean bias is 4.6%); Post-matching there was 0% bias for the smoking variable which is lower than for other matched variables. • In our submission, we have recognised the limitations of a single-arm, open label extension study and that the PS-matched analysis resulted in a smaller sample size of 99 (from 195 patients in the LTE with ≥5 years follow up). We disagree with the ERG's assertion that patients who continued having belimumab at 5 years were likely to have progressed less or had a better response than patients who had belimumab for 1 to 4 years before stopping treatment, to the degree of significantly biasing the results in favour of belimumab. Out of the 268 patients entering the US long-term extension study, only 28% (n=76) of patients withdrew by the end of Year 5, of which 63 patients withdrew due to reasons other than lack of efficacy (i.e., adverse events, lost to follow-up, non-compliance with study drug, physician decision, protocol deviation, withdrawal by patient or other). Therefore, the majority of patients (72%) did continue for at least 5 years. In addition, it is conceivable that many of the patients who withdrew due to a reason other than lack of efficacy could have potentially continued to receive the benefits of belimumab until year 5 if they were to continue treatment. Therefore, GSK disagrees that patients remaining in the study at year 5 are a particularly enriched population and we believe these data are valid for a comparative analysis with the TLC. • In addition, when we consulted with two leading UK Rheumatologists, they were of the opinion that these LTE data were important to clinical management in the UK and the most relevant data available to demonstrate the effectiveness of belimumab plus ST compared to ST alone on organ damage progression; this included assessment of disease activity and cumulative corticosteroid use.	
8	Consultee (company)	GSK	**It is inappropriate to completely dismiss the application of the PS-matched analysis results showing the positive benefit of belimumab on organ damage progression to the economic model.** ***The clinical relationship between oral corticosteroids, disease activity (measured by SS) and organ damage*** • In a clinical setting the continued use of oral corticosteroids and increased disease activity as defined by flares, all contribute to organ damage progression which is irreversible in nature and contributes to most of the detriment in outcomes including health related quality of life and mortality risk in SLE (Lopez et al 2012). Belimumab offers steroid sparing activity	The committee understood why organ damage progression had been adjusted in the original model to reflect the observed long-term data now available for belimumab but had concerns about how this had been implemented. It concluded that the calibration factor was not appropriate for decision making. See FAD sections 3.11 to 3.12.

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			(that we have been unable to capture adequately in the model) and a proven reduction in disease activity. It therefore makes sense clinically that belimumab would have a positive impact on reducing organ damage progression. ***Organ damage progression captured in the model used to support TA397*** • The model submitted as part of TA397 utilised data from the Johns Hopkins (JH) cohort to inform the natural history models for organ damage progression. The JH cohort data was only able to provide a historical correlated relationship between disease activity (SS score) and organ damage for patients who received standard therapy (ST) treatment alone. It did not capture the direct treatment effect of belimumab on organ damage progression. • Data from the pivotal BLISS-52 and BLISS-76 trials were used to inform the SS scores for the first 12 months. The model submitted as part of TA397 relied on a series of time to event regression models derived from the JH registry that estimated a standard therapy (ST) or belimumab patient's organ damage progression (and SDI score) as a relationship to their SELENA-SLEDAI (SS) scores in each given year. • It is incorrect to state that the assumption in the previous model regarding a constant treatment effect of belimumab on disease activity reduction beyond 1 year (based on the trial data), in terms of the long-term treatment effect with belimumab, is "optimistic". It is very clearly stated in Section 4.25 of the previous TA397 FAD that- "Deriving cost data from different sources may have led to some inconsistencies in the estimates and the company may have underestimated some of the benefits associated with delaying certain types of organ damage." ***Organ damage progression captured in the model used to support this re-appraisal*** • We wanted to ensure that the model accurately reflected the newly available evidence on organ damage progression made available from the PS-matched analysis. By running the TA397 model (having adjusted the baseline characteristics to the PS-matched analysis population), we found that the model over-predicted the organ damage progression seen in belimumab responders and underestimated it for the ST arm. • We adjusted the absolute organ damage progression for patients who received and responded to belimumab to match the rate of organ damage progression as seen in the PS-matched analysis for a maximum of 6 years. The adjustment was made by the use of a 'coefficient', which is called in our current submission a 'calibration factor' and is applied on an annualised basis to belimumab responders so that the absolute organ damage progression shown in the model (for belimumab responders) closely aligns to the PS-matched analysis. ***Absolute change in SDI (as a result of the application of the calibration factor)***	

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			• The original uncalibrated economic model submitted as part of TA397 suggested that the 5-year SDI increase for patients was 0.568 for patients who received belimumab whilst it was 0.611 for patients who received standard therapy alone. When calibration factors derived from the robust PS-matched analysis are applied, belimumab patients experienced an SDI increase of 0.283 (suggesting that the uncalibrated model was overestimating organ damage increase by 0.258) whilst patients on standard therapy alone experienced a greater increase of 0.717 (suggesting that the uncalibrated model was underestimating organ damage progression by 0.106). Although the robust PS-matched analysis suggested that the rate of organ damage on the standard therapy arm of the original TA397 model was likely under-estimated, no correction was made to the ST arm in the model submitted as part of the current base case to reflect this increased rate of organ damage accumulation, when this was an entirely reasonable approach. This has likely resulted in an underestimation of costs and overestimation of benefits of the ST arm, and therefore reflects poorly on belimumab in a comparative scenario. ***Committee discussion of the application of the PS-matched analysis to the model*** • GSK strongly believe that clinical experts at the Committee Meeting were unable to engage in this part of the discussion because the focus was on the size of the calibration factor. We believe for the discussion to have been meaningful for decision making, it should have focused on the clinical plausibility of the absolute increase assumed for belimumab responders on organ damage progression. We believe this would have helped the Committee understand that despite the size of the calibration factor, what is represents clinically does reflect clinical plausibility for those responding patients. GSK therefore believes there is a clear benefit of having clinical experts present at any subsequent Committee meeting. ***Residual uncertainty on assumed long-term organ damage progression*** Whilst GSK believes that the PS-matched analysis provides clinically relevant and important evidence on the comparative effectiveness of Benlysta versus ST on the long-term progression of organ damage, we do acknowledge that there is uncertainty in its application in the economic model. Several significantly conservative steps were taken to apply the comparative PS-matched study data in the health economic modelling: • The calibration factor was derived using a matched intention to treat (ITT) population from	

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			Urowitz et al. 2019. As our target sub-population demonstrated a higher benefit on disease activity (as measured by SS score), it is perfectly plausible that this translates to an additional benefit in slowing down organ damage progression. • The calibration was applied to belimumab responders only. • The benefits of the calibration factor were applied to only 6 years despite belimumab being continued up to lifetime in the model and clinical practice. It is clinically plausible that patients will continue to benefit from belimumab for as long as they continue to take it. • No adjustment was made to the standard therapy arm. The annual calibration factor to adjust the SDI score of patients on belimumab to that observed on the LTE was derived from a PS-matched analysis conducted over a period of 5 years. In the model, if a responder patient on the belimumab arm spent less than 6 years in the model, they only received benefits proportionally to the amount of time they remained in the model, provided they entered into the second year of the model. Modelled patients who did not have 4 points or more reduction on SS by week 24 were classified as "non-responders" and derived no benefits at all. GSK recognises the uncertainty in applying this constant calibration factor to patients who discontinued at years 2, 3, and 4 in the model, as this assumes patients received full benefit proportionally to the time spent in the model, whereas it may be the case that patients would receive less benefit if they discontinued for any given reason before the full 5-years. To account for this, GSK took the conservative approach, as detailed above, to the application of the new organ damage progression data in the model. We would also like to remind the committee that the model does not fully capture disease flares (due to the Johns Hopkins dataset not directly capturing these). Had flares been sufficiently captured, this would have likely given extra benefits to patients on belimumab as the BLISS RCTs have demonstrated that patients receiving belimumab experienced a reduced number of flares compared with patients on standard therapy alone. In addition, we have not incorporated carer utilities in our model, but this is relevant to patients with this disease as the symptoms can be very debilitating e.g. prolonged fatigue and arthritic pain, whereby the sufferer requires in some cases significant support from family members and other carers. **<u>References</u>** Lopez, R., Davidson, J.E., Beeby, M.D., Egger, P.J. and Isenberg, D.A., 2012. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. *Rheumatology*, 51(3), pp.491-498. Urowitz, M.B., Ohsfeldt, R.L., Wielage, R.C., Kelton, K.A., Asukai, Y. and Ramachandran, S., 2019. Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. *Annals of the rheumatic diseases*, *78*(3), pp.372-379.	
9	Consultee	GSK	**The modelled response to treatment for belimumab 'non-responders' is consistent with**	Comments noted. The committee

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td>(company)</td><td></td><td>
management of UK patients in clinical practice

In line with the Summary of Product Characteristics (SmPC) and current NICE guidance (TA397), patients on belimumab who are determined to be non-responders (<4-point reduction in SELENA-SLEDAI (SS) score at week 24) will cease treatment with belimumab and revert to receiving standard therapy (ST) alone. This is not to say these “non-responder” patients experienced no benefit from belimumab in the first 24 weeks of treatment i.e., some patients may have experienced a 1 to 3-point reduction in SELENA-SLEDAI by week 24. However, mindful of NHS resources, it was agreed during TA397, that we would restrict “responders” to those that had a clinically relevant improvement by week 24 (i.e., ≥4-point SS score reduction). According to clinical experts, some of these “non-responder” patients will still have very active disease, and their background standard therapy would need to be further optimised encompassing an increase in steroid dose at the very minimum to try and gain better control of their active disease state.
Furthermore, GSK has now conducted a further post-hoc analysis of the pooled 52/76 IV BLISS trial data which demonstrates that in the HDA-2 subgroup out of the 87 patients who were considered to be non-responders at week 24 (<4-point reduction in SS score), 30 (34.5%) of patients achieve a ≥4-point reduction in SS score at week 52 (Table 1). This is with no change to their medication i.e., they continued belimumab, which suggests a slow response to this medicine for some patients. This demonstrates that these week 24 non-responder patients can respond later, which suggests it is plausible that others, when treated with additional ST medications are also likely to have their disease activity levels improved. Therefore, GSK disagrees with the Committee’s conclusions that it is not clinically plausible that nearly half of the “non-responders” would not respond on ST by week 52.

Table 1. SELENA-SLEDAI score responders at week 24 compared with week 52 in HDA-2 subgroup
<table>
<tr><th></th><th>belimumab non-responder at week 24 (n=87)</th></tr>
<tr><td>belimumab responder at week 52</td><td>30 (34.5%)</td></tr>
<tr><td>belimumab non-responder at week 52</td><td>57 (65.5%)</td></tr>
</table>

GSK acknowledges the ERG’s concern that no detriment has been applied to the belimumab non-responders in the model if we assume that these patients take the average ST disease activity score at week 52. Therefore, as an additional scenario analysis, we have added a cost of £600 assigned to the belimumab non-responders during Year 1 in the model to cover the costs related to additional ST medication and two extra out-patient

</td><td>discussed the modelled response to treatment for belimumab ‘non-responders’. It concluded that it was still unclear whether disease activity in the model for belimumab ‘non-responders’ is consistent with the BLISS trials. The committee discussed how in the model ‘non-responders’ to belimumab had the same reduction in disease activity as people having standard therapy at 52 weeks. It concluded that disease activity for people whose condition has not responded to belimumab should be based on the BLISS trials for the first 52 weeks. See FAD sections 3.13 to 3.14.</td></tr>
</table>

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			physician visits to treat their high disease activity. Costs were proportionally applied to the belimumab arm of the models, based on the percentage of non-responders for each formulation and were not applied to patients who were non-responders in the standard therapy arm. The resultant ICERS were £25,190 and £25,248 per QALY gained for the IV and SC formulations, respectively. • GSK would like to confirm that the regression model to determine a patient's change in SS score at week 52 was provided both as part of the economic model, and in Section 6.3 of the submission provided as part of TA397. • GSK notes that the ACD suggests moving to a model cycle of 6 months. However, SLE is better represented by a model using yearly cycles to capture the chronic nature of the disease.	
10	Consultee (company)	GSK	**In the health economic model disease activity is based on the BLISS trials for the first 52 weeks, however belimumab non-responders assume the standard therapy (ST) arm average disease activity score at Week 52 to align with how patients will be managed in UK clinical practice.** • As explained in the responses to both the clarification questions and the Technical Engagement document the economic model does not contain any errors related to how SELENA-SLEDAI (SS) score is modelled. It is an assumption that belimumab non-responders take the average ST score (regression coefficient) rather than the belimumab non-responder regression coefficient from week 52 onwards. This assumption was made as patients who do not respond on belimumab at week 24 switch to ST and continue ST for the remainder of the modelled time horizon within the belimumab arm of the model i.e., the remaining 28 weeks of the first year and any remaining cycles thereafter. The economic model's treatment continuation criterion (achieving a ≥4-point reduction in the SS score at week 24, "responder") is based on the belimumab SmPC and consistent with UK clinical practice and reflecting the terms agreed under the managed access agreement. It is standard practice in the UK and consistent with regulatory approval, that clinicians will assess improvement in the patients' disease activity after six months of treatment with belimumab and those patients who are not deemed to have experienced benefit from treatment with belimumab will be taken off the medicine. • This assumption was also validated with experts for TA397 and has been re-validated with two UK clinical experts for this re-appraisal. The feedback from the clinical experts is that when patients discontinue belimumab at week 24 due to not meeting the responder criterion their ongoing management will depend on the severity of their disease and level of disease activity. Typically, their steroid dose could be increased alongside a change of immunosuppressant depending on prior treatments. If disease is severe, patients could receive IV cyclophosphamide or rituximab preceded by a dose of IV methylprednisolone to control symptoms in the short term. The aim of treatment is to stabilise their disease as	Comments noted. The committee discussed how in the model 'non-responders' to belimumab had the same reduction in disease activity as people having standard therapy at 52 weeks. It concluded that disease activity for people whose condition has not responded to belimumab should be based on the BLISS trials for the first 52 weeks. See section 3.14 of the FAD.

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			soon as possible which could be achieved anytime from 3-months after stopping belimumab if they respond to the alternative treatment regimen. We therefore maintain that our base case assumption is valid. • However, as part of the technical engagement response, GSK provided scenario analyses where belimumab non-responders assumed the average SS score of ST patients by year 1.5 (Week 76) instead of at Week 52 (our base case) in the model. These scenario analyses have now been updated with the revised PAS discount and show that the IV and SC formulations result in ICERs of £26,630 and £27,716 per QALY gained, respectively. The model files showing these updated scenario analyses have been shared with NICE.	
11	Consultee	British Society for Rheumatology	**Has all the relevant evidence been taken in to account?** We are aware that further evidence in support of belimumab has accumulated since the 'cut-off' date adopted by NICE. We believe these are relevant and should be considered before a final decision is made. 1) Two-year, randomised, controlled trial of belimumab in lupus nephritis. Furie R, Rovin BH et al. N. Eng. J. Med. 2020 17;383:1117-1128 2) OP0129 Belimumab after Rituximab significantly reduced IgG anti-dsDNA antibodies and prolonged time to severe flare in patients with systemic lupus erythematosus. http://dx.doi.org/10.1136/annrheumdis-2021-eular.553 We do note that the committee reviewing the evidence did not contain any rheumatologist, nephrologist or dermatologist who may be familiar with this disease or the complexities of management and wonder whether this may have hampered interpretation of the information.	Comments noted. The committee has considered all the relevant evidence for its decision making in line with NICE's guide to the processes of technology appraisal. This includes input from clinical experts who have experience in the management of systemic lupus erythematosus in NHS clinical practice. The company considered that the use of belimumab in people with lupus nephritis was outside of the scope of this appraisal.
12	Consultee	British Society for Rheumatology	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We would comment that a considerable amount of the data on which the decisions have been made appear to be redacted and therefore external scrutiny is hard, but we have some observations to make that do raise concerns about the interpretation of the cost effectiveness of belimumab. a) Estimating the costs associated with damage accrual in lupus and long-term disease activity are methodologically difficult and of course not directly addressed (or addressable) in a controlled-trial setting. Attempts have been made to estimate these costs as part of the technology appraisal but we have concerns this process may have significantly underestimated these costs associated with active lupus and the resulting damage accrual.. b) We note the ERG concerns with the propensity matched analysis using the Toronto Lupus Cohort, in particular the use of calibration factors. We understand concerns with this analysis, but would also have concerns with the use of the Toronto Cohort as an appropriate comparator at all. Firstly it is clear that it was difficult to clearly match patients	Comments noted. Please see individual responses below: Uncertainties in the evidence The committee discussed there were uncertainties in the clinical evidence and that some of the assumptions used in the modelling were not appropriate. It considered that there was uncertainty about the cost-effectiveness estimates. However, it also considered that there were additional benefits of belimumab that may not be captured in the cost-effectiveness analysis. See FAD sections 3.16 and 3.19.

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			with the proposed HAD-1 group in the UK. It is also a large cohort of patients managed in a different country up to 30 years ago (only patients prior to 1990 excluded). Considerable changes in medical care have taken place over this time frame that might influence the development of damage and the cost associated with it. This may be the only available comparator group but there are clearly methodological issues in its use that risk considerable error in the estimate of 'standard or care' lupus costs.. c) We also note that assumptions are made about the cause of patients discontinuing belimumab, with the assumption that it must largely be due to inefficacy. The cause of patients discontinuing medication is however much more nuanced than that. In this population of predominantly young women some patients will choose to discontinue belimumab to attempt a pregnancy and others because of the inconvenience of regular infusions. Some patients who are doing well make a decision to step-down their therapy because they feel much better. We cannot make assumptions about the reasons for discontinuation if the data is not available. d) We would note that the BLISS clinical trial populations are not well matched with the group of patients currently receiving belimumab in the UK. UK rules stipulate the requirement for a much higher level of disease activity and more refractory disease than required for enrolment in to clinical trials. e) We would disagree that rituximab is a relevant comparator for belimumab in UK practice, because NHS commissioning rules specifically delineate a pathway for patients appropriate for rituximab from a pathway for patients appropriate for belimumab. These are therefore different patient populations with different characteristics (in general those getting Rituximab have renal disease, central nervous system disease or rather milder disease of skin and joints, while those getting belimumab have more active multisystem involvement not including kidneys or nervous system). f) We agree that the lack of 'trial quality' long-term data is frustrating (although methodologically understandable given the nature of the disease), however we are not aware that trial-quality long-term data has been required for any other autoimmune or rheumatic disease for which biologic therapies have been assessed at technology appraisal. Why is lupus considered different in this regard? g) In estimating the costs of lupus-related damage, the analysis has referenced work looking at the costs of single organ complications (often not in patients with lupus and many very dated studies) and not considered the additional costs of supporting these problems in a patients with multisystem disease. We do not believe the approach of inflating NHS reference costs from 2005/6 is going to accurately estimate the costs of managing these complications. Clinical practise will have changed considerably over the intervening 15 years with additional therapeutic options and improved life-expectancy in patient living with damage. We are unclear how the 'weightings' have been applied in table 67. It is difficult to understand in table 71 why no costs are considered to apply to gonadal failure or skin disease, given the costs of fertility preservation/infertility treatment, skin camouflage, psychological morbidity due to skin disfigurement, wigs etc. etc. h) The disease activity costings appear to be based on the SELENA-SLEDAI system domains, which do not capture all items of disease activity (in comparison with the BILAG 2004 index). The cost of flares does not seem to be accounted for.	<u>Propensity score-matched analysis</u> The committee discussed the propensity score-matched analysis comparing organ damage progression in people having treatment with belimumab or standard therapy with 5 or more years of follow-up. It considered that the results of the propensity score-matched analysis may not be relevant to NHS clinical practice and were likely biased in favour of belimumab. See FAD sections 3.8 to 3.9. <u>Treatment discontinuation</u> The committee heard that in clinical practice people may decide to stop maintenance treatment for reasons other than lack of efficacy, such as their disease being well controlled or in remission, or because they are planning to start a family. See FAD section 3.9. <u>Treatment continuation</u> The committee decided to recommend belimumab for active autoantibody-positive systemic lupus erythematosus, providing that treatment beyond 24 weeks should only continue if there is an improvement in disease activity (assessed by an improvement in SELENA-SLEDAI score of ≥4 points). This in line with the summary of product characteristics for belimumab. See FAD section 1.1. <u>Rituximab as a comparator</u> The committee discussed the appropriate comparators for the

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			i) The cost of managing disease and treatment-associated infection does not seem to be accounted for although this is an important complication of lupus and its treatment. j) We cannot agree with the base-case cost assumptions related to steroids as summarised in table 73. The assumption that belimumab and standard therapy groups would be receiving the same dose of oral steroids must be flawed given the demonstrated steroid sparing effect of belimumab. The expectation is that belimumab will allow lower oral steroid dosing. k) Costing needs to consider the specific commissioning rules that are applicable for belimumab in the UK population – in particular the stipulation that treatment is withdrawn if sufficient improvement in disease activity has not been seen at three months. Only good responders are treated with belimumab beyond three months, so this is a selected population who are responding better that the average patient seen in the clinical trial populations.	population being considered in this appraisal. It concluded that rituximab is a relevant comparator. See section 3.4 of the FAD.
13	Consultee	British Society for Rheumatology	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We do feel that further consideration needs to be given to the decision to decline usage of one of only three licenced therapies for this condition, in favour of promoting a standard of care based largely on unlicensed therapy options. We feel that further consideration needs to be given to both the clinical consequences and the perceived cost effectiveness of a 'standard of care' model based on the fact that the provisional commissioning arrangements for belimumab have focussed use on a small group of the sickest lupus patients. Many of these patients have already failed numerous standard of care options. What is left for them is prolonged use of unacceptably high doses of steroid, or cumulative high doses of cytotoxic therapies, with resultant risks of infection, malignancy and cumulative lupus 'damage'. The 'cost' of this option cannot be based on the standard of care cost for an average lupus patient, because it is a specific group of refractory high-disease activity patients. There is considerable anecdotal evidence that patients on belimumab frequently flare within weeks of medication cessation. We feel that more weight needs to be given to the good safety data around belimumab and consider this in comparison with the well documented morbidity associated with steroids and cytotoxics. There may be additional data around the relative safety of belimumab in relation to COVID-19, in comparison with Rituximab that may be associated with vaccine inefficiency and worsening COVID-19 outcomes. We would re-iterate the point made in section 2 that current guidelines for NHS usage stipulate belimumab is withdrawn from patients not making a good response at 6 months, so only patients in whom this drug is proving effective will be on it in the long-term. NHS practice, quite rightly, adheres closely to national and international consensus guidelines on management. The most recent lupus guidelines published by EULAR (European Alliance of Associations for Rheumatology) and the British Society of Rheumatology promote belimumab as a treatment option for lupus that has failed treatment with steroids, hydroxycholoroquine and	Comments noted. The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19.

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			immunosuppressants, with a high degree of concordance among the experts reviewing the evidence (http://dx.doi.org/10.1136/annrheumdis-2019-215089, https://doi.org/10.1093/rheumatology/kex286) We do support the premise that use of belimumab is applicable to the HDA-2 population and not just the HDA-1 population, and would comment that many patients with high disease activity and damaging disease do not have both low complement and high dsDNA antibody levels, or often do at some point in their disease course but normalise one or the other due to initial treatment attempts even if the clinical manifestations of disease remain active. We do support the premise that the subcutaneous formulation of belimumab is effective and offers considerable advantages to may patient who are otherwise discriminated against due to their geographical location away from a specialist centre who provides intravenous therapy. This may have additional economic benefits but reducing work absence (6.5 working days a year lost through infusions). We recognise some of the uncertainties around the modelling of long-term cost effectiveness but would argue that the alternative costs of 'standard of care' are considerable in a cohort of sick patient exposed to high doses of steroid and cytotoxic agents. In summary we understand the outcome of the technology appraisal is to decline belimumab usage on the grounds of cost effectiveness, but we feel that there is significant risk that the evidence, assumptions and extrapolations required to assess cost effectiveness is subject to considerable uncertainty and risk of inaccuracy. We welcome the recognition that this is clinically effective and has met its endpoint in four randomised controlled trials. We are also aware the UK national registry and commissioning arrangement limit usage to a small group of patients and allow real-time evaluation of efficacy over time. We would argue an extension of the current arrangements, even if on a ongoing provisional basis would be the most appropriate outcome. We are also concerned about the fate of the existing patients receiving belimumab. The prospect of stopping treatment and 'transitioning' them on to an alternative therapy, when most of these patients have already failed on these alternative therapies is unrealistic and will be devastating for these patients. At the very least patients on this treatment should be allowed to continue.	
15	Consultee	British Society for Rheumatology	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** There are some potentially discriminatory elements to this policy: a) We are aware that lupus as a whole, but also more severe lupus, is over-represented in patients from a non-European ancestral background. This is the population that is therefore going to be particularly affected by the decision to decline usage of this drug. b) The suggestion that gonadal failure should not be considered as accumulating 'costs'	Comments noted. The committee discussed potential equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See FAD section 3.18.

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			implies that it is felt this should not be managed or treated as a complication of lupus therapy. Lupus predominantly affects women of childbearing age for who the desire to have children is an important part of treatment decision making. Again the promotion of a 'standard of care' that can include gonodotoxic agents has a potentially discriminatory element to it.	
16	Consultee	LUPUS UK	We are concerned that this recommendation will make a treatment, that has been shown to be clinically safe and effective, unavailable for patients who rely upon it with no suitable alternative. Belimumab is currently reserved for severe and/or refractory lupus for which standard therapy alone has proved ineffective or insufficient. Withdrawing belimumab would leave only rituximab as a possible addition/alternative to standard therapy. Unfortunately, for many, rituximab is not an effective therapy. Analysis of BILAG BR data by McCarthy (2017) found response to rituximab in 49% of patients - https://academic.oup.com/rheumatology/article/57/3/470/4688912. People with severe and/or refractory lupus who cannot be sufficiently treated with standard therapy and rituximab will be left with no other available treatment options. This will result in increased dependence on corticosteroids, worsened quality of life and increased flares requiring hospitalisation. Belimumab should continue to be available as a treatment option for patients who are unresponsive or intolerant to rituximab and standard therapy. Here are some first-hand experiences of people currently treated with belimumab: • *I was on rituximab (amongst other treatments) before Benlysta, and that flared my lupus up 'generally'. Once I started Benlysta, after a year to two years, they wanted to try and get rid of some remaining symptoms, for example some existing joint pain. So, I was put onto methotrexate and within a couple of weeks (of a very low dose) my liver inflamed six times the 'normal' level, and it took 12-18 months to drop back to normal.* *I am now on mycophenolate (with a few others) to try and help with the symptoms that are not controlled by Benylsta, it helps to an extent- I think?!* *I have had lupus just under 9 years now and it has never been in remission and have always found it tricky to live with on a daily basis if I'm honest! Benlysta has been the only thing that I've noticed that has made the most difference with the least amount of nasty side effects. Injections would be great as I have to travel 1:30hr into central London every time!* • *I was on lots of medication before and I use to be on another infusion (cannot remember the name of it but can ask my consultant if you need the name). These did not improve my condition but the belimumab helps a lot. I do notice the difference. I still have weak days but compared to before, it is working.* • *I am 33 years old and was diagnosed with SLE when I was 19. I was stable for many years and then I wasn't and over a number of years I ran out of treatment options. Azathioprine - failed due to poor liver function results. Mycophenolate - no positive response. Methotrexate - some response but not sufficient on its own. Rituximab - no response.*	Comments noted. The committee considered the views of people with systemic lupus erythematosus when formulating its recommendations. It discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19.

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			Belimumab - positive response! *Belimumab has finally given me a treatment that means I have good days and bad days rather than just all bad days. It has also allowed me to start rebuilding my life again. Before getting this treatment I had lost any social life. I live on my own and all I was doing was the minimum to keep going, maintain a job and I was needing a lot of help from family to keep up with jobs around the home. Everything I did took more and more energy from me and gave me more pain. It was a very lonely existence. Due to the nature of all of these treatments and needing to give them time to work I probably had 2.5 years of living in 12-week chunks before I was reassessed and doses were tweaked or we moved on to the next drug, it was beyond frustrating and felt like I was throwing such valuable time away. When I started belimumab I probably felt a benefit from around 6 months, and I feel like I can rely on it now to keep as much of my lupus at bay as possible.* *On a practical note, the routine of getting my infusions is very easy to manage (much easier than 6 hours for rituximab) and I experience no side effects.* *For me, it is a huge worry about what would happen to me if this drug was not an option anymore given my experiences with the others.* • *Prior to starting belimumab in December 2020, I was at the end of my tether with autoimmune disease including SLE, Sjögren's, Raynaud's and scleritis. It's been a 15-year struggle since diagnosis with increasing medication and reducing benefit over time. During this time, I also had breast cancer and a recurrence, resulting in a double mastectomy. Exhaustion meant I had a maximum of five functional hours a day, could no longer work, had no social life and could barely take care of myself. I couldn't speak towards the end of the day; my voice was too quiet and people couldn't hear me on the phone. I was sleeping around 10 hours a day. I was in constant pain from sore joints, badly healed fractures, scleritis flares, headaches and chest pain. Despite taking more than 30 tablets a day, my health continued to deteriorate and filling the pillbox every night was just a depressing reminder of how bad things had become. I no longer cared to live.* *When my rheumatologist suggested belimumab, I was more than happy to try, but to be honest, I didn't really expect that it would work for me. I was just ticking off the options so that I could tell myself at least I'd tried everything.* *About a week after the first infusion, I actually felt a subtle change, but put that to wishful thinking. After the second infusion I felt more certain that something was happening. By the third infusion I was sure. I had more energy and less pain. Now, three months since beginning the drug, I have eight useful hours in the day, and sleep eight to nine hours. While I am still using painkillers, I now experience very little pain. I have been able to exercise much more and my fitness levels have increased.* *Regaining some control over my body means regaining control in my life and the difference is like night and day. As a writer, I feel my mind is sharper and I am now able to entertain the idea of new projects. Having recently lost a crown, I am now considering a dental implant, something that wouldn't have even been an option before.* *All my friends comment on the change, apparently I sound very different. In an unexpected development, my libido has returned after an absence of more than six years. Until now, I would never have considered being able to partner anyone again as I had nothing to offer*	

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			and would only be a burden. Tentatively, I'm beginning to see a possible future and to make plans. *As I become accustomed to the fact that these changes are real, I have also begun to reduce my reliance on prednisolone from 10mg a day to 9mg, aiming for 7.5mg initially, with an increasingly optimistic goal of coming off it altogether – an inconceivable aim prior to belimumab.* • *I was diagnosed with lupus 15 years ago and since diagnosis have always had very active lupus. This has resulted in frequent hospital admissions due to flares and subsequent health complications as a result. I have been receiving belimumab for 18 months and during that time have only had one hospital admission. This is unprecedented for me since diagnosis. Receiving belimumab has also resulted in a reduction of my medications for the first time since diagnosis. I have spoken to other patients receiving this treatment and have only heard positive outcomes.*	
17	Consultee	LUPUS UK	New evidence has been published following the appraisal committee meeting from a trial investigating the combination of rituximab and belimumab in the treatment of SLE. BEAT-LUPUS (Belimumab after B cell depletion in SLE) was a 52-week phase IIb, randomised, double-blind, placebo-controlled clinical trial investigating the safety and efficacy of intravenous belimumab after B cell depletion therapy (rituximab). This trial met its primary endpoint, a significant reduction in IgG anti-dsDNA antibody levels, and demonstrated that belimumab prolongs the time to severe flare compared to placebo. The results suggest that belimumab after rituximab is a safe and effective treatment for patients with SLE and supports further development of this combination as a novel therapeutic strategy. The published results can be found at https://ard.bmj.com/content/80/Suppl_1/74.2 These findings suggest that belimumab may be used, in ways other than as a comparator to rituximab, to improve patient outcomes.	Comments noted. The committee has considered all the relevant evidence for its decision making in line with NICE's guide to the processes of technology appraisal.
18	Consultee	LUPUS UK	We are concerned about the ERG and committee's assumptions concerning the modelled response to treatment for belimumab 'non-responders'. Within item 3.11 of the document, it states that *"the committee did not think it was clinically plausible that nearly half of these 'non-responders' would have had a SELENA-SLEDAI score reduction of 4 or more at 52 weeks on standard therapy alone"* however, during the committee meeting the clinical experts did consider it plausible, especially given the likely high doses of corticosteroids and other immunosuppressive medications used as part of standard therapy. The committee did not give due consideration to the considerable experience of the clinical experts regarding this matter.	Comments noted. The committee considered a range of evidence, including clinical expert opinion, to inform its conclusion on modelled response to treatment for belimumab 'non-responders'. See FAD section 3.13.
19	Consultee	LUPUS UK	We are concerned that the appraisal process has not given appropriate consideration to the	Comments noted. The committee

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			challenges of obtaining sufficient quality data for a disease such as SLE. The heterogeneous, fluctuating nature of the disease presents considerable difficulty in measuring clinical effectiveness, with many lupus trials failing. Recruitment and retention of patients within trials is a significant barrier and modelling will often be required to present findings. People living with lupus in England should not be punished with the removal of this important treatment option due to the logistical challenges associated with obtaining data of sufficient quality to meet the NICE health technology appraisal standards. One patient provided the following comment: • *I feel it is extremely unfair that assessment for the efficacy of the treatment relies on consistent sufficient data. The nature of lupus is inconsistent and symptoms/treatment/experiences will vary from one patient to another.*	discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19.
20	Consultee	LUPUS UK	Item 3.14 in the document indicates that the ERG presented an analysis with modelling assumptions using the BLISS trial evidence. We are concerned that the BLISS trials' HRQoL measure was modelled using EQ-5D. EQ-5D has been reported to "lack sensitivity or fail to capture important aspects of health in SLE" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6178935/#b20-prom-9-339. This would therefore suggest that the model estimates understate the cost-effectiveness of belimumab.	Comments noted. Please note that the EQ-5D is the preferred measure of health-related quality of life in adults, as outlined in the reference case in NICE's guide to the methods of technology appraisal.
21	Consultee	LUPUS UK	Item 3.4 in the document states that *"the committee heard that, if belimumab is not recommended for routine commissioning, more people would potentially have treatment with rituximab in its absence"*. Has the committee given sufficient consideration to the potential impact this could have for vulnerability to COVID-19 infection? The COVID-19 pandemic has introduced additional need for vaccinations and, as a B-cell depleter, rituximab can present challenges for important vaccinations. "It is recommended to wait for vaccination **at least 6 months after rituximab infusion**. However, if a vaccine, such as influenza, needs to be administered within a certain time interval, vaccination should be done, although lower vaccine effectiveness is expected." https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5042271/ Early reports from studies have indicated that rituximab, but not other antirheumatic therapies, is associated with impaired serological response to COVID-19 vaccination. https://ard.bmj.com/content/early/2021/05/10/annrheumdis-2021-220604. The potential increased vulnerability to COVID-19 infection needs to be carefully considered if	Comments noted. The committee discussed that there may be additional benefits of belimumab that may not be captured in the cost-effectiveness analysis, including expert testimony that it may have a less severe impact on COVID-19 vaccine efficacy compared with rituximab. See section 3.19 of the FAD.

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			comparing rituximab and belimumab. The impact will go beyond risk to physical health and will also affect socioeconomic and psychosocial health. One patient commented: • *Regardless of effectiveness, under COVID-19 or other future pandemic conditions, it is possibly more of a risk to immunocompromised patients to have rituximab with 6-monthly infusions than belimumab with either 4-weekly infusions or weekly injections where the drug can be cleared from the body more quickly.*	
22	Consultee	LUPUS UK	We are concerned that withdrawing subcutaneous injections of belimumab will increase inequalities in access to treatment for people with lupus. Rituximab is only available as an intravenous infusion, administered over a period of six hours at specialist centres. A Rare Disease UK study (https://www.raredisease.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 significant barrier to access for some patients, especially those in employment, those with childcare responsibilities, those who live in remote areas and those on lower incomes who cannot afford travel and/or time away from work. This same barrier is not present with subcutaneous belimumab. A decision to withdraw subcutaneous belimumab will disproportionately impact those who have lower incomes and those who do not have access to a specialist centre. It may limit their treatment to standard care despite the guidance calling for an additional biologic therapy in their case.	Comments noted. The committee discussed potential equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See section 3.18 of the FAD.
23	Public	Patient 1	**3.3 Rituximab is a relevant comparator** Regardless of effectiveness, under Covid-19 or other future pandemic conditions, it is possibly more of a risk to immunocompromised patients to have rituximab with 6-monthly infusions than belimumab with either 4-weekly infusions or weekly injections where the drug can be cleared from the body more quickly. **3.15 There are no equality issues that can be addressed in this technology appraisal** As 90% of the UK's 50,000 SLE patients are women, the removal of belimumab as a treatment option would disproportionately affect women. The pain, fatigue and brain fog of SLE can severely undermine one's ability to earn a living and one's sense of self. As SLE is a predominantly 'women's disease', I wonder if the same consideration to withdraw belimumab would apply if SLE negatively affected more men? **3.17 Belimumab is not recommended for routine use** Not just a treatment - SLE remains a very complex, poorly understood disease with many elements that are difficult to quantify. Aside from being the only treatment focusing on SLE itself, belimumab is	Comments noted. The committee considered the views of people with systemic lupus erythematosus when formulating its recommendations. Please see individual responses below: <u>Belimumab is recommended</u> The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the

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			also part of the desperately needed work that will help us better understand the immune system and develop more new generation drugs for a wide range of autoimmune disease. The immune response is pivotal to many illnesses, including cancers, Covid-19 etc, and understanding it will impact across a wide swathe of disease. Belimumab is not just an autoimmune disease treatment, but part of a longer process of trying to improve outcomes and predict who will benefit from what approach. Please consider at least extending the appraisal period for a further five years to allow for the collection of more data to demonstrate real-world cost-effectiveness for this relatively new drug. On a personal level, six months since beginning belimumab, I have gone from five to eight useful hours in the day, and sleep eight to nine hours instead of 11 or 12. While I am still using painkillers, I now experience significantly less pain. I have been able to exercise much more and my fitness levels have increased. Regaining some control over my body means regaining control in my life and the difference is like night and day. As a writer, I feel my mind is sharper and I am now able to entertain the idea of new projects and, after a year's hiatus, maybe even to work again. For the past six years exhaustion and pain meant I have had almost no social life. Towards the end of the day, through fatigue my voice was too quiet and people couldn't hear me on the phone. Now my friends comment on the change, apparently I look and sound very different. In an unexpected development, my libido has returned after an absence of more than six years. Until now, I would never have considered being able to partner anyone again as I had nothing to offer and would only be a burden. I understand many relationships don't survive the demands of SLE. Mine didn't. Tentatively, I'm beginning to see a possible future and to make some plans. I have been able to reduce my reliance on prednisolone (which I detest) from 10mg a day to 9mg, aiming for 7.5mg, though I understand I'm far too dependent on it now to consider coming off it altogether. Rather than lose belimumab, I would love to see it become more widely available to SLE patients and earlier in the disease path, where it might spare people from SLE-caused organ damage and the dreadful side-effects of corticosteroids. Those people might have a chance at real lives, rather than a depressing existence on a downward spiral.	cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19. Equality The committee discussed potential equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See section 3.18 of the FAD.
24	Public	Patient 2	**3 Belimumab as a treatment option** I have been having belimumab for 3 years. Firstly as an IV infusion and in the last year since the start of Covid S/C injection which i can administer myself at home. I have had no side effects from Belimumab. Since starting Belimumab I have felt so much better. No further hospital admissions. My symptoms have improved greatly and I have been able to reduce my steroid dose which is significant as the side effects from the steroids are misrable. I am now able to work full time as a nurse. A job I thought I would have to give up because I was so unwell with multipul sick days. My quality of life has increased and my skin rash has improved giving me more confidence to go out socially. Being able to give myself the injections at home has reduced my hospital visits monthly and enables me to continue with a regular work patten. This drug has made such a differance to my life where there was no responce to other medication that had been tried over many years.	Comments noted. The committee considered the views of people with systemic lupus erythematosus when formulating its recommendations. It discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, the committee took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness

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			I feel discontinuing the use of Belimumab as a treatment for lupus will have a devastating impact on many patient's mental and physical wellbeing impacting on the ability to work and maintain an inderpendant life. I urge you to reconsider.	results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19.
25	Public	British Isles Lupus Activity Group (BILAG)	To Whom it may concern, I'm writing on behalf of the British Isles Lupus Activity Group – a group of NHS rheumatologists with a special interest in SLE, and the steering group of the BILAG Biologics Register. We note the preliminary review of belimumab, which proposes to no longer fund this treatment for SLE patients in the UK. We feel that this decision does not take account of all the facts or the needs of patients with SLE and should be reversed. Please note the following reasons. 1. SLE is an uncommon condition, and still has an increased mortality risk and a devastating effect on quality of life on those who survive. 2. Patients with SLE require markedly greater use of medical resource than most other rheumatic conditions in terms of hospital and intensive care admissions, clinic attendances, and multi-speciality care. Yet, treatments options are fewer that other autoimmune rheumatic diseases such as rheumatoid arthritis, and most of these are unlicensed and not proven to be effective in clinical trials. 3. SLE is highly diverse in terms of organs affected, severity and response to therapy. This problem therefore requires a flexible approach to therapeutic options. and also allowance made for the challenges of conducting and the interpretation of clinical trials, where imperfect outcomes measures have to capture changes in every organ system that is affected by SLE. 4. Belimumab is the only licensed therapy other than hydroxychloroquine and glucocorticoids. In a disease with often unsatisfactory treatment options, we feel that patients have a right to treatments with proven efficacy where available. 5. Belimumab is central to European (EULAR) guidelines for treatment of refractory SLE if refractory to methotrexate or azathioprine, as well as BSR guidelines. The UK would be deviating from internationally agreed treatment pathways if belimumab were not available. This would result in worse outcomes for patients in England compared to those treated in Europe. 6. Adherence is a major problem in SLE with oral immunosuppressants, which may relate to	Comments noted. The committee discussed the effects of SLE on people with the condition, the lack of effective treatment options and the relevant comparators. See FAD sections 3.1, 3.3 and 3.4. The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19.

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			neuropsychiatric effects of the disease itself. Intravenous therapies are often therefore be invaluable to ensure control of disease. 7. While rituximab is valuable for resistant SLE, not all patients can be maintained with rituximab. Some patients have good but short responses, requiring more frequent dosing. In such patients, with each flare or relapse, additional damage and toxic glucocorticoid exposure may accrue. Multiple cycles of rituximab may lead to hypogammaglobulinaemia, with high rates of severe infection and requirement for expensive IVIg therapy. Belimumab can avoid this problem due to regular dosing ensuring stable control of disease activity, with an impressive safety record. 8. Getting the right treatment first time is important in SLE, with cumulative harms of disease activity, damage, glucocorticoids and quality of life if multiple therapies are tried and failed. Belimumab has proven stratification variables that can identify the patients most suitable, so that for these patients they are more likely to get the right drug first time. If patients do not respond the treatment is stopped after 6 months or sooner. 9. If belimumab is not available as a treatment option, patients who are refractory to other therapies, and suffer from persistently active disease are likely to be treated with high dose steroids, with all the associated adverse effects, including serious infection, cardiovascular disease, depression, osteoporosis and fractures, as well as increased risk of severe COVID (both steroids and active disease are a risk factor for severe COVID). This would be contrary to best practice and EULAR guidelines, which recommends the use of lowest possible steroid dosage, ideally below 7.5mg/day. 10. An alternative treatment for refractory SLE is cyclophosphamide but it must be noted that this treatment is not suitable for long-term use due to cumulative malignancy risk and other severe toxicities. 11. The number of SLE patients who actually require belimumab is small. 12. The BILAG-BR data on belimumab data may underestimate its potential future efficacy. Many patients had already received rituximab, and were therefore more resistant than the populations in belimumab clinical trials. This was a legacy of the period when such patients had no therapeutic options and would not represent future long-term usage. 13. SLE is treated in specialist centres. The UK SLE community is well connected with regular BILAG meetings, local MDT processes and registry data so that we are able to ensure belimumab is used in only the most appropriate patients and monitored appropriately. When other therapeutic options that may be more appropriate are available, including unlicensed therapies or enrolment into clinical trials, we will ensure these options are used. 14. We note that the appendix to the managed access agreement stipulates that patients who are currently receiving belimumab and are responding well will need to stop therapy within 12 months of this negative decision. This is particularly problematic: most of these patients have	

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			already failed other options and would be forced back into severely active disease if their treatment were withdrawn, that may include recurrence of disability, hospitalisation, organ failure or death. We consider this to be unethical when there is a licensed therapy that can prevent such an outcome.	
26	Public	Web comment	**Has all of the relevant evidence been taken into account?** I defer to colleagues from BILAG in answering this question. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I am not an expert in health economics and it appears that belimumab is judged as too expensive over other cheaper, unlicensed drugs. **Are the recommendations sound and a suitable basis for guidance to the NHS?** These recommendations will remove an option for patients who are refractory to other drugs and thus increase their steroid burden and treatment with other unlicensed therapies. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The removal of this monoclonal antibody biologic therapy that may be used in early stages of pregnancy due to limited placental transfer in first trimester will limit therapeutic options to women considering pregnancy and increase chance of disease flare in those in whom it is stopped. Therefore, women of reproductive age will be disadvantaged by withdrawal of belimumab.	Comments noted. Please see individual responses below: <u>Belimumab is recommended</u> The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19. <u>Equality</u> The committee discussed potential equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See FAD section 3.18.
27	Public	Web comment	**Has all of the relevant evidence been taken into account?** Unable to comment **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**	Comments noted. Please see individual responses below: <u>Belimumab is recommended</u> The committee discussed the uncertainties in the clinical

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			Cost effective analysis does not seem to include the paediatric cohort between 5 years to 12 years who has no access to rituximab according to the commissioning policy **Are the recommendations sound and a suitable basis for guidance to the NHS?** - Rituximab is not licensed in SLE and currently is the only NHSE funded biologic for refractory SLE; there is no alternative product for refractory SLE patients who cannot tolerate rituximab or developed severe allergic reaction to rituximab. Belimumab is a good alternative for these type of patients. - Belimumab is recommended as an add on therapy in the 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. It is considered in the previous appraisal however it failed to justify the reason why the decision was made to differ from European practices. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** - There is no licensed biological disease-modifying antirheumatic drugs product for children after failing standard immunosuppressants and DMARDs. Uncertain where the evidence stands for recommending an off-label use of biologics over a licensed product for children over 5 years or more - Currently commissioning policy for using rituximab in SLE only applies for post-pubescent children; leaving an unmet needs and potentially discriminating children from 5 – 12 who have no access to any funded biological agent (cannot access via the medicine for children commissioning policy as no paediatric licence and dose not in the BNFC)	evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19. Equality The committee discussed potential equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See FAD section 3.18.
28	Public	Web comment	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No. 1. The committee have considered flawed, indirect comparisons as "evidence". 2. The problem that besets SLE outcome ascerntainment are abstract, multi-faceted clinical scoring systems that are very vulnerable to misscoring (eg mistaking damage for activity or vice versa). The fact is that I have observed substanial and sustained improved in belimumab treated patients that has allowed significant steroid sparing. Belimumab clearly has very significant clinical efficicacy - the use of the various abstract metrics and scores serves to obscure this fact. The recent data on belimumab in lupus nephritis provides further evidence to back this up when looking at hard endpoints. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No. Notably, these recommendations are completely at odds with practice in Europe, Australia and	Comments noted. Please see individual responses below: Belimumab is recommended The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It

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			America. How did the committee committee reach a conclusion opposite to their counterparts in these countries (which include those with publically funded health systems)? **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The SLE patient group most in need of belimumab are BAME patients (enriched for severe disease). Not approving belimumab disproportionately affects them. I find this to be a bizarre decision. Belimumab is the first new drug for SLE in over 50 years, and has RCT data to back it up. As a clinician in a specialise lupus centre, I have used belimumab in many patients with previously refractory disease. The effect has been dramatic: to keep them well, reduce relapses and avoid the need for acute hospitalisations. NICE's decision is completely at odds with practice in other developed nations. It is also clearly discriminatory since SLE is disease that affects females to men 10:1, and severe disease disproportionately affects BAME individuals. **1 Recommendations** 'rituximab' Rituximab didn't show efficacy in RCTs. Belimumab did. Yet the former can be given in the NHS- this decision makes no sense! 'considers an acceptable use of NHS resources' If NICE don't approve belimumab, there will be more use of NHS resources (eg acute admissions, complications from increased steroid use eg hip fracture, avascular necrosis, diabetes) and cost savings from not funding it will be lost **3.6 Belimumab improves the Systemic Lupus Erythematosus Responder Index (SRI) 4 response rate at 52 weeks compared with standard therapy** 'The committee noted that the long-term extension studies did not have comparator arms. It concluded that they did not provide long-term effectiveness evidence for belimumab compared with standard therapy.' There was no comparator arm - how can the committee make any conclusion on long-term efficicacy? You don't know what the outcome would have been if they were not on belimumab (probably much worse). This is clinical trials 101. **3.7 An indirect treatment comparison between belimumab and rituximab is preferred** 'The company considered that there was a high likelihood of confounding and selection bias in this analysis.'	considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19. Equality The committee discussed potential equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See section 3.18 of the FAD. Rituximab as a comparator The committee considered that because rituximab is a relevant comparator, it would have preferred to see an indirect treatment comparison between belimumab and rituximab based on the data collected from the BILAG-BR substudy. It concluded that in the absence of this comparison, the uncertainty about the relative clinical and cost effectiveness of belimumab and rituximab remains. See FAD sections 3.4 and 3.7.

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			The company is completely correct. **3.15 There are no equality issues that can be addressed in this technology appraisal** 'It noted a stakeholder comment that double-stranded-DNA antibodies are less common in people from an African family background' This is not true - higher positivity for dsDNA Abs in African ancestry patients cf European ancestry. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3490432/ and https://academic.oup.com/rheumatology/article/56/suppl_1/i67/2629213 **3.17 Belimumab is not recommended for routine use** 'an indirect comparison with rituximab (see section 3.7)' Indirect comparisons are uninterpretable	
29	Public	Freeman Hospital Rheumatology Department, CTD specialist centre	**Has all of the relevant evidence been taken into account?** Therapeutic options are limited in SLE. In sharp contrast to Rheumatoid arthritis which can be debilitating but is rarely life threatening. A large number of high cost drugs are licenced for RA. Belimumab is a useful alternative to Rituximab which has raised concerns about covid vaccination response. Belimumab met primary end points in the BLISS trials. SLE is a rare condition. Currently Belimumab is one of only three drugs licensed for use in SLE (prednisolone and hydroxychloroquine). The length of the key Belimumab trials (BLISS) were similar to the length of RA trials, though the document states the BLISS trials were limited by their short length Subcutaneous Belimumab has been of significant benefit to patients with fewer hospital attendances during the COVID-19 pandemic and less time off work. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** It is likely that healthcare costs of patients who are currently being treated with Belimumab or are currently eligible for this will increase significantly if this drug is withdrawn. Patients will require increased hospital admissions, requirement for high dose steroids (with associated risks of diabetes, osteoporotic fractures, weight gain, hypertension, glaucoma, skin thinning and muscle atrophy) and potential need for organ support e.g. dialysis. I do not agree with the calculations of cost effectiveness stated which do not adequately reflect the health care costs of repeated hospital admissions and long term steroid morbidity.	Comments noted. Please see individual responses below: <u>Belimumab is recommended</u> The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19. <u>Equality</u> The committee discussed potential

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			Are the recommendations sound and a suitable basis for guidance to the NHS? I do not agree with the NICE decision not to fund Belimumab for patients with SLE living in England. Lupus is a life limiting and can be an organ or life threatening condition. There is a significant burden of disease and treatment related damage and toxicity. In our unit in Newcastle Upon Tyne connective tissue disease specialist centre, we have a small but significant, select number of patients who have shown significant clinical response to Belimumab who have been refractory to disease modifying drugs, steroids and, in most cases, Rituximab. They have fulfilled current criteria for initiation of the drug following regional MDT discussion and continuation according to current NHS England guidelines. The use of the drug has been limited to patients with very severe, refractory, SLE. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Withdrawing Belimumab would potentially be discriminatory towards childbearing women. In some cases Belimumab is the only alternative to IV cyclophosphamide treatment which can result in infertility. Licencing for use in children will prevent the need for large cumulative doses of iv cyclophosphamide and resulting infertility.	equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See section 3.18 of the FAD.
30	Public	Web comment	**Has all of the relevant evidence been taken into account?** Not really. There is excellent real world long term data on safety and efficacy. No patient stays on a drug for 7+ years unless they think it's working - especially if coming up to clinic for infusions etc. There's evidence of steroid sparing with long term belimumab - a major goal in the management of lupus. If patients have to stop they will end up on much increased steroid dosing. It's not all about short term costs but long term gains to patients. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No It is not reasonable to use rituximab as a comparator - I use rituximab a lot in renal lupus but it is not licensed, it has not been proven in trials and yes many of us use it but many don't have access even with the new commissioning. It also is different in its mode of action, more likely to lead to low immunoglobulins, impairs responses to vaccines (very relevant in the COVID era) and many lupus patients become allergic over time (we have seen no allergies to belimumab. It is absurd to say we should be using a non licensed drug over a drug that is licensed, been tested in RCTs and met its primary endpoints and now has long real world data to support its use. I can't really comment on the details of the economic models but it seemed to me watching the open part of the committee meeting that the NICE team were determined to ignore all the suggestions GSK made and insist the	Comments noted. Please see individual responses below: Evidence The committee has considered all the relevant evidence for its decision making in line with NICE's guide to the processes of technology appraisal. Rituximab as a comparator The committee discussed that rituximab was included in the final scope for the appraisal and is being used in clinical practice through the NHS England clinical commissioning policy on rituximab for refractory systemic lupus erythematosus in adults and post-pubescent children. It concluded

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			pricing was too high. Somehow the patient has got lost in all of this - belimumab is the FIRST and only drug licensed for the treatment of lupus in 50 years. It reduces the use of steroids in these patients - long recognised as the major cause of long term damage in these patients. "The committee concluded that, because rituximab is a relevant comparator (see section 3.4), it would have preferred to see an indirect treatment comparison between belimumab and rituximab in the relevant population". The patients who are allowed to get rituximab for lupus in the UK are different from those receiving belimumab as they are supposed to get belimumab first. So direct comparisons are almost certainly inappropriate and the committee's rejection of GSK's arguments seem spurious. But equally, rituximab is not ideal for everyone, can rarely be given to induce control over years (due to low IgG or allergy) and is not licensed. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No. Firstly it is completely wrong to say that patients established on belimumab have to transition off it with the next year if this is your final guidance. To get on belimumab in the first place they had largely failed most standard treatments so what you are condemning them to is flaring, more steroid and a greater likelihood of damage from their lupus or from steroids. Rituximab isn't the panacea for all and you are asking them to change treatment when their treatment is working fine (by definition because they have stayed on it). This is morally wrong and likely to cause direct patient harm and enormous distress. Why would patients on the NHS be the only patients in high income countries be denied belimumab for the treatment of their lupus. It is widely used in the EU and the USA and on the basis of needing either high dsDNA ab or low complement, not both. This should be the case in the UK and you are putting UK patients at a major disadvantage compared to peers in other similar economies. The logic around people stopping treatment before 5 years is opaque - it means that if not efficacious (and many drugs are only efficacious for some time in this most variable of diseases) it would be stopped and the costs would disappear. But there are a group of patients who clearly gain long term benefit. Also likely to reduce renal flares (based on Lupus nephritis data) which would save a huge amount of money in the long term. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Absolutely - this is an entirely discriminatory appraisal; lupus predominantly affects younger women of colour - the ratio of women to men is 8:1 and it is much more common in people from non European non white backgrounds. To deny this already disadvantaged population a licensed proven treatment is simply wrong.	that rituximab is a relevant comparator. See section 3.4 of the FAD. <u>Belimumab is recommended</u> The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19. <u>Equality</u> The committee discussed potential equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See FAD section 3.18.

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31	Public	Louise Coote Lupus Unit, Guy's & St Thomas' NHS Foundation Trust	**Has all of the relevant evidence been taken into account?** No. Please see general comments in particular the recent FDA approval of belimumab for lupus nephritis (December 2020) and the need for a non-B cell depleting agent to treat active SLE given the ongoing COVID-19 pandemic. The lack of such an option places our SLE patients at high risk of severe and life threatening Covid-19 infection and therefore hospitalisation and death, which is unacceptable in our opinion. The risk of "long Covid-19" and its potential long term sequelae is also currently unknown in this patient cohort. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I cannot comment on the cost effectiveness calculations as this is outside my area of expertise. I disagree with the summary of clinical effectiveness, however. A long term (> 12 months) head to head comparison is sought between treatment with belimumab and either standard of care or rituximab. This is difficult in the UK cohort due to the 2016 NICE / NHSE commissioning agreement. The 2016 NICE / NHSE guidance specified that patients fulfilling certain criteria (inc SLEDAI >10) should preferentially be treated with belimumab over rituximab hence there is no comparative real world data for this group. Our own data also show that 41% of our cohort of 48 currently active belimumab treated SLE patients failed to respond to prior treatment with rituximab. Many patients also failed treatment courses of highly cytotoxic drugs such as cyclophosphamide prior to being commenced on belimumab. The long term safety and benefit of belimumab in our patient cohort is clear. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No. Belimumab is a highly effective and safe drug for the treatment of patients with multisystem SLE who have failed standard of care. The drug is widely used both intravenously and subcutaneously throughout the world to great patient benefit. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No	Comments noted. Please see individual responses below: Lupus nephritis The company considered that the use of belimumab in people with lupus nephritis was outside of the scope of this appraisal. Rituximab as a comparator The committee discussed that rituximab was included in the final scope for the appraisal and is being used in clinical practice through the NHS England clinical commissioning policy on rituximab for refractory systemic lupus erythematosus in adults and post-pubescent children. It considered that because rituximab is a relevant comparator, it would have preferred to see an indirect treatment comparison between belimumab and rituximab based on the data collected from the BILAG-BR substudy. It concluded that in the absence of this comparison, the uncertainty about the relative clinical and cost effectiveness of belimumab and rituximab remains. See FAD sections 3.4 and 3.7. Belimumab is recommended The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19.
32	Public	Newcastle Upon Tyne NHS Trust	The team at Newcastle Upon Tyne NHS Trust do not agree with the NICE decision not to fund Belimumab for patients with SLE living in England. Lupus is a life limiting and can be an organ or life threatening condition. There is a significant burden of disease and treatment related damage and toxicity. In our unit in Newcastle Upon Tyne connective tissue disease specialist centre, we have a small but significant, select number of patients who have shown significant clinical response to Belimumab who have been refractory to disease modifying drugs, steroids and, in most cases, Rituximab. They have fulfilled current criteria for initiation of the drug following regional MDT discussion and continuation according to current NHS England guidelines. The use of the drug has been limited to patients with very severe, refractory, SLE. Therapeutic options are limited in SLE. In sharp contrast to Rheumatoid arthritis which can be debilitating but is rarely life threatening. A large number of high cost drugs are licenced for RA. Belimumab is a useful alternative to Rituximab which has raised concerns about covid vaccination response. It is likely that healthcare costs of patients who are currently being treated with Belimumab or are currently eligible for this will increase significantly if this drug is withdrawn. Patients will require increased hospital admissions, requirement for high dose steroids (with associated risks of diabetes, osteoporotic fractures, weight gain, hypertension, glaucoma, skin thinning and muscle atrophy) and potential need for organ support e.g. dialysis. Subcutaneous Belimumab has been of significant benefit to patients with fewer hospital attendances during the COVID-19 pandemic and less time off work. I do not agree with the calculations of cost effectiveness stated which do not adequately reflect the health care costs of repeated hospital admissions and long term steroid morbidity. Belimumab met primary end points in the BLISS trials. SLE is a rare condition. Currently Belimumab is one of only three drugs licensed for use in SLE (prednisolone and hydroxychloroquine). Withdrawing Belimumab would potentially be discriminatory towards childbearing women. In some cases Belimumab is the only alternative to IV cyclophosphamide treatment which can result in	Comments noted. Please see individual responses below: <u>Belimumab is recommended</u> The committee discussed the uncertainties in the clinical evidence and around the cost-effectiveness estimates. However, the committee took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are additional benefits of belimumab that may not be captured in the cost-effectiveness results. It considered that the most likely estimates are within what NICE normally considers an acceptable use of NHS resources. So, the committee decided to recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus. See FAD sections 1.1, 3.16 to 3.17 and 3.19. <u>Equality</u> The committee discussed potential equality issues raised during the appraisal. It considered that there are no equality issues that can be addressed in this appraisal. See FAD section 3.18.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			infertility.	

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 25 June 2021 Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	GSK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose.
Name of commentator person completing form:	[redacted]

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 25 June 2021 Please submit via NICE Docs.

Comment number	Section	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1		Since embarking on seeking NHS access for baseline commissioning of belimumab in 2011, GSK remains as equally as committed to ensuring belimumab continues to offer a clinically proven treatment option for systemic lupus erythematosus (SLE) patients with high disease activity in England and Wales. We offer a revised PAS to share the risk of outstanding uncertainty but believe our base case remains the most appropriate for decision making. Whilst the volume and duration of outcome data captured from the BILAG-Biologics Registry (BILAG-BR) for patients commencing on belimumab was limited, we are pleased that a revised population, HDA-2 (a requirement of a SELENA-SLEDAI [SS] score ≥ 10 and only one serological biomarker) has been accepted by the Committee as appropriate for decision making. We agree with the Committee that the long-term extension (LTE) studies do not provide long-term comparative effectiveness evidence for belimumab versus standard therapy (ST) alone. However, this is no different to clinical trial programs for other chronic diseases; it would simply not be ethical to run such studies. In the absence of long-term comparative effectiveness, we do not believe it is a reasonable nor a fair assessment to dismiss in its entirety, the comparative evidence presented from the Propensity Score (PS)-Matched analysis between belimumab and ST on a highly clinically relevant end point, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). The dismissal of the PS-matched study is also a disservice to those SLE patients in need. It is well documented that an increasing SDI score is linked to worse long-term outcomes and an increased risk of morbidity and mortality in SLE patients. In addition, we do not believe that the Committee's assessment that the results from the PS-matched analysis are biased in favour of belimumab is accurate, based on the matching-exercise and the withdrawal data from the LTEs (details presented later). Irrespective of an HTA assessment, such degree of bias towards an intervention, if of concern, would question the robustness and reliability of the study which has never been the case working with Canadian Lupus Experts and indeed the independent peer review of the resultant publications. A robust PS-matched comparative analysis serves as the most appropriate and robust alternative to address the evidence gap. The key driver of the presented base case cost-effectiveness analyses is the additional benefit experienced by belimumab responders in terms of slower organ damage progression compared with ST, which is implemented via a derived calibration factor, the results for the 5-year change in SDI from the PS-matched analysis. Disappointingly, the Committee Meeting focused on the size of the calibration factor (0.491) applied to belimumab responders to 6 years in the model, and not the assumed incremental absolute SDI benefit which would have allowed clinical expert inclusion in the discussion. This is critically important to reassure the Committee that belimumab does offer additional benefit in terms of slowing down the rate of organ damage progression over a long period and that we are not in any way double counting

		projected model-derived benefit. We believe the benefits seen on organ damage progression are clinically plausible given the impact belimumab has on reducing disease activity and because patients controlled with belimumab will be able to reduce their exposure to oral steroids; both of these (steroid use and disease activity) lead to organ damage accrual. We suggest that clinical experts are invited to comment at the next ACM on the impact of organ damage to patients with SLE and the clinical plausibility of PS-matched analysis. In the uncalibrated model, the 5-year SDI increase (between years 1.5 and 6.5) was projected at 0.568 units and the application of the calibration factor reduced this change to 0.283 units. GSK acknowledges the uncertainty of the application of the PS-matched analysis results to the economic model. Therefore, our approach was that by applying the benefit conservatively i.e., by applying to belimumab responders only and not making any adjustment to the ST arm, to 6 years of a lifetime model, and assuming the same level of benefit from an ITT population to a HDA-2 population, that this would in effect underwrite the uncertainty. We do not agree with a complete dismissal of some implementation of benefit for belimumab responder patients; this is not an appropriately, evidence-based decision. Because of the complexity of the model structure, offering an alternative modelling approach is not feasible. We recognise that our conservative approach to implementation is not deemed adequate by the Committee at this stage in sharing the risk of decision error with the NHS. We therefore offer a revised PAS comprising a [redacted] discount on the list price across both formulations, bringing the base case cost-effectiveness analysis to £25,042 and £24,952 per QALY gained for the SC and IV models respectively.
2	3.2	**GSK welcomes the acceptance of the updated sub-group (HDA-2 population) as being relevant for decision making** • The acceptance of the HDA-2 population will allow better identification of appropriate patients who could potentially benefit from belimumab. • Please note typo of “HAD-1” at bottom of page 6.
3	3.4	**GSK acknowledges that if belimumab was not available, a small proportion of overlapping patients could potentially receive rituximab** • In accordance with the NHSE clinical commissioning policy for rituximab, patients are only eligible for rituximab if they have failed one or more immunosuppressants, one of which must be mycophenolate or cyclophosphamide. This is not the case for those receiving belimumab in the clinical trials and clinical practice. Cyclophosphamide and mycophenolate are usually prescribed to patients with lupus nephritis or CNS involvement, which falls outside of the scope of this appraisal. • Belimumab is an ongoing maintenance treatment to achieve a long-term sustained response and therefore reserved for patients with ongoing active disease uncontrolled by standard therapy. Rituximab, however, is not prescribed in a similar manner (i.e., on-going maintenance) and therefore a proportion of patients can experience re-population of their B-cells following initial B-cell depletion with rituximab. In essence, these drugs are prescribed very differently in clinical practice and under different circumstances.

		• GSK recognises that if belimumab was not available, a small proportion of overlapping patients could potentially receive rituximab. This reflects the unmet need in the absence of licensed effective treatments. • It is worth noting that the 'NHSE interim clinical commissioning policy statement for rituximab for treatment of SLE in adults' was published in 2013 when belimumab was not available. At this time, clinicians had no choice than to use rituximab in patients who were not responding to standard therapies. As the treatment landscape has since evolved, the 2020 published 'NHS England clinical commissioning policy for rituximab for refractory SLE' now recommends consideration of belimumab, an effective, well studied licensed treatment, prior to the use of rituximab. Therefore, a proportion of the current prescribing of rituximab in patients with SLE is likely to be habitual and from previous experience acquired prior to the availability of belimumab in 2016 and does not necessarily translate into rituximab being an appropriate comparator.
4	3.5	**Information only: belimumab improves SRI4 response rate in the new HDA-2 subpopulation** • The results from the HDA-2 subgroup analysis of BLISS IV (52/76) and SC trials have now been published and no longer need to be marked as confidential (http://lupus.bmj.com/cgi/content/full/8/1/e000459).
5	3.6	**Long-term effectiveness evidence for belimumab compared with standard therapy** • GSK would like to highlight that the 52 and 76-week follow up periods in the Phase 3 studies are in line with EMA guidance and other comparative trials in SLE. • At the time of the last appraisal (TA397), there was limited long-term data for belimumab, and the Committee were uncertain whether the treatment effect seen with belimumab in the clinical trials would be maintained over time. Therefore, as part of this appraisal, we provided additional published data to demonstrate the long-term efficacy and safety of belimumab. Whilst this is not direct comparative data to ST alone, the wealth of long-term evidence in belimumab is extremely relevant to understanding the impact of belimumab on organ damage accrual and therefore, should not be disregarded. It is well documented in guidelines that the aim of treatment is remission of disease symptoms and signs, prevention of damage accrual and minimisation of drug side effects. The data presented demonstrates this and provides clinicians with the reassurance on the safety and tolerability of belimumab up to 13 years, as well as evidence of a sustained treatment response and low damage accrual. Furthermore, GSK would like to point out this is a large dataset to have available for any biological drug being appraised by NICE. • GSK would like to reiterate that it is not feasible to conduct a long-term placebo-controlled study in patients with SLE comparing belimumab plus ST to ST alone, as this would be highly unethical in a patient group who are at an increased risk of morbidity and mortality, particularly where the pivotal trials demonstrated significant benefit on treatment with belimumab plus ST compared to ST alone. Therefore, a robust and well-designed propensity-score matched comparative analysis between patients receiving belimumab in the BLISS-US long-term extension study compared with a real-world cohort of patients with SLE (Toronto Lupus Cohort [TLC]), serves as the most appropriate and reasonable alternative.

		• GSK would like to correct the information provided regarding the BLISS-76 US long-term extension study. The primary outcome of this trial was to measure long-term safety of belimumab, frequency of adverse events [AEs] and damage assessed using the SDI, not the SRI 4 response as per the Phase 3 BLISS-76 trial. • GSK would also like to correct the information provided regarding the BLISS-SC extension study. The outcomes measured in the extension study included safety and efficacy, and changes in biomarker and B cell levels. The ACD states 61.4% of patients achieved an SRI 4 response in the total population at 6 months This is incorrect and should say 'At week 24, a SRI4 response was achieved in 16.1% of patients in the placebo-to-belimumab group and 76.3% patients in the belimumab group.' It was in the BLISS-SC pivotal trial that 61.4% of patients receiving belimumab achieved a SRI4 response, but this was at week 52.
6	3.7	**Indirect treatment comparison between belimumab and rituximab in the relevant population remains challenging** • Whilst the Committee would have preferred to have seen an indirect treatment comparison between belimumab and rituximab, this is not possible in the relevant population i.e., HDA-2 as the BILAG-BR collected data for the HDA-1 population only. • GSK would like to reiterate due to the lack of positive and robust randomised controlled trial and long-term effectiveness data for rituximab in patients with SLE, GSK does not believe that a reliable robust indirect treatment comparison can be conducted. The ERG acknowledged the associated methodological challenges (which too, were also acknowledged by the previous ERG in TA397).
7	3.8	**Results of the propensity score-matched analysis is not biased in favour of belimumab** • GSK disagrees with the Committee's conclusion that the PS-matched analysis is biased in favour of belimumab. • GSK does not agree that important variables were not matched on. The most clinically relevant variables, as identified by a systemic literature review and validated by non-GSK clinical experts, were matched on in the primary analysis of the study, including baseline disease activity and baseline SDI. However, it is not suitable to match on variables such as disease progression and disease activity over time (as suggested in the ACD) as they would be considered as potential confounders in the analysis. GSK acknowledges that a social deprivation (SD) index was not available to use as a matching variable in the PS-matched study, however household income and educational attainment were matched variables and will in some way act as a proxy for SD. • GSK acknowledges that there were some differences in the baseline characteristics between the two cohorts compared in the analysis (the US LTE study cohort and the TLC) pre- and post-matching. However, study arms were tested for statistically significant differences in patient baseline characteristics (using Welch's t-test) and the standardised mean difference was also determined for each covariate. GSK agrees that smoking can affect outcomes in patients with SLE and whilst prior to the propensity score matching, the cohort samples were not well balanced, once PS-matched, the samples of 99 LTE and 99 TLC patients were well

		balanced with a bias of less than 5% for nine of the seventeen variables, and less than 10% for all variables (the mean bias is 4.6%); Post-matching there was 0% bias for the smoking variable which is lower than for other matched variables. • In our submission, we have recognised the limitations of a single-arm, open label extension study and that the PS-matched analysis resulted in a smaller sample size of 99 (from 195 patients in the LTE with ≥5 years follow up). We disagree with the ERG's assertion that patients who continued having belimumab at 5 years were likely to have progressed less or had a better response than patients who had belimumab for 1 to 4 years before stopping treatment, to the degree of significantly biasing the results in favour of belimumab. Out of the 268 patients entering the US long-term extension study, only 28% (n=76) of patients withdrew by the end of Year 5, of which 63 patients withdrew due to reasons other than lack of efficacy (i.e., adverse events, lost to follow-up, non-compliance with study drug, physician decision, protocol deviation, withdrawal by patient or other). Therefore, the majority of patients (72%) did continue for at least 5 years. In addition, it is conceivable that many of the patients who withdrew due to a reason other than lack of efficacy could have potentially continued to receive the benefits of belimumab until year 5 if they were to continue treatment. Therefore, GSK disagrees that patients remaining in the study at year 5 are a particularly enriched population and we believe these data are valid for a comparative analysis with the TLC. • In addition, when we consulted with two leading UK Rheumatologists, they were of the opinion that these LTE data were important to clinical management in the UK and the most relevant data available to demonstrate the effectiveness of belimumab plus ST compared to ST alone on organ damage progression; this included assessment of disease activity and cumulative corticosteroid use.
8	3.10	**It is inappropriate to completely dismiss the application of the PS-matched analysis results showing the positive benefit of belimumab on organ damage progression to the economic model.** ***The clinical relationship between oral corticosteroids, disease activity (measured by SS) and organ damage*** • In a clinical setting the continued use of oral corticosteroids and increased disease activity as defined by flares, all contribute to organ damage progression which is irreversible in nature and contributes to most of the detriment in outcomes including health related quality of life and mortality risk in SLE (Lopez et al 2012). Belimumab offers steroid sparing activity (that we have been unable to capture adequately in the model) and a proven reduction in disease activity. It therefore makes sense clinically that belimumab would have a positive impact on reducing organ damage progression. ***Organ damage progression captured in the model used to support TA397*** • The model submitted as part of TA397 utilised data from the Johns Hopkins (JH) cohort to inform the natural history models for organ damage progression. The JH cohort data was only able to provide a historical correlated relationship between disease activity

		(SS score) and organ damage for patients who received standard therapy (ST) treatment alone. It did not capture the direct treatment effect of belimumab on organ damage progression. • Data from the pivotal BLISS-52 and BLISS-76 trials were used to inform the SS scores for the first 12 months. The model submitted as part of TA397 relied on a series of time to event regression models derived from the JH registry that estimated a standard therapy (ST) or belimumab patient's organ damage progression (and SDI score) as a relationship to their SELENA-SLEDAI (SS) scores in each given year. • It is incorrect to state that the assumption in the previous model regarding a constant treatment effect of belimumab on disease activity reduction beyond 1 year (based on the trial data), in terms of the long-term treatment effect with belimumab, is "optimistic". It is very clearly stated in Section 4.25 of the previous TA397 FAD that- "Deriving cost data from different sources may have led to some inconsistencies in the estimates and the company may have underestimated some of the benefits associated with delaying certain types of organ damage." ***Organ damage progression captured in the model used to support this re-appraisal*** • We wanted to ensure that the model accurately reflected the newly available evidence on organ damage progression made available from the PS-matched analysis. By running the TA397 model (having adjusted the baseline characteristics to the PS-matched analysis population), we found that the model over-predicted the organ damage progression seen in belimumab responders and underestimated it for the ST arm. • We adjusted the absolute organ damage progression for patients who received and responded to belimumab to match the rate of organ damage progression as seen in the PS-matched analysis for a maximum of 6 years. The adjustment was made by the use of a 'coefficient', which is called in our current submission a 'calibration factor' and is applied on an annualised basis to belimumab responders so that the absolute organ damage progression shown in the model (for belimumab responders) closely aligns to the PS-matched analysis. ***Absolute change in SDI (as a result of the application of the calibration factor)*** • The original uncalibrated economic model submitted as part of TA397 suggested that the 5-year SDI increase for patients was 0.568 for patients who received belimumab whilst it was 0.611 for patients who received standard therapy alone. When calibration factors

		derived from the robust PS-matched analysis are applied, belimumab patients experienced an SDI increase of 0.283 (suggesting that the uncalibrated model was overestimating organ damage increase by 0.258) whilst patients on standard therapy alone experienced a greater increase of 0.717 (suggesting that the uncalibrated model was underestimating organ damage progression by 0.106). Although the robust PS-matched analysis suggested that the rate of organ damage on the standard therapy arm of the original TA397 model was likely under-estimated, no correction was made to the ST arm in the model submitted as part of the current base case to reflect this increased rate of organ damage accumulation, when this was an entirely reasonable approach. This has likely resulted in an underestimation of costs and overestimation of benefits of the ST arm, and therefore reflects poorly on belimumab in a comparative scenario. ***Committee discussion of the application of the PS-matched analysis to the model*** • GSK strongly believe that clinical experts at the Committee Meeting were unable to engage in this part of the discussion because the focus was on the size of the calibration factor. We believe for the discussion to have been meaningful for decision making, it should have focused on the clinical plausibility of the absolute increase assumed for belimumab responders on organ damage progression. We believe this would have helped the Committee understand that despite the size of the calibration factor, what is represents clinically does reflect clinical plausibility for those responding patients. GSK therefore believes there is a clear benefit of having clinical experts present at any subsequent Committee meeting. ***Residual uncertainty on assumed long-term organ damage progression*** Whilst GSK believes that the PS-matched analysis provides clinically relevant and important evidence on the comparative effectiveness of Benlysta versus ST on the long-term progression of organ damage, we do acknowledge that there is uncertainty in its application in the economic model. Several significantly conservative steps were taken to apply the comparative PS-matched study data in the health economic modelling: • The calibration factor was derived using a matched intention to treat (ITT) population from Urowitz et al. 2019. As our target sub-population demonstrated a higher benefit on disease activity (as measured by SS score), it is perfectly plausible that this translates to an additional benefit in slowing down organ damage progression. • The calibration was applied to belimumab responders only. • The benefits of the calibration factor were applied to only 6 years despite belimumab being continued up to lifetime in the model and clinical practice. It is clinically plausible that patients will continue to benefit from belimumab for as long as they continue to take it.

		• No adjustment was made to the standard therapy arm. The annual calibration factor to adjust the SDI score of patients on belimumab to that observed on the LTE was derived from a PS-matched analysis conducted over a period of 5 years. In the model, if a responder patient on the belimumab arm spent less than 6 years in the model, they only received benefits proportionally to the amount of time they remained in the model, provided they entered into the second year of the model. Modelled patients who did not have 4 points or more reduction on SS by week 24 were classified as "non-responders" and derived no benefits at all. GSK recognises the uncertainty in applying this constant calibration factor to patients who discontinued at years 2, 3, and 4 in the model, as this assumes patients received full benefit proportionally to the time spent in the model, whereas it may be the case that patients would receive less benefit if they discontinued for any given reason before the full 5-years. To account for this, GSK took the conservative approach, as detailed above, to the application of the new organ damage progression data in the model. We would also like to remind the committee that the model does not fully capture disease flares (due to the Johns Hopkins dataset not directly capturing these). Had flares been sufficiently captured, this would have likely given extra benefits to patients on belimumab as the BLISS RCTs have demonstrated that patients receiving belimumab experienced a reduced number of flares compared with patients on standard therapy alone. In addition, we have not incorporated carer utilities in our model, but this is relevant to patients with this disease as the symptoms can be very debilitating e.g. prolonged fatigue and arthritic pain, whereby the sufferer requires in some cases significant support from family members and other carers. **References** Lopez, R., Davidson, J.E., Beeby, M.D., Egger, P.J. and Isenberg, D.A., 2012. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. *Rheumatology*, 51(3), pp.491-498. Urowitz, M.B., Ohsfeldt, R.L., Wielage, R.C., Kelton, K.A., Asukai, Y. and Ramachandran, S., 2019. Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. *Annals of the rheumatic diseases*, *78*(3), pp.372-379.
9	3.11	**The modelled response to treatment for belimumab 'non-responders' is consistent with management of UK patients in clinical practice** • In line with the Summary of Product Characteristics (SmPC) and current NICE guidance (TA397), patients on belimumab who are determined to be non-responders (<4-point reduction in SELENA-SLEDAI (SS) score at week 24) will cease treatment with belimumab and revert to receiving standard therapy (ST) alone. This is not to say these "non-responder" patients experienced no benefit from belimumab in the first 24 weeks of treatment i.e., some patients may have experienced a 1 to 3-point reduction in SELENA-SLEDAI by week 24. However, mindful of NHS resources, it was agreed during TA397, that we would restrict "responders" to those that had a clinically relevant improvement by week 24 (i.e., ≥4-point SS score reduction). According to clinical experts, some

of these "non-responder" patients will still have very active disease, and their background standard therapy would need to be further optimised encompassing an increase in steroid dose at the very minimum to try and gain better control of their active disease state.

- Furthermore, GSK has now conducted a further post-hoc analysis of the pooled 52/76 IV BLISS trial data which demonstrates that in the HDA-2 subgroup out of the 87 patients who were considered to be non-responders at week 24 (<4-point reduction in SS score), 30 (34.5%) of patients achieve a ≥4-point reduction in SS score at week 52 (Table 1). This is with no change to their medication i.e., they continued belimumab, which suggests a slow response to this medicine for some patients. This demonstrates that these week 24 non-responder patients can respond later, which suggests it is plausible that others, when treated with additional ST medications are also likely to have their disease activity levels improved. Therefore, GSK disagrees with the Committee's conclusions that it is not clinically plausible that nearly half of the "non-responders" would not respond on ST by week 52.

Table 1. SELENA-SLEDAI score responders at week 24 compared with week 52 in HDA-2 subgroup

	belimumab non-responder at week 24 (n=87)
belimumab responder at week 52	30 (34.5%)
belimumab non-responder at week 52	57 (65.5%)

- GSK acknowledges the ERG's concern that no detriment has been applied to the belimumab non-responders in the model if we assume that these patients take the average ST disease activity score at week 52. Therefore, as an additional scenario analysis, we have added a cost of £600 assigned to the belimumab non-responders during Year 1 in the model to cover the costs related to additional ST medication and two extra out-patient physician visits to treat their high disease activity. Costs were proportionally applied to the belimumab arm of the models, based on the percentage of non-responders for each formulation and were not applied to patients who were non-responders in the standard therapy arm. The resultant ICERS were £25,190 and £25,248 per QALY gained for the IV and SC formulations, respectively.
- GSK would like to confirm that the regression model to determine a patient's change in SS score at week 52 was provided both as part of the economic model, and in Section 6.3 of the submission provided as part of TA397.
- GSK notes that the ACD suggests moving to a model cycle of 6 months. However, SLE is better represented by a model using yearly cycles to capture the chronic nature of the disease.

10	3.12	**In the health economic model disease activity is based on the BLISS trials for the first 52 weeks, however belimumab non-responders assume the standard therapy (ST) arm average disease activity score at Week 52 to align with how patients will be managed in UK clinical practice.** • As explained in the responses to both the clarification questions and the Technical Engagement document the economic model does not contain any errors related to how SELENA-SLEDAI (SS) score is modelled. It is an assumption that belimumab non-responders take the average ST score (regression coefficient) rather than the belimumab non-responder regression coefficient from week 52 onwards. This assumption was made as patients who do not respond on belimumab at week 24 switch to ST and continue ST for the remainder of the modelled time horizon within the belimumab arm of the model i.e., the remaining 28 weeks of the first year and any remaining cycles thereafter. The economic model's treatment continuation criterion (achieving a ≥4-point reduction in the SS score at week 24, "responder") is based on the belimumab SmPC and consistent with UK clinical practice and reflecting the terms agreed under the managed access agreement. It is standard practice in the UK and consistent with regulatory approval, that clinicians will assess improvement in the patients' disease activity after six months of treatment with belimumab and those patients who are not deemed to have experienced benefit from treatment with belimumab will be taken off the medicine. • This assumption was also validated with experts for TA397 and has been re-validated with two UK clinical experts for this re-appraisal. The feedback from the clinical experts is that when patients discontinue belimumab at week 24 due to not meeting the responder criterion their ongoing management will depend on the severity of their disease and level of disease activity. Typically, their steroid dose could be increased alongside a change of immunosuppressant depending on prior treatments. If disease is severe, patients could receive IV cyclophosphamide or rituximab preceded by a dose of IV methylprednisolone to control symptoms in the short term. The aim of treatment is to stabilise their disease as soon as possible which could be achieved anytime from 3-months after stopping belimumab if they respond to the alternative treatment regimen. We therefore maintain that our base case assumption is valid. • However, as part of the technical engagement response, GSK provided scenario analyses where belimumab non-responders assumed the average SS score of ST patients by year 1.5 (Week 76) instead of at Week 52 (our base case) in the model. These scenario analyses have now been updated with the revised PAS discount and show that the IV and SC formulations result in ICERs of £26,630 and £27,716 per QALY gained, respectively. The model files showing these updated scenario analyses have been shared with NICE.
11		**Scenario analyses with the updated Patient Access Scheme (PAS) discount**

GSK would like to remind the Committee of the scenario analyses we provided in our submission, now with the addition of the updated PAS price. Please see Table 2 for a summary of the IV and SC model ICERs with the updated PAS for HDA-2 populations, with ICERs from our submission provided for comparison.

Table 2. Summary of the IV and SC model ICERs with the updated PAS for HDA-2 populations, with ICERs from our submission provided for comparison

	IV Model – HDA-2		SC Model – HDA-2	
Description of Scenario	**As per PAS offered at first Appraisal Committee Meeting** [redacted]	**Updated PAS price** [redacted]	**As per PAS offered at first Appraisal Committee Meeting** [redacted]	**Updated PAS price** [redacted]
Base case	£29,162	**£24,952**	£30,566	**£25,042**
1. Source of patient weight is BLISS trials	£27,299	**£23,306**		
2. Belimumab treatment duration and effect restricted to 10 years	£19,776	**£16,220**	£21,396	**£16,763**
3. Calibration factors applied to both the belimumab and ST for 6 years	£22,633	**£18,694**	£23,353	**£18,332**
4. Calibration factors applied to belimumab only for patient lifetime	£23,417	**£19,553**	£24,188	**£19,163**
5. Discount rates 1.5% for both benefits and costs	£21,384	**£18,217**	£22,556	**£18,387**
6. Discount rates 1.5% for benefits and 3.5% for costs	£19,264	**£16,483**	£20,241	**£16,583**
7. New Scenario: Additional costs assigned to belimumab arm for non-responders*		**£25,190**		**£25,248**

		* In a further a scenario analysis based on the updated PAS, an additional £600 was assigned to the belimumab arm of the models, to cover additional costs related to additional ST medication and two extra out-patient physician visits for belimumab non-responders only. Costs were proportionally applied to the belimumab arm of the models, based on the percentage of non-responders for each formulation and were not applied to patients who were non-responders in the standard therapy arm

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

1. Please clarify which group of patients the company used to derive its calibration factor. It is unclear whether all patients on belimumab including non-responders were used or it belimumab responders only at a certain time point. The ERG noted on page 64 of the original company submission the responder rule was disabled for the calibration exercise suggesting that all patients in the model may have been used to calibrate modelled SDI to the PSM SDI.

    - which patients were used to estimate the PSM SDI value vs which patients are in the model (in terms of whether they were still on belimumab or not)
    - what does 'responder rule disabled' mean? Is it that non-responders were not moved to the SoC arm in the model?

LTE patient population used to derive the calibration factor

The PS-matched analysis used the BLISS-76 US LTE cohort to represent belimumab patients. This cohort included a mixture of patients who continued belimumab after exiting from the BLISS-76 randomised controlled trial (RCT), and patients who received placebo during the BLISS-76 RCT but were swapped to belimumab on entry to the BLISS-76 US LTE. Therefore, patients who were belimumab naive who entered the BLISS-76 US LTE had the potential to discontinue belimumab for the same reasons as patients who were initiated on belimumab at the start of the BLISS RCTs.

No continuation rule for belimumab based on the reduction of a set number in SELENA-SELDAI (SS) points by any given time point was used in the RCT or the LTE. To be clear, all patients who were receiving belimumab in the LTE up to 5 years were used to derive the calibration factor, and not just patients who attained a certain level of benefit.

To represent patients on standard therapy (ST), the PS-matched analysis used patients from the Toronto Lupus Cohort (TLC). The absolute change in SDI values for both belimumab and ST patients over a 5-year period were used for the calibration of the economic model.

Modelled patient population to derive the calibration factor

When deriving the calibration factor, the economic model used the characteristics of the total pooled BLISS-52 and BLISS-76 intention to treat (ITT) population. This ITT population was represented in both the belimumab arm, where patients received belimumab, and in the ST arm, where patients were on ST alone. The economic base case presented by GSK as part of the current submission uses a subset of the patient population of total pooled BLISS-52 and BLISS-76 ITT population comprising

those who meet the HDA-2 criteria, to which any calibration factor adjustments are applied.

How strategy arms in the model accrue benefit

At the start of the economic model, patients initially receiving either belimumab or standard therapy alone are represented in the following two strategies:

1. belimumab arm
2. standard therapy (ST) alone arm

Although all patients in the belimumab strategy initially receive belimumab, if they were to discontinue belimumab for any reason at any time point (adverse reactions, lack of efficacy due to the discontinuation rule etc.), and revert to receiving standard therapy only, they would continue to remain in the belimumab arm strategy of the model where their ongoing costs and QALYs would continue to be counted as a consequence of the belimumab strategy. To be clear, a patient who discontinued belimumab due to any reason and resumed standard therapy alone, would not swap to the standard therapy arm of the model.

Responder rule

The responder rule refers to the continuation rule implemented for patients on belimumab, as defined in section 1.1 of the final guidance issued as part of TA397. That is, that patients who do not experience an improvement of least 4 points or greater reduction in their baseline SELENA-SELDAI (SS) score by week 24 are no longer permitted to continue receiving belimumab. This rule was absent during the BLISS clinical trials and LTEs.

When deriving the calibration factor, the setting in the model was ‘responder rule disabled’. This means that, in line with the clinical trials (BLISS RCT and LTE), the total pooled BLISS-52 and BLISS-76 ITT population used to derive the calibration factor were permitted to continue to receive belimumab even though they may not have achieved a 4-point or greater reduction in their baseline SS score by week 24.

Scenario analysis using only belimumab responder patients

A scenario analysis to derive a calibration factor based on belimumab responders only (i.e. those who experienced a 4-point or greater reduction at week 24) in the model was conducted. It is worth noting that modelled belimumab responder patients would have a better SDI progression over time as compared to the overall belimumab strategy arm of the model (which includes a mixture of both belimumab responders and non-responders). However, belimumab patients observed on the BLISS-76 US LTE as used in the PS-matched analysis, still have a comparatively better (and slower) SDI progression compared even to modelled belimumab responder patients.

Compared with the original calibration factor of 0.491, the scenario analysis resulted in a calibration factor of 0.536, which is marginally less favourable for belimumab. The calibration factor is worse, because the co-efficient is required to adjust the

modelled progression of SDI in belimumab responders to the values of SDI observed of belimumab patients in the BLISS-76 US LTE is smaller. This is expected, because the disaggregated belimumab responder patients on the belimumab strategy of the model would have a slower progression of SDI, and would be closer to the SDI progression of the belimumab patients on the LTE than the overall aggregated modelled belimumab patients. This means the co-efficient (or calibration factor) required to bring the modelled organ damage of the disaggregated belimumab responder patients in to line with the belimumab patients observed on the LTE is closer to 1, and is therefore a worse calibration factor, indicating less of a change required to be made to the modelled belimumab responder patients to match the observed belimumab patients in the BLISS-76 US LTE. Detailed SDI score progressions for the various populations are provided in the answer to question 2 below.

The results of the IV model for the HDA-2 population, using the alternative belimumab calibration factor of 0.536, are shown in Table 1. The impact of this alternative calibration factor is small, with the ICER increasing from £24,952 to £26,467.

Table 1. Base case and scenario analysis results for the IV model, HDA-2 population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
IV model – Base case using current discount rate and calibration factor of 0.491							
ST	£160,470	16.90	9.81				
Belimumab IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,952
IV model – Base case using current discount rate and scenario analysis calibration factor of 0.536							
ST	£160,470	16.90	9.81				
Belimumab IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,467

All model outcomes presented are discounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Calibration factor is only applied to the belimumab arm of the model and not applied to the standard therapy arm

The calibration factors derived (and implemented in the current base case) showed a greater benefit for belimumab as compared with the unadjusted model (i.e. a slower rate of organ damage progression for patients who received belimumab) and an unfavourable benefit for patients who received ST alone (i.e. a greater rate of organ damage progression for patients who received ST alone). To maintain a conservative approach, GSK only applied the calibration factor for belimumab into the company base submitted to NICE, and although it would have been reasonable to do so, did not apply the calibration factor for ST, which would have further enhanced the cost-effectiveness of belimumab.

2. Please provide the following in a graph format to demonstrate organ damage progression for:

    - modelled belimumab responders,
    - belimumab non-responders and
    - patients in the ST arm and
    - the overall belimumab arm in the model (all with and without the use of the calibration factor).

Figure 1 shows the SLICC scores over time in a scenario without the use of the calibration factor. The stratified trajectories show that the SLICC trajectories of belimumab non-responders and ST patients are similar and show the steepest increase over time. Belimumab responders show a less steep trajectory. Belimumab overall represents the weighted average of the responder and non-responder trajectory.

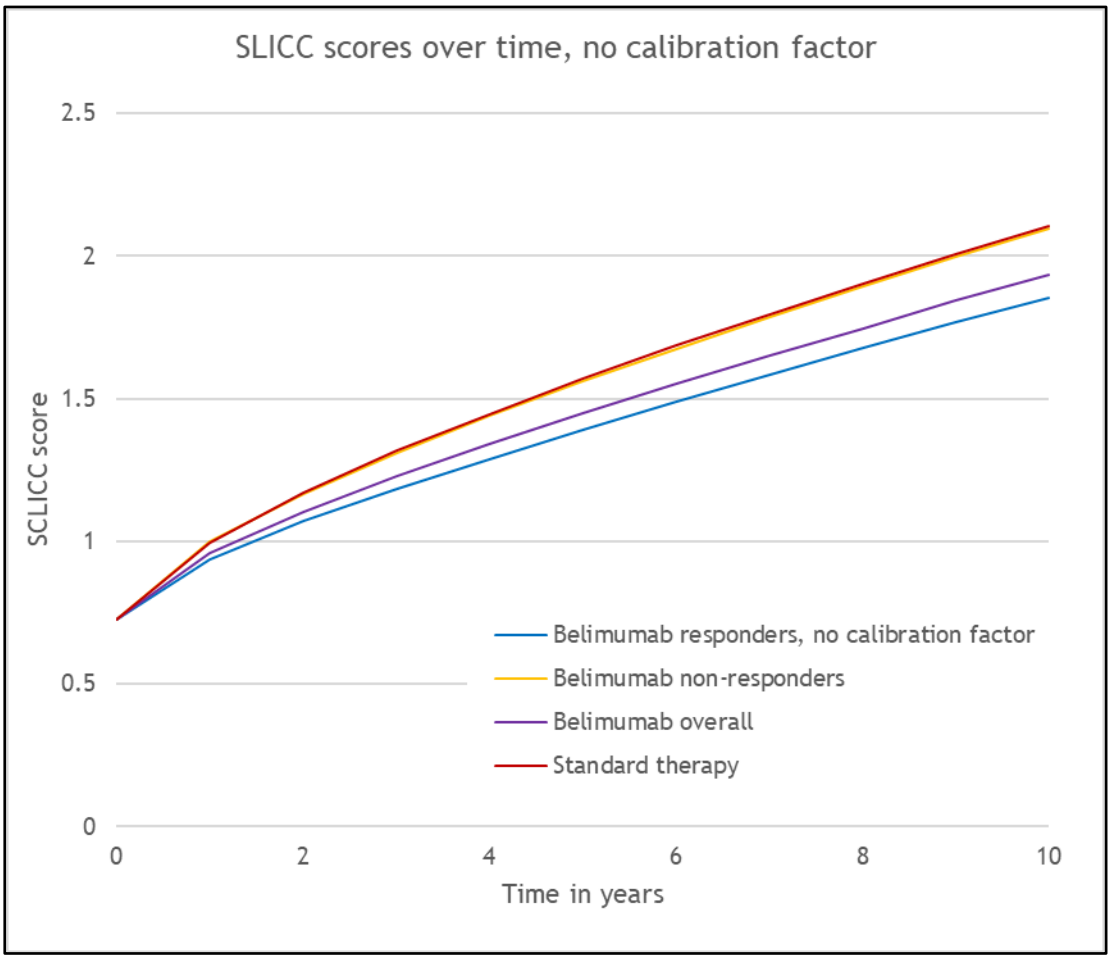


Figure 1. SLICC scores in a scenario analysis using no calibration factor

Figure 2 shows the SLICC scores over time in the base case where the calibration factor of 0.491 is applied.

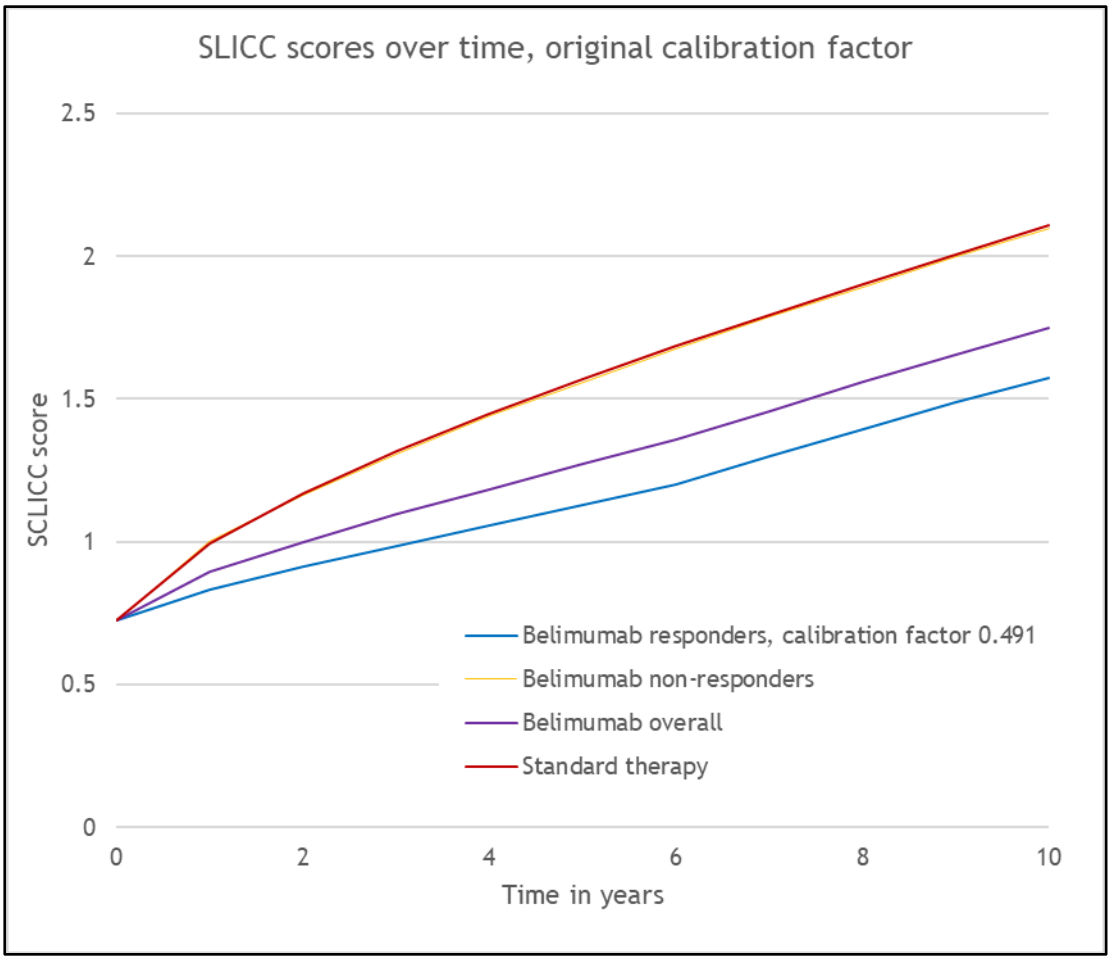


Figure 2. SLICC scores in the base case using a calibration factor of 0.491

Figure 3 presents SLICC scores in the overall belimumab arm using the calibration factor applied in the base case, the alternative calibration factor of 0.536**Error! Reference source not found.**, and SLICC scores in the ST arm (where no calibration factor applies). It shows minimal impact on the SLICC score progression of belimumab overall when using the alternative calibration factor, based on a responder only population.

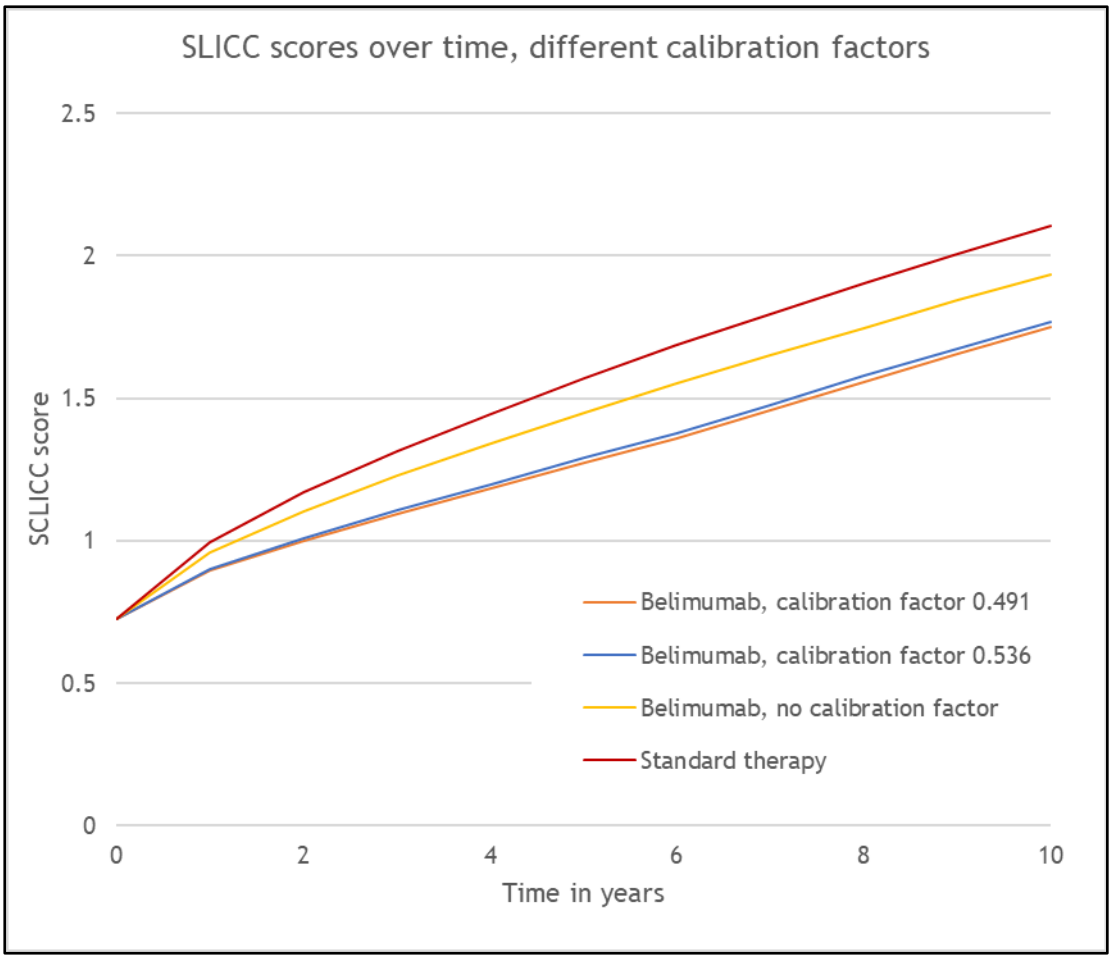


Figure 3. SLICC scores - belimumab strategy and standard therapy strategy - comparing different calibration factors

Figure 4 provides further insight into the derivation of the two calibration factors by plotting the underlying SLICC scores over time, i.e. the trajectory of the entire belimumab arm with the responder rule disabled for the derivation of the original calibration factor, and the trajectory of belimumab responders only for the derivation of the alternative calibration factor. The curves show a small increment with the belimumab responder only cohort having lower SLICC scores over time. This translates into the (slightly) higher calibration factor when using the responder only cohort for comparison with the LTE study data.

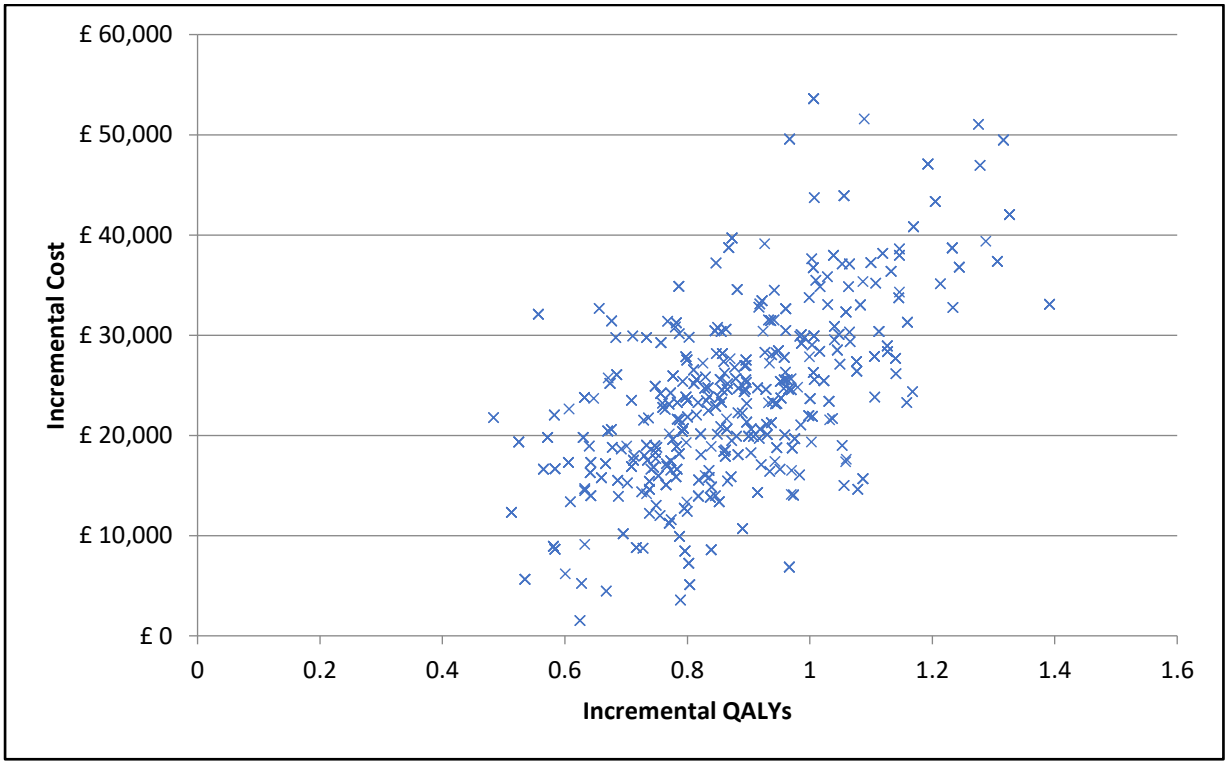
Figure 4. SLICC scores used for the estimation of the calibration factors

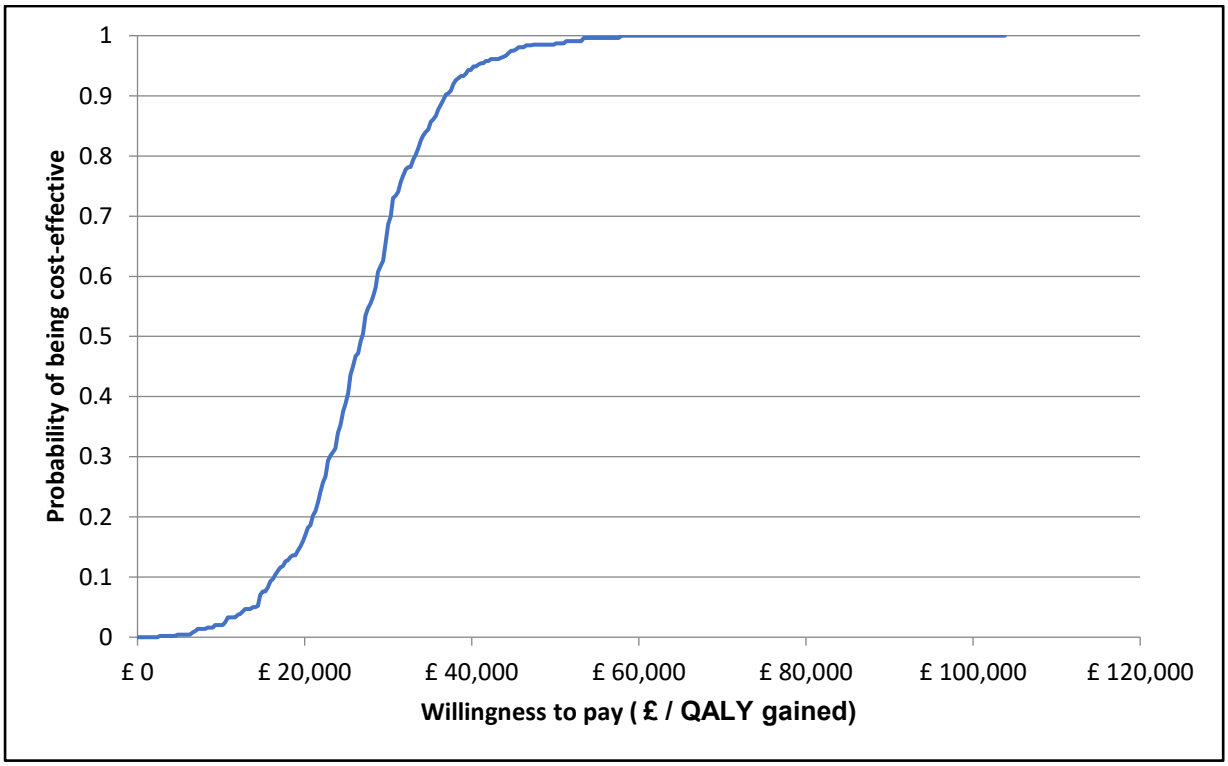
PSA Results

PSA Results for Benlysta IV [redacted]

	Average Incremental Cost	Average Incremental Utility	ICER
Benlysta IV vs ST	[redacted]	[redacted]	£27,148

Reference Deterministic ICER: £24,952 per QALY gained

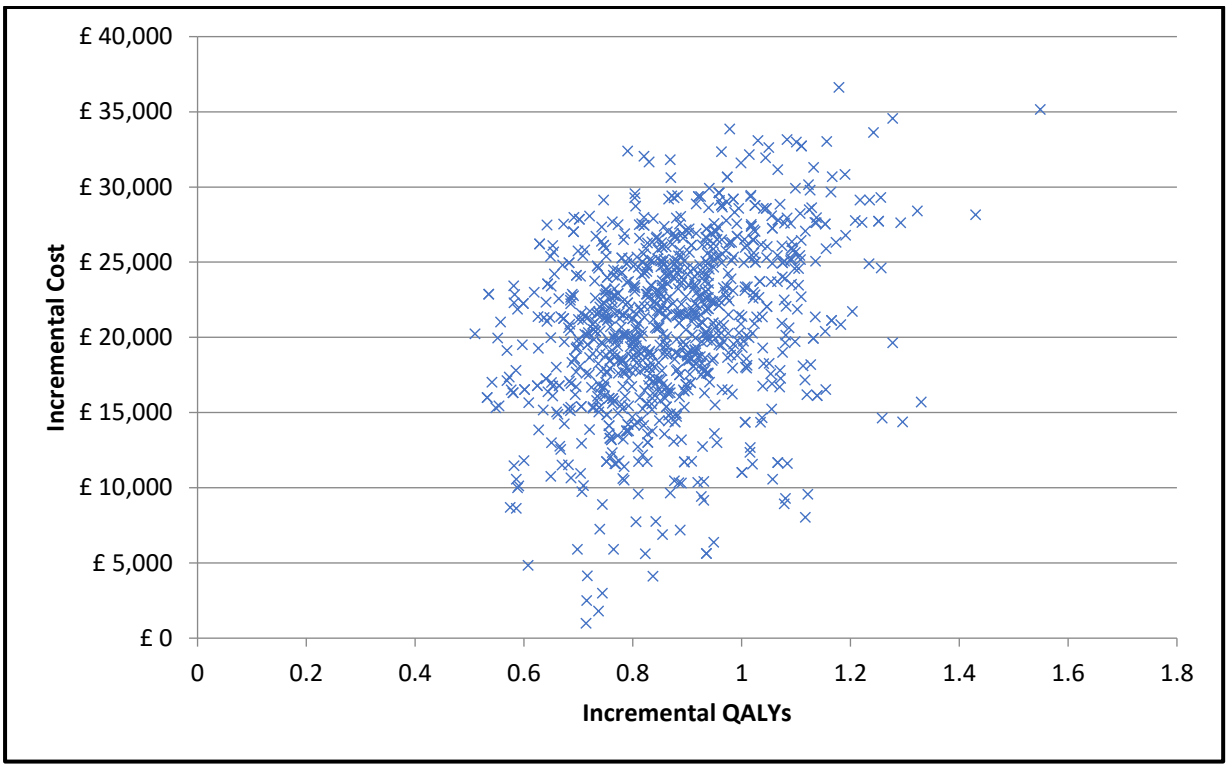


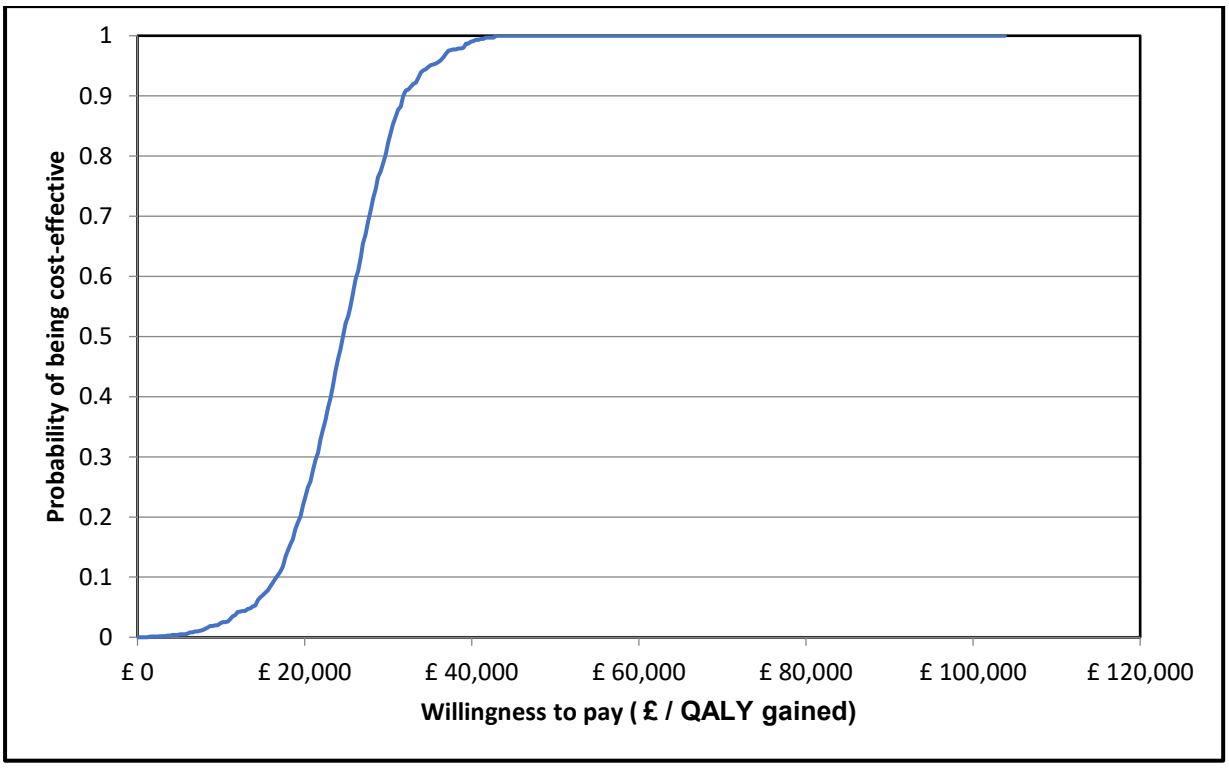


PSA Results for Benlysta SC [redacted]

	Average Incremental Cost	Average Incremental Utility	ICER
Benlysta SC vs ST	[redacted]	[redacted]	£24,110

Reference Deterministic ICER: £25,042 per QALY gained





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6 September 2021

Dear Chair and Committee,

Reference: ID1591 Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus

Following the NICE Appraisal Committee Meeting for the above technology on 12 May 2021 and the resultant negative ACD, GSK hosted an advisory board with prominent UK clinical experts experienced with the management of SLE and the use of belimumab to discuss the relevance of, and obtain their views on, the evidence provided in relation to the effect of belimumab in reducing organ damage in adult patients with SLE, and how this could be clearly articulated during the NICE appraisal. Below is a summary of the key questions asked of clinical experts and their responses. The responses have been drafted in collaboration with the clinical experts.

What drives organ damage in patients with SLE and how useful is the SLICC/ACR Damage Index (SDI) instrument for monitoring organ damage accumulation?

There are four main factors that drive organ damage:

- Persistent, ongoing, uncontrolled disease activity, including disease flares
- Glucocorticoid use
- Natural ageing
- Coincidental events such as cancer or accidents causing certain fractures etc

New, effective treatments can have a positive impact on the first two listed factors and hence this should translate into reducing the amount and rate of organ damage accrual.

The SDI is a simple to use and pragmatic tool. The index has 41 items covering 12 systems. It includes specific clinical items or events that can occur after the diagnosis of SLE but, as described above are not all directly attributable to the SLE process. Manifestations should be recorded as damage only if they develop after the onset of lupus and persist continuously for 6 months or be associated with an immediate pathological scar indicative of damage (for example, a myocardial infarction). Some items can score two for recurrent events, such as repeated strokes and avascular necrosis at two sites. The maximum score is 47 but patients rarely score above 12 points. Over time, the majority of SLE patients will accrue organ damage and damage is irreversible.

The SDI is a useful tool for helping to identify more vulnerable patients who have very little reserve for dealing with further flares and organ damage. It is also useful for disentangling what is potentially reversible, and what is not. It also helps to highlight those with a poor prognosis.

Accumulation of damage as assessed by the SDI tool is not linear. Having developed any organ damage is a good predictor for the accumulation for further organ damage and mortality (Bruce et al., 2015). In this situation, efforts should be redoubled to avoid further organ damage and restrict use of corticosteroids, so biologic treatments, such as belimumab

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that can control the disease activity and prevent the need for further corticosteroid use are really important in the management of SLE patients.

Data from Bruce et al., 2015 show that patients who had an SDI score of 1 or more at baseline develop organ damage at a greater rate than those who had an SDI score of zero at baseline i.e., the study data shows that the estimated probability of remaining damage-free at 2 years is 0.844 if a patient has no damage at baseline, whereas if there is one unit of damage, the estimated probability is 0.664 (and similar for more than one).Consistent with previous studies, this study showed that the level of disease activity, use of corticosteroids and comorbid hypertension all significantly influenced damage accrual. The significant interaction between disease activity and steroid therapy on new damage suggests that both act together to enhance the development of irreversible organ changes.

The use of a Propensity Score Matching (PSM) study to estimate long-term organ damage and the relevance of the Toronto Lupus Cohort to the UK?

In the absence of a long-term placebo controlled RCT in SLE for a licenced medicine for SLE, which would not be ethical or feasible, the next best alternative is a propensity score matching study, as long as it is designed in a robust way. The Urowitz et al, 2019 PSM study is considered a well-designed study. It allows the long-term effects of belimumab to be compared with a standard of care cohort with similar baseline characteristics. However, it has some limitations common to most PSM studies; when doing propensity modelling, there is always a trade off in in the number of characteristics matched for versus the number of patients you lose before the numbers become too small to be useful.

The Toronto Lupus Cohort (TLC) used in the PSM study can be considered comparable to the UK population, as the Canadian population has a comparable distribution of ethnic groups and it is also a public funded healthcare system. Ethnicity is particularly relevant to the manifestation and severity of SLE.

The proposed eligible patient population for Benlysta in the UK are overall a more severe cohort with greater disease activity than those from the belimumab long-term extension studies of the Phase 3 RCTs used for the PS-matched analysis, this is due to the more stringent UK eligibility criteria (SELENA-SLEDAI score >=10). Therefore, clinically, we would expect greater organ damage progression in the untreated proposed belimumab eligible group due to more active disease.

It is worth noting that discontinuation of belimumab treatment is not always due to loss of efficacy or adverse events. Often female patients who have been successfully treated with belimumab and feel that their disease is now under control may interrupt their regimen of belimumab as they wish to fall pregnant.

What is the role of belimumab in SLE?

Belimumab has shown, in both clinical trials and in real world experience, its ability to control disease activity, and reduce flares and steroid exposure over time, all of which contribute to reducing accumulation of irreversible organ damage.

Belimumab has been shown from the Phase 3 studies to have a greater benefit in patients with high disease activity. As the population in the PSM analysis used to derive the calibration factors in the health economic model are on the whole less severe than the patient population who are eligible to receive belimumab in the UK, it is clinically plausible that benefits attributed to belimumab patients have been underestimated in the model. It is reasonable to expect a more severe SLE patient population with a high risk of organ damage accrual to derive greater benefit from belimumab in terms of avoiding irreversible long term organ damage. It is important to note that the benefit on reducing organ damage accrual from the PSM study was only applied in the model to the patients who responded to belimumab after six months and the benefit was not applied beyond six years of treatment even though patients would continue to receive belimumab and derive benefit in controlling their disease.

When the "calibration factor" (the adjustment to the rate of organ damage accrual) of 0.491 is applied to either formulation of the belimumab arm of the model for HDA-2 patients, there is an observed benefit of approximately 0.3 SDI points in favour of belimumab compared with the standard therapy arm after 6 years. This would translate to just one in four patients avoiding the development of an organ damage item on the SDI tool over 6 years which does not seem unreasonable given the benefit belimumab demonstrates on reducing disease activity *and* the need for corticosteroids. In the same model where no calibration factor is applied, the benefit of belimumab relative to standard therapy arm is only 0.1 SDI points and is likely a significant underestimate of the effectiveness of belimumab in reducing organ damage, especially given the highly active disease state of the patients modelled. Based on the above information, we are confident that the outputs of the economic model are reasonable and applicable to the UK.

Without access to new, effective medicines then the only recourse would be to give patients high doses of steroids over a prolonged period of time to control their disease activity and flares. This is highly problematic and clinically unacceptable due to the clear increased risk of organ damage driven by glucocorticoid therapy including key items such as cataracts, osteoporotic fractures, avascular necrosis, diabetes mellitus and muscle atrophy. In addition, glucocorticoids exacerbate many classic cardiovascular risk factors including body mass index, hypertension and an adverse lipid profile.

References

Bruce, I.N., O'Keeffe, A.G., Farewell, V., Hanly, J.G., Manzi, S., Su, L., Gladman, D.D., Bae, S.C., Sanchez-Guerrero, J., Romero-Diaz, J. and Gordon, C., 2015. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. *Annals of the rheumatic diseases*, *74*(9), pp.1706-1713.

Urowitz, M.B., Ohsfeldt, R.L., Wielage, R.C., Kelton, K.A., Asukai, Y. and Ramachandran, S., 2019. Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. *Annals of the rheumatic diseases*, *78*(3), pp.372-379.

1 Derivation of an alternative calibration factor

Please provide a model file or technical note that would enable the ERG to replicate the scenario analysis presented in your response using belimumab responders only to derive a calibration factor.

To provide a response to this request, GSK has included two model files:

- 2021.09.09 - ID1591 - IV model validation responders only for alternative CF
  - This model file is useful to see what was done when deriving the alternative calibration factor based on belimumab responders only.
- 2021.09.09 - ID1591 - IV model validation original CF
  - This file allows the technical team to see what was done when the original calibration factor was derived.

A scenario analysis was conducted using a calibration factor that was derived based on the comparison of belimumab responders only with the LTE data. As for the derivation of the original calibration factor, the modelled population used the characteristics of the total pooled BLISS-52 and BLISS-76 intention to treat (ITT) population (set **Scenario!J8** to **"Total BLISS population"**). For the responders-only calibration factor, model settings were defined so that 100% of the population would meet the responder criteria (set **'Baseline Pat Chars'!AD7:AD38** to **1**). As a result of this, the modelled population in the belimumab arm to compare against the LTE study consisted entirely of belimumab responders only (i.e had a reduction of 4 points or more on the SELENA-SELDAI (SS) score as compared to baseline)..

The calibration factor itself was then calculated from the mean change in SLICC score over a period of 5 years between 1.5 and 6.5 years, comparing the LTE data to the belimumab arm in the model consisting of only responders (see **Results!W9**).

(Note: The original calibration factor was optimized by manually trying different co-efficient values to reduce the difference between the modelled SLICC increase and the LTE SLICC increase to 0.00 (two decimal places after 0). Although this optimization (to two decimal places) was not conducted when deriving the adjusted calibration factor, the impact of this would be minimal.)

2 Organ damage utility regression coefficient

Please provide the results presented in Tables 9 and 10 of your technical engagement response (Issue 11: violation in utility estimation) using the updated belimumab PAS.

The results in Table 1 and Table 3 indicate the change in ICER compared to the company's base case in the HDA-2 population for the IV and SC models, respectively, when the utility coefficient is either increased or decreased by one standard deviation. It should be noted that an increase or decrease of the coefficients by one standard deviation (SD) is an arbitrary choice and might be considered a substantial change.

Table 2 and Table 4 present the ICERs obtained from each of the analyses and Figure 1 and Figure 2 visualize these compared to the company's base case ICERs for the IV and SC models, respectively.

Table 1. Impact of utility coefficients on ICER compared to company base case (in %) IV model (HDA-2)

	Coefficient decreased by one standard deviation	Coefficient increased by one standard deviation
Utility coefficient (log of) age	10.3%	-10.3%
Utility coefficient constant	9.4%	-9.2%
Utility coefficient Sledai score	-0.6%	0.6%
Utility coefficient Black ethnicity	0.3%	-0.2%

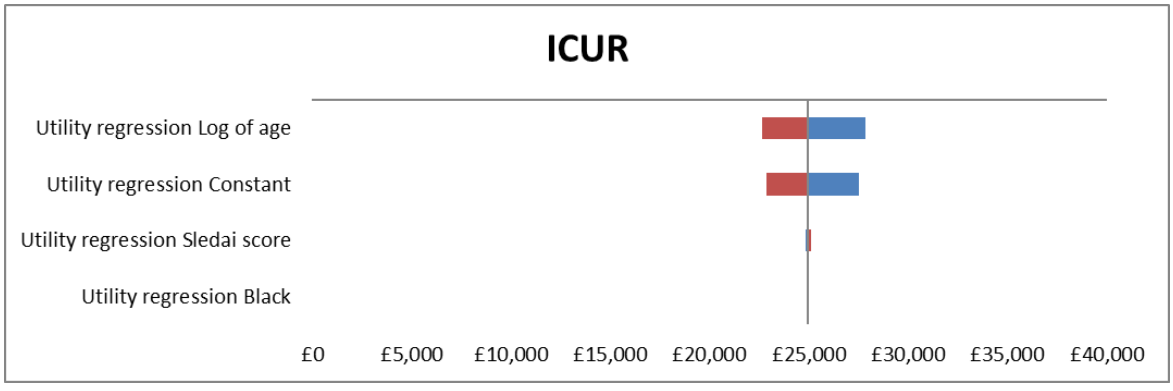

Figure 1. Tornado plot ICERs of the IV model (HDA-2)

Table 2. Utility coefficients used and ICERs obtained from sensitivity analysis compared with the base case analysis - IV model (HDA-2)

Utility coefficient	Base case coefficient	Coefficient decreased by one SD	Coefficient increased by one SD	Base case ICER	ICER coefficient decreased	ICER coefficient increased
log of age	-0.1448	-0.1643	-0.1253	£24,952	£27,824	£22,624
constant	1.2970	1.2248	1.3674		£27,534	£22,860
SLEDAI score	-0.0091	-0.0097	-0.0085		£24,809	£25,096
Black ethnicity	-0.0538	-0.0752	-0.0336		£25,015	£24,893

Table 3. Impact of utility coefficients on ICER compared to company base case (in %) SC model (HDA-2)

	Coefficient decreased by one standard deviation	Coefficient increased by one standard deviation
Utility coefficient (log of) age	10.5%	-10.4%
Utility coefficient constant	9.5%	-9.3%
Utility coefficient Sledai score	-0.5%	0.5%
Utility coefficient Black ethnicity	0.4%	-0.4%

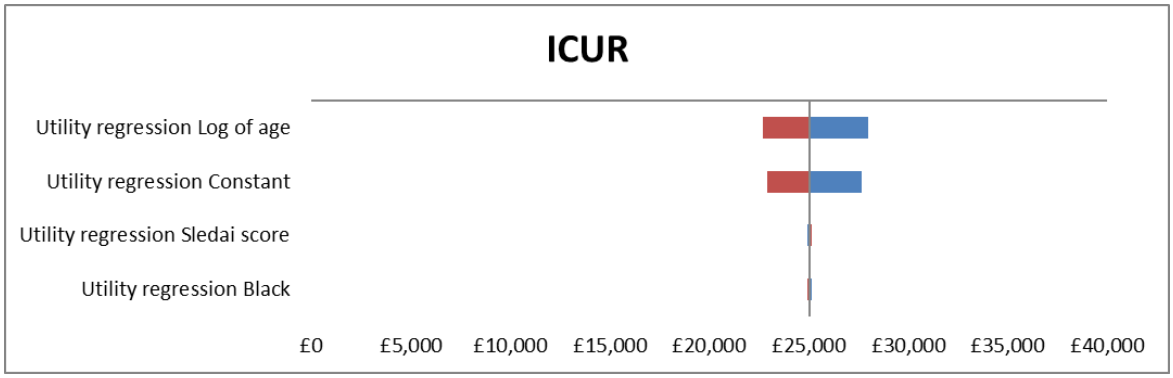

Figure 2. Tornado plot ICERs of the SC model (HDA-2)

Table 4. Utility coefficients used and ICERs obtained from sensitivity analysis compared with the base case analysis – SC Model (HDA-2)

Utility coefficient	Base case coefficient	Coefficient decreased by one SD	Coefficient increased by one SD	Base case ICER	ICER coefficient decreased	ICER coefficient increased
log of age	-0.1448	-0.1643	-0.1253	£25,041	£27,966	£22,676
constant	1.2970	1.2248	1.3674		£27,675	£22,911
SLEDAI score	-0.0091	-0.0097	-0.0085		£24,917	£25,165
Black ethnicity	-0.0538	-0.0752	-0.0336		£25,139	£24,949

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11th October 2021

Dear Committee D Lead Team and Helen Knight,

RE: Systemic lupus erythematosus (active, autoantibody positive) - belimumab (review of TA397) [ID1591]

Post the second appraisal committee meeting for belimumab which was held on 16th September 2021, GSK has had further internal discussion and would like to request that the Committee consider a new patient access scheme (PAS) to support patients with Systemic Lupus Erythematosus (SLE) to have continued access to belimumab.

I appreciate that this is a late intervention in offering a revised PAS, however GSK believes it is important given the unusual circumstances of this topic appraisal. The consequences of a negative final outcome would be significant for the several hundred patients who are currently performing well on belimumab and where there is a substantial unmet need with few alternative safe and effective licensed medicines available if they had to stop taking this treatment. There are also other SLE patients with high disease activity uncontrolled on standard care therapies who have not yet had the chance to try belimumab for accessibility reasons and we believe these patients deserve this opportunity.

GSK understands from the discussion at the second committee meeting that the Committee felt there is still uncertainty in the degree of long-term benefit afforded by belimumab in slowing down the accrual of organ damage, which is a key driver of the cost-effectiveness. In order to help reduce the Committee's concern regarding the decision risk for this appraisal, GSK has agreed to increase the PAS discount offered to the NHS from the currently proposed [redacted] to a new discount of [redacted] This new discount level has the effect of reducing the ERG's base case ICERs for the subcutaneous and IV formulations to £29,313 per QALY and £30,278 per QALY, respectively. Please see the summary of cost-effectiveness results in the appendix attached to this letter.

I hope that with this new PAS offer the Committee will be reassured with the level of decision risk and that a final positive recommendation for Benlysta in SLE can be secured from NICE.

Kind Regards

[redacted]

[redacted]

Appendix:
Summary of cost-effectiveness results for both the GSK and ERG's preferred base case assumptions relating to the benefit afforded to belimumab on preventing organ damage progression in the health economic model with the new proposed PAS discount

GSK Base Case with new [redacted] discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
IV model							
ST	£160,470	16.90	9.81				
Belimumab IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,335
SC model							
ST	£151,999	17.12	10.06				
Belimumab SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,480

All model outcomes presented are discounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

ERG Base Case with new [redacted] discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
IV model							
ST	£160,470	16.90	9.81				
Belimumab IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,278
SC model							
ST	£151,999	17.12	10.06				
Belimumab SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,313

All model outcomes presented are discounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**LUPUS UK**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation will make a treatment, that has been shown to be clinically safe and effective, unavailable for patients who rely upon it with no suitable alternative. Belimumab is currently reserved for severe and/or refractory lupus for which standard therapy alone has proved ineffective or insufficient. Withdrawing belimumab would leave only rituximab as a possible addition/alternative to standard therapy. Unfortunately, for many, rituximab is not an effective therapy. Analysis of BILAG BR data by McCarthy (2017) found response to rituximab in 49% of patients - https://academic.oup.com/rheumatology/article/57/3/470/4688912. People with severe and/or refractory lupus who cannot be sufficiently treated with standard therapy and rituximab will be left with no other available treatment options. This will result in increased dependence on corticosteroids, worsened quality of life and increased flares requiring hospitalisation. Belimumab should continue to be available as a treatment option for patients who are unresponsive or intolerant to rituximab and standard therapy. Here are some first-hand experiences of people currently treated with belimumab: • *I was on rituximab (amongst other treatments) before Benlysta, and that flared my lupus up 'generally'. Once I started Benlysta, after a year to two years, they wanted to try and get rid of some remaining symptoms, for example some existing joint pain. So, I was put onto methotrexate and within a couple of weeks (of a very low dose) my liver inflamed six times the 'normal' level, and it took 12-18 months to drop back to normal.* *I am now on mycophenolate (with a few others) to try and help with the symptoms that are not controlled by Benylsta, it helps to an extent- I think?!* *I have had lupus just under 9 years now and it has never been in remission and have always found it tricky to live with on a daily basis if I'm honest! Benlysta has been the only thing that I've noticed that has made the most difference with the least amount of nasty side effects. Injections would be great as I have to travel 1:30hr into central London every time!* • *I was on lots of medication before and I use to be on another infusion (cannot remember the name of it but can ask my consultant if you need the name). These did not improve my condition but the belimumab helps a lot. I do notice the difference. I still have weak days but compared to before, it is working.* • *I am 33 years old and was diagnosed with SLE when I was 19. I was stable for many years and then I wasn't and over a number of years I ran out of treatment options. Azathioprine - failed due to poor liver function results. Mycophenolate - no positive response. Methotrexate - some response but not sufficient on its own. Rituximab - no response. Belimumab - positive response!* *Belimumab has finally given me a treatment that means I have good days and bad days rather than just all bad days. It has also allowed me to start rebuilding my life again. Before getting this treatment I had lost any social life. I live on my own and all I was doing was the minimum to keep going, maintain a job and I was needing a lot of help from family to keep up with jobs around the home. Everything I did took more and more energy from me and gave me more pain. It was a very lonely existence. Due to the nature of all of these treatments and needing to give them time to work I probably had 2.5 years of living in 12-week chunks before I was reassessed and doses were tweaked or we moved on to the next drug, it was beyond frustrating and felt like I was throwing such valuable time away. When I started*

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	belimumab I probably felt a benefit from around 6 months, and I feel like I can rely on it now to keep as much of my lupus at bay as possible. *On a practical note, the routine of getting my infusions is very easy to manage (much easier than 6 hours for rituximab) and I experience no side effects.* *For me, it is a huge worry about what would happen to me if this drug was not an option anymore given my experiences with the others.* • *Prior to starting belimumab in December 2020, I was at the end of my tether with autoimmune disease including SLE, Sjögren's, Raynaud's and scleritis. It's been a 15-year struggle since diagnosis with increasing medication and reducing benefit over time. During this time, I also had breast cancer and a recurrence, resulting in a double mastectomy. Exhaustion meant I had a maximum of five functional hours a day, could no longer work, had no social life and could barely take care of myself. I couldn't speak towards the end of the day; my voice was too quiet and people couldn't hear me on the phone. I was sleeping around 10 hours a day. I was in constant pain from sore joints, badly healed fractures, scleritis flares, headaches and chest pain. Despite taking more than 30 tablets a day, my health continued to deteriorate and filling the pillbox every night was just a depressing reminder of how bad things had become. I no longer cared to live.* *When my rheumatologist suggested belimumab, I was more than happy to try, but to be honest, I didn't really expect that it would work for me. I was just ticking off the options so that I could tell myself at least I'd tried everything.* *About a week after the first infusion, I actually felt a subtle change, but put that to wishful thinking. After the second infusion I felt more certain that something was happening. By the third infusion I was sure. I had more energy and less pain. Now, three months since beginning the drug, I have eight useful hours in the day, and sleep eight to nine hours. While I am still using painkillers, I now experience very little pain. I have been able to exercise much more and my fitness levels have increased.* *Regaining some control over my body means regaining control in my life and the difference is like night and day. As a writer, I feel my mind is sharper and I am now able to entertain the idea of new projects. Having recently lost a crown, I am now considering a dental implant, something that wouldn't have even been an option before.* *All my friends comment on the change, apparently I sound very different. In an unexpected development, my libido has returned after an absence of more than six years. Until now, I would never have considered being able to partner anyone again as I had nothing to offer and would only be a burden. Tentatively, I'm beginning to see a possible future and to make plans.* *As I become accustomed to the fact that these changes are real, I have also begun to reduce my reliance on prednisolone from 10mg a day to 9mg, aiming for 7.5mg initially, with an increasingly optimistic goal of coming off it altogether – an inconceivable aim prior to belimumab.* • *I was diagnosed with lupus 15 years ago and since diagnosis have always had very active lupus. This has resulted in frequent hospital admissions due to flares and subsequent health complications as a result. I have been receiving belimumab for 18 months and during that time have only had one hospital admission. This is unprecedented for me since diagnosis. Receiving belimumab has also resulted in a reduction of my medications for the first time since diagnosis. I have spoken to other patients receiving this treatment and have only heard positive outcomes.*
2	New evidence has been published following the appraisal committee meeting from a trial investigating the combination of rituximab and belimumab in the treatment of SLE. BEAT-LUPUS (Belimumab after B cell depletion in SLE) was a 52-week phase IIb, randomised, double-blind, placebo-controlled clinical trial investigating the safety and efficacy of intravenous

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	belimumab after B cell depletion therapy (rituximab). This trial met its primary endpoint, a significant reduction in IgG anti-dsDNA antibody levels, and demonstrated that belimumab prolongs the time to severe flare compared to placebo. The results suggest that belimumab after rituximab is a safe and effective treatment for patients with SLE and supports further development of this combination as a novel therapeutic strategy. The published results can be found at https://ard.bmj.com/content/80/Suppl_1/74.2 These findings suggest that belimumab may be used, in ways other than as a comparator to rituximab, to improve patient outcomes.
3	We are concerned about the ERG and committee's assumptions concerning the modelled response to treatment for belimumab 'non-responders'. Within item 3.11 of the document, it states that *"the committee did not think it was clinically plausible that nearly half of these 'non-responders' would have had a SELENA-SLEDAI score reduction of 4 or more at 52 weeks on standard therapy alone"* however, during the committee meeting the clinical experts did consider it plausible, especially given the likely high doses of corticosteroids and other immunosuppressive medications used as part of standard therapy. The committee did not give due consideration to the considerable experience of the clinical experts regarding this matter.
4	We are concerned that the appraisal process has not given appropriate consideration to the challenges of obtaining sufficient quality data for a disease such as SLE. The heterogeneous, fluctuating nature of the disease presents considerable difficulty in measuring clinical effectiveness, with many lupus trials failing. Recruitment and retention of patients within trials is a significant barrier and modelling will often be required to present findings. People living with lupus in England should not be punished with the removal of this important treatment option due to the logistical challenges associated with obtaining data of sufficient quality to meet the NICE health technology appraisal standards. One patient provided the following comment: • *I feel it is extremely unfair that assessment for the efficacy of the treatment relies on consistent sufficient data. The nature of lupus is inconsistent and symptoms/treatment/experiences will vary from one patient to another.*
5	Item 3.14 in the document indicates that the ERG presented an analysis with modelling assumptions using the BLISS trial evidence. We are concerned that the BLISS trials' HRQoL measure was modelled using EQ-5D. EQ-5D has been reported to "lack sensitivity or fail to capture important aspects of health in SLE" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6178935/#b20-prom-9-339. This would therefore suggest that the model estimates understate the cost-effectiveness of belimumab.
6	Item 3.4 in the document states that *"the committee heard that, if belimumab is not recommended for routine commissioning, more people would potentially have treatment with rituximab in its absence"*. Has the committee given sufficient consideration to the potential impact this could have for vulnerability to COVID-19 infection? The COVID-19 pandemic has introduced additional need for vaccinations and, as a B-cell depleter, rituximab can present challenges for important vaccinations. "It is recommended to wait for vaccination **at least 6 months after rituximab infusion**. However, if a vaccine, such as influenza, needs to be administered within a certain time interval, vaccination should be done, although lower vaccine effectiveness is expected." https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5042271/

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	Early reports from studies have indicated that rituximab, but not other antirheumatic therapies, is associated with impaired serological response to COVID-19 vaccination. https://ard.bmj.com/content/early/2021/05/10/annrheumdis-2021-220604. The potential increased vulnerability to COVID-19 infection needs to be carefully considered if comparing rituximab and belimumab. The impact will go beyond risk to physical health and will also affect socioeconomic and psychosocial health. One patient commented: • *Regardless of effectiveness, under COVID-19 or other future pandemic conditions, it is possibly more of a risk to immunocompromised patients to have rituximab with 6-monthly infusions than belimumab with either 4-weekly infusions or weekly injections where the drug can be cleared from the body more quickly.*
7	We are concerned that withdrawing subcutaneous injections of belimumab will increase inequalities in access to treatment for people with lupus. Rituximab is only available as an intravenous infusion, administered over a period of six hours at specialist centres. A Rare Disease UK study (https://www.raredisease.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 significant barrier to access for some patients, especially those in employment, those with childcare responsibilities, those who live in remote areas and those on lower incomes who cannot afford travel and/or time away from work. This same barrier is not present with subcutaneous belimumab. A decision to withdraw subcutaneous belimumab will disproportionately impact those who have lower incomes and those who do not have access to a specialist centre. It may limit their treatment to standard care despite the guidance calling for an additional biologic therapy in their case.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Rheumatology
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1	Has all the relevant evidence been taken in to account? We are aware that further evidence in support of belimumab has accumulated since the 'cut-off' date adopted by NICE. We believe these are relevant and should be considered before a final decision is made. 1) Two-year, randomised, controlled trial of belimumab in lupus nephritis. Furie R, Rovin BH et al. N. Eng. J. Med. 2020 17;383:1117-1128 2) OP0129 Belimumab after Rituximab significantly reduced IgG anti-dsDNA antibodies and prolonged time to severe flare in patients with systemic lupus erythematosus. http://dx.doi.org/10.1136/annrheumdis-2021-eular.553 We do note that the committee reviewing the evidence did not contain any rheumatologist, nephrologist or dermatologist who may be familiar with this disease or the complexities of management and wonder whether this may have hampered interpretation of the information.
2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We would comment that a considerable amount of the data on which the decisions have been made appear to be redacted and therefore external scrutiny is hard, but we have some observations to make that do raise concerns about the interpretation of the cost effectiveness of belimumab. a) Estimating the costs associated with damage accrual in lupus and long-term disease activity are methodologically difficult and of course not directly addressed (or addressable) in a controlled-trial setting. Attempts have been made to estimate these costs as part of the technology appraisal but we have concerns this process may have significantly underestimated these costs associated with active lupus and the resulting damage accrual.. b) We note the ERG concerns with the propensity matched analysis using the Toronto Lupus Cohort, in particular the use of calibration factors. We understand concerns with this analysis, but would also have concerns with the use of the Toronto Cohort as an appropriate comparator at all. Firstly it is clear that it was difficult to clearly match patients with the proposed HAD-1 group in the UK. It is also a large cohort of patients managed in a different country up to 30 years ago (only patients prior to 1990 excluded). Considerable changes in medical care have taken place over this time frame that might influence the development of damage and the cost associated with it. This may be the only available comparator group but there are clearly methodological issues in its use that risk considerable error in the estimate of 'standard or care' lupus costs.. c) We also note that assumptions are made about the cause of patients discontinuing belimumab, with the assumption that it must largely be due to inefficacy. The cause of patients discontinuing medication is however much more nuanced than that. In this population of predominantly young women some patients will choose to discontinue belimumab to attempt a pregnancy and others because of the inconvenience of regular infusions. Some patients who are doing well make a decision to step-down their therapy because they feel much better. We cannot make assumptions about the reasons for discontinuation if the data is not available. d) We would note that the BLISS clinical trial populations are not well matched with the group of patients currently receiving belimumab in the UK. UK rules stipulate the requirement for a much higher level of disease activity and more refractory disease than required for enrolment in to clinical trials. e) We would disagree that rituximab is a relevant comparator for belimumab in UK practice, because NHS commissioning rules specifically delineate a pathway for patients appropriate for rituximab from a pathway for patients appropriate for belimumab. These are therefore

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	different patient populations with different characteristics (in general those getting Rituximab have renal disease, central nervous system disease or rather milder disease of skin and joints, while those getting belimumab have more active multisystem involvement not including kidneys or nervous system). f) We agree that the lack of 'trial quality' long-term data is frustrating (although methodologically understandable given the nature of the disease), however we are not aware that trial-quality long-term data has been required for any other autoimmune or rheumatic disease for which biologic therapies have been assessed at technology appraisal. Why is lupus considered different in this regard? g) In estimating the costs of lupus-related damage, the analysis has referenced work looking at the costs of single organ complications (often not in patients with lupus and many very dated studies) and not considered the additional costs of supporting these problems in a patients with multisystem disease. We do not believe the approach of inflating NHS reference costs from 2005/6 is going to accurately estimate the costs of managing these complications. Clinical practise will have changed considerably over the intervening 15 years with additional therapeutic options and improved life-expectancy in patient living with damage. We are unclear how the 'weightings' have been applied in table 67. It is difficult to understand in table 71 why no costs are considered to apply to gonadal failure or skin disease, given the costs of fertility preservation/infertility treatment, skin camouflage, psychological morbidity due to skin disfigurement, wigs etc. etc. h) The disease activity costings appear to be based on the SELENA-SLEDAI system domains, which do not capture all items of disease activity (in comparison with the BILAG 2004 index). The cost of flares does not seem to be accounted for. i) The cost of managing disease and treatment-associated infection does not seem to be accounted for although this is an important complication of lupus and its treatment. j) We cannot agree with the base-case cost assumptions related to steroids as summarised in table 73. The assumption that belimumab and standard therapy groups would be receiving the same dose of oral steroids must be flawed given the demonstrated steroid sparing effect of belimumab. The expectation is that belimumab will allow lower oral steroid dosing. k) Costing needs to consider the specific commissioning rules that are applicable for belimumab in the UK population – in particular the stipulation that treatment is withdrawn if sufficient improvement in disease activity has not been seen at three months. Only good responders are treated with belimumab beyond three months, so this is a selected population who are responding better that the average patient seen in the clinical trial populations.
3	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? . We do feel that further consideration needs to be given to the decision to decline usage of one of only three licenced therapies for this condition, in favour of promoting a standard of care based largely on unlicensed therapy options. We feel that further consideration needs to be given to both the clinical consequences and the perceived cost effectiveness of a 'standard of care' model based on the fact that the provisional commissioning arrangements for belimumab have focussed use on a small group of the sickest lupus patients. Many of these patients have already failed numerous standard of care options. What is left for them is prolonged use of unacceptably high doses of steroid, or cumulative high doses of cytotoxic therapies, with resultant risks of infection, malignancy and cumulative lupus 'damage'. The 'cost' of this option cannot be based on the standard of care cost for an average lupus patient, because it is a specific group of refractory high-disease activity patients. There is considerable anecdotal evidence that patients on belimumab frequently flare within weeks of medication cessation. We feel that more weight needs to be given to the good safety data around belimumab and consider this in comparison with the well documented morbidity associated with steroids and cytotoxics. There may be additional data around the relative safety of belimumab in relation to COVID-19, in comparison with Rituximab that may be associated with vaccine inefficiency and worsening COVID-

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	19 outcomes. We would re-iterate the point made in section 2 that current guidelines for NHS usage stipulate belimumab is withdrawn from patients not making a good response at 6 months, so only patients in whom this drug is proving effective will be on it in the long-term. NHS practice, quite rightly, adheres closely to national and international consensus guidelines on management. The most recent lupus guidelines published by EULAR (European Alliance of Associations for Rheumatology) and the British Society of Rheumatology promote belimumab as a treatment option for lupus that has failed treatment with steroids, hydroxycholoroquine and immunosuppressants, with a high degree of concordance among the experts reviewing the evidence (http://dx.doi.org/10.1136/annrheumdis-2019-215089, https://doi.org/10.1093/rheumatology/kex286) We do support the premise that use of belimumab is applicable to the HDA-2 population and not just the HDA-1 population, and would comment that many patients with high disease activity and damaging disease do not have both low complement and high dsDNA antibody levels, or often do at some point in their disease course but normalise one or the other due to initial treatment attempts even if the clinical manifestations of disease remain active. We do support the premise that the subcutaneous formulation of belimumab is effective and offers considerable advantages to may patient who are otherwise discriminated against due to their geographical location away from a specialist centre who provides intravenous therapy. This may have additional economic benefits but reducing work absence (6.5 working days a year lost through infusions). We recognise some of the uncertainties around the modelling of long-term cost effectiveness but would argue that the alternative costs of 'standard of care' are considerable in a cohort of sick patient exposed to high doses of steroid and cytotoxic agents. In summary we understand the outcome of the technology appraisal is to decline belimumab usage on the grounds of cost effectiveness, but we feel that there is significant risk that the evidence, assumptions and extrapolations required to assess cost effectiveness is subject to considerable uncertainty and risk of inaccuracy. We welcome the recognition that this is clinically effective and has met its endpoint in four randomised controlled trials. We are also aware the UK national registry and commissioning arrangement limit usage to a small group of patients and allow real-time evaluation of efficacy over time. We would argue an extension of the current arrangements, even if on a ongoing provisional basis would be the most appropriate outcome. We are also concerned about the fate of the existing patients receiving belimumab. The prospect of stopping treatment and 'transitioning' them on to an alternative therapy, when most of these patients have already failed on these alternative therapies is unrealistic and will be devastating for these patients. At the very least patients on this treatment should be allowed to continue.
4	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? There are some potentially discriminatory elements to this policy: a) We are aware that lupus as a whole, but also more severe lupus, is over-represented in patients from a non-European ancestral background. This is the population that is therefore going to be particularly affected by the decision to decline usage of this drug. b) The suggestion that gonadal failure should not be considered as accumulating 'costs' implies

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		that it is felt this should not be managed or treated as a complication of lupus therapy. Lupus predominantly affects women of childbearing age for who the desire to have children is an important part of treatment decision making. Again the promotion of a 'standard of care' that can include gonodotoxic agents has a potentially discriminatory element to it.
5		
6		

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Conflict	N/A
Comments on the ACD:	

3.3 Rituximab is a relevant comparator

Regardless of effectiveness, under Covid-19 or other future pandemic conditions, it is possibly more of a risk to immunocompromised patients to have rituximab with 6-monthly infusions than belimumab with either 4-weekly infusions or weekly injections where the drug can be cleared from the body more quickly.

3.15 There are no equality issues that can be addressed in this technology appraisal

As 90% of the UK's 50,000 SLE patients are women, the removal of belimumab as a treatment option would disproportionately affect women. The pain, fatigue and brain fog of SLE can severely undermine one's ability to earn a living and one's sense of self. As SLE is a predominantly 'women's disease', I wonder if the same consideration to withdraw belimumab would apply if SLE negatively affected more men?

3.17 Belimumab is not recommended for routine use

Not just a treatment - SLE remains a very complex, poorly understood disease with many elements that are difficult to quantify. Aside from being the only treatment focusing on SLE itself, belimumab is also part of the desperately needed work that will help us better understand the immune system and develop more new generation drugs for a wide range of autoimmune disease. The immune response is pivotal to many illnesses, including cancers, Covid-19 etc, and understanding it will impact across a wide swathe of disease. Belimumab is not just an autoimmune disease treatment, but part of a longer process of trying to improve outcomes and predict who will benefit from what approach. Please consider at least extending the appraisal period for a further five years to allow for the collection of more data to demonstrate real-world cost-effectiveness for this relatively new drug.

On a personal level, six months since beginning belimumab, I have gone from five to eight useful hours in the day, and sleep eight to nine hours instead of 11 or 12. While I am still using painkillers, I now experience significantly less pain. I have been able to exercise much more and my fitness levels have increased.

Regaining some control over my body means regaining control in my life and the difference is like night and day. As a writer, I feel my mind is sharper and I am now able to entertain the idea of new projects and, after a year's hiatus, maybe even to work again.

For the past six years exhaustion and pain meant I have had almost no social life. Towards the end of the day, through fatigue my voice was too quiet and people couldn't hear me on the phone. Now my friends comment on the change, apparently I look and sound very different. In an unexpected development, my libido has returned after an absence of more than six years. Until now, I would never have considered being able to partner anyone again as I had nothing to offer and would only be a burden. I understand many relationships don't survive the

demands of SLE. Mine didn't. Tentatively, I'm beginning to see a possible future and to make some plans.
I have been able to reduce my reliance on prednisolone (which I detest) from 10mg a day to 9mg, aiming for 7.5mg, though I understand I'm far too dependent on it now to consider coming off it altogether.
Rather than lose belimumab, I would love to see it become more widely available to SLE patients and earlier in the disease path, where it might spare people from SLE-caused organ damage and the dreadful side-effects of corticosteroids. Those people might have a chance at real lives, rather than a depressing existence on a downward spiral.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

3 Belimumab as a treatment option

I have been having belimumab for 3 years. Firstly as an IV infusion and in the last year since the start of Covid S/C injection which i can administer myself at home. I have had no side effects from Belimumab. Since starting Belimumab I have felt so much better. No further hospital admissions. My symptoms have improved greatly and I have been able to reduce my steroid dose which is significant as the side effects from the steroids are misrable.
I am now able to work full time as a nurse. A job I thought I would have to give up because I was so unwell with multipul sick days.
My quality of life has increased and my skin rash has improved giving me more confidence to go out socially.
Being able to give myself the injections at home has reduced my hospital visits monthly and enables me to continue with a regular work patten.
This drug has made such a differance to my life where there was no responce to other medication that had been tried over many years.
I feel discontinuing the use of Belimumab as a treatment for lupus will have a devastating impact on many patient's mental and physical wellbeing impacting on the ability to work and maintain an inderpendant life. I urge you to reconsider.

Name	[redacted]
Organisation	British Isles Lupus Activity Group
Conflict	N/A

Comments on the ACD:

To Whom it may concern,

I'm writing on behalf of the British Isles Lupus Activity Group – a group of NHS rheumatologists with a special interest in SLE, and the steering group of the BILAG Biologics Register. We note the preliminary review of belimumab, which proposes to no longer fund this treatment for SLE patients in the UK.

We feel that this decision does not take account of all the facts or the needs of patients with SLE and should be reversed. Please note the following reasons.

1. SLE is an uncommon condition, and still has an increased mortality risk and a devastating effect on quality of life on those who survive.

2. Patients with SLE require markedly greater use of medical resource than most other rheumatic conditions in terms of hospital and intensive care

admissions, clinic attendances, and multi-speciality care. Yet, treatments options are fewer that other autoimmune rheumatic diseases such as rheumatoid arthritis, and most of these are unlicensed and not proven to be effective in clinical trials.

3. SLE is highly diverse in terms of organs affected, severity and response to therapy. This problem therefore requires a flexible approach to therapeutic options. and also allowance made for the challenges of conducting and the interpretation of clinical trials, where imperfect outcomes measures have to capture changes in every organ system that is affected by SLE.

4. Belimumab is the only licensed therapy other than hydroxychloroquine and glucocorticoids. In a disease with often unsatisfactory treatment options, we feel that patients have a right to treatments with proven efficacy where available.

5. Belimumab is central to European (EULAR) guidelines for treatment of refractory SLE if refractory to methotrexate or azathioprine, as well as BSR guidelines. The UK would be deviating from internationally agreed treatment pathways if belimumab were not available. This would result in worse outcomes for patients in England compared to those treated in Europe.

6. Adherence is a major problem in SLE with oral immunosuppressants, which may relate to neuropsychiatric effects of the disease itself. Intravenous therapies are often therefore be invaluable to ensure control of disease.

7. While rituximab is valuable for resistant SLE, not all patients can be maintained with rituximab. Some patients have good but short responses, requiring more frequent dosing. In such patients, with each flare or relapse, additional damage and toxic glucocorticoid exposure may accrue. Multiple cycles of rituximab may lead to hypogammaglobulinaemia, with high rates of severe infection and requirement for expensive IVIg therapy. Belimumab can avoid this problem due to regular dosing ensuring stable control of disease activity, with an impressive safety record.

8. Getting the right treatment first time is important in SLE, with cumulative harms of disease activity, damage, glucocorticoids and quality of life if multiple therapies are tried and failed. Belimumab has proven stratification variables that can identify the patients most suitable, so that for these patients they are more likely to get the right drug first time. If patients do not respond the treatment is stopped after 6 months or sooner.

9. If belimumab is not available as a treatment option, patients who are refractory to other therapies, and suffer from persistently active disease are likely to be treated with high dose steroids, with all the associated adverse effects, including serious infection, cardiovascular disease, depression, osteoporosis and fractures, as well as increased risk of severe COVID (both steroids and active disease are a risk factor for severe COVID). This would be contrary to best practice and EULAR guidelines, which recommends the use of lowest possible steroid dosage, ideally below 7.5mg/day.

10. An alternative treatment for refractory SLE is cyclophosphamide but it must be noted that this treatment is not suitable for long-term use due to cumulative malignancy risk and other severe toxicities.

11. The number of SLE patients who actually require belimumab is small.

12. The BILAG-BR data on belimumab data may underestimate its potential future efficacy. Many patients had already received rituximab, and were therefore more resistant than the populations in belimumab clinical trials. This was a legacy of the period when such patients had no therapeutic options and would not represent future long-term usage.

13. SLE is treated in specialist centres. The UK SLE community is well connected with regular BILAG meetings, local MDT processes and registry data so that we are able to ensure belimumab is used in only the most appropriate patients and monitored appropriately. When other therapeutic options that may be more appropriate are available, including unlicensed therapies or enrolment into clinical trials, we will ensure these options are used.

14. We note that the appendix to the managed access agreement stipulates that patients who are currently receiving belimumab and are responding well will need to stop therapy within 12 months of this negative decision. This is particularly problematic: most of these patients have already failed other options and would be forced back into severely active disease if their treatment were withdrawn, that may include recurrence of disability, hospitalisation, organ failure or death. We consider this to be unethical when there is a licensed therapy that can prevent such an outcome.

Yours Sincerely

[redacted]

On behalf of the British Isles Lupus Activity Group:

[redacted]

Name	[redacted]
Organisation	N/A

Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

I defer to colleagues from BILAG in answering this question.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not an expert in health economics and it appears that belimumab is judged as too expensive over other cheaper, unlicensed drugs.

Are the recommendations sound and a suitable basis for guidance to the NHS?

These recommendations will remove an option for patients who are refractory to other drugs and thus increase their steroid burden and treatment with other unlicensed therapies.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The removal of this monoclonal antibody biologic therapy that may be used in early stages of pregnancy due to limited placental transfer in first trimester will limit therapeutic options to women considering pregnancy and increase chance of disease flare in those in whom it is stopped. Therefore, women of reproductive age will be disadvantaged by withdrawal of belimumab.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

Unable to comment

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Cost effective analysis does not seem to include the paediatric cohort between 5 years to 12 years who has no access to rituximab according to the commissioning policy

Are the recommendations sound and a suitable basis for guidance to the NHS?

- Rituximab is not licensed in SLE and currently is the only NHSE funded biologic for refractory SLE; there is no alternative product for refractory SLE patients who cannot tolerate rituximab or developed severe allergic reaction to rituximab. Belimumab is a good alternative for these type of patients.
- Belimumab is recommended as an add on therapy in the 2019 update of the EULAR recommendations for the management of systemic lupus

erythematosus. It is considered in the previous appraisal however it failed to justify the reason why the decision was made to differ from European practices.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

- There is no licensed biological disease-modifying antirheumatic drugs product for children after failing standard immunosuppressants and DMARDs. Uncertain where the evidence stands for recommending an off-label use of biologics over a licensed product for children over 5 years or more
- Currently commissioning policy for using rituximab in SLE only applies for post-pubescent children; leaving an unmet needs and potentially discriminating children from 5 – 12 who have no access to any funded biological agent (cannot access via the medicine for children commissioning policy as no paediatric licence and dose not in the BNFC)

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.
1. The committee have considered flawed, indirect comparisons as "evidence".
2. The problem that besets SLE outcome ascerntainment are abstract, multi-faceted clinical scoring systems that are very vulnerable to misscoring (eg mistaking damage for activity or vice versa).
The fact is that I have observed substanial and sustained improved in belimumab treated patients that has allowed significant steroid sparing.
Belimumab clearly has very significant clinical efficicacy - the use of the various abstract metrics and scores serves to obscure this fact. The recent data on belimumab in lupus nephritis provides further evidence to back this up when looking at hard endpoints.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Notably, these recommendations are completely at odds with practice in Europe, Australia and America. How did the committee committee reach a conclusion opposite to their counterparts in these countries (which include those with publically funded health systems)?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The SLE patient group most in need of belimumab are BAME patients (enriched for severe disease). Not approving belimumab disproportionately affects them.

I find this to be a bizarre decision. Belimumab is the first new drug for SLE in over 50 years, and has RCT data to back it up. As a clinician in a specialise lupus centre, I have used belimumab in many patients with previously refractory disease. The effect has been dramatic: to keep them well, reduce relapses and avoid the need for acute hospitalisations. NICE's decision is completely at odds with practice in other developed nations. It is also clearly discriminatory since SLE is disease that affects females to men 10:1, and severe disease disproportionately affects BAME individuals.

1 Recommendations
'rituximab'

Rituximab didn't show efficacy in RCTs. Belimumab did. Yet the former can be given in the NHS- this decision makes no sense!

'considers an acceptable use of NHS resources'

If NICE don't approve belimumab, there will be more use of NHS resources (eg acute admissions, complications from increased steroid use eg hip fracture, avascular necrosis, diabetes) and cost savings from not funding it will be lost

3.6 Belimumab improves the Systemic Lupus Erythematosus Responder Index (SRI) 4 response rate at 52 weeks compared with standard therapy
'The committee noted that the long-term extension studies did not have comparator arms. It concluded that they did not provide long-term effectiveness evidence for belimumab compared with standard therapy.'

There was no comparator arm - how can the committee make any conclusion on long-term efficicacy? You don't know what the outcome would have been if they were not on belimumab (probably much worse). This is clinical trials 101.

3.7 An indirect treatment comparison between belimumab and rituximab is preferred
'The company considered that there was a high likelihood of confounding and selection bias in this analysis.'

The company is completely correct.

3.15 There are no equality issues that can be addressed in this technology appraisal
'It noted a stakeholder comment that double-stranded-DNA antibodies are less common in people from an African family background'

This is not true - higher positivity for dsDNA Abs in African ancestry patients cf European ancestry.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3490432/
and
https://academic.oup.com/rheumatology/article/56/suppl_1/i67/2629213

3.17 Belimumab is not recommended for routine use
'an indirect comparison with rituximab (see section 3.7)'

Indirect comparisons are uninterpretable

Name	[redacted]

Organisation	Freeman Hospital Rheumatology Department, CTD specialist centre
Conflict	N/A

Comments on the ACD:

Has all of the relevant evidence been taken into account?

Therapeutic options are limited in SLE. In sharp contrast to Rheumatoid arthritis which can be debilitating but is rarely life threatening. A large number of high cost drugs are licenced for RA.

Belimumab is a useful alternative to Rituximab which has raised concerns about covid vaccination response.

Belimumab met primary end points in the BLISS trials. SLE is a rare condition. Currently Belimumab is one of only three drugs licensed for use in SLE (prednisolone and hydroxychloroquine). The length of the key Belimumab trials (BLISS) were similar to the length of RA trials, though the document states the BLISS trials were limited by their short length

Subcutaneous Belimumab has been of significant benefit to patients with fewer hospital attendances during the COVID-19 pandemic and less time off work.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is likely that healthcare costs of patients who are currently being treated with Belimumab or are currently eligible for this will increase significantly if this drug is withdrawn. Patients will require increased hospital admissions, requirement for high dose steroids (with associated risks of diabetes, osteoporotic fractures, weight gain, hypertension, glaucoma, skin thinning and muscle atrophy) and potential need for organ support e.g. dialysis.

I do not agree with the calculations of cost effectiveness stated which do not adequately reflect the health care costs of repeated hospital admissions and long term steroid morbidity.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not agree with the NICE decision not to fund Belimumab for patients with SLE living in England.
Lupus is a life limiting and can be an organ or life threatening condition. There is a significant burden of disease and treatment related damage and toxicity.

In our unit in Newcastle Upon Tyne connective tissue disease specialist centre, we have a small but significant, select number of patients who have shown significant clinical response to Belimumab who have been refractory to disease modifying drugs, steroids and, in most cases, Rituximab. They have fulfilled current criteria for initiation of the drug following regional MDT discussion and continuation according to current NHS England guidelines. The use of the drug has been limited to patients with very severe, refractory, SLE.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group

of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Withdrawing Belimumab would potentially be discriminatory towards childbearing women. In some cases Belimumab is the only alternative to IV cyclophosphamide treatment which can result in infertility. Licencing for use in children will prevent the need for large cumulative doses of iv cyclophosphamide and resulting infertility.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

Has all of the relevant evidence been taken into account?

Not really. There is excellent real world long term data on safety and efficacy. No patient stays on a drug for 7+ years unless they think it's working - especially if coming up to clinic for infusions etc. There's evidence of steroid sparing with long term belimumab - a major goal in the management of lupus. If patients have to stop they will end up on much increased steroid dosing. It's not all about short term costs but long term gains to patients.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No
It is not reasonable to use rituximab as a comparator - I use rituximab a lot in renal lupus but it is not licensed, it has not been proven in trials and yes many of us use it but many don't have access even with the new commissioning. It also is different in its mode of action, more likely to lead to low immunoglobulins, impairs responses to vaccines (very relevant in the COVID era) and many lupus patients become allergic over time (we have seen no allergies to belimumab. It is absurd to say we should be using a non licensed drug over a drug that is licensed, been tested in RCTs and met its primary endpoints and now has long real world data to support its use. I can't really comment on the details of the economic models but it seemed to me watching the open part of the committee meeting that the NICE team were determined to ignore all the suggestions GSK made and insist the pricing was too high. Somehow the patient has got lost in all of this - belimumab is the FIRST and only drug licensed for the treatment of lupus in 50 years. It reduces the use of steroids in these patients - long recognised as the major cause of long term damage in these patients.

"The committee concluded that, because rituximab is a relevant comparator (see section 3.4), it would have preferred to see an indirect treatment comparison between belimumab and rituximab in the relevant population". The patients who are allowed to get rituximab for lupus in the UK are different from those receiving belimumab as they are supposed to get belimumab first. So direct comparisons are almost certainly inappropriate and the committee's rejection of GSK's arguments seem spurious. But equally, rituximab is not ideal for everyone, can rarely be given to induce control over years (due to low IgG or allergy) and is not licensed.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No.
Firstly it is completely wrong to say that patients established on belimumab have to transition off it with the next year if this is your final guidance. To get on belimumab in the first place they had largely failed most standard treatments so what you are condemning them to is flaring, more steroid and a greater likelihood of damage from their lupus or from steroids. Rituximab isn't the panacea for all and you are asking them to change treatment when their treatment is working fine (by definition because they have stayed on it). This is morally wrong and likely to cause direct patient harm and enormous distress.

Why would patients on the NHS be the only patients in high income countries be denied belimumab for the treatment of their lupus. It is widely used in the EU and the USA and on the basis of needing either high dsDNA ab or low complement, not both. This should be the case in the UK and you are putting UK patients at a major disadvantage compared to peers in other similar economies.

The logic around people stopping treatment before 5 years is opaque - it means that if not efficacious (and many drugs are only efficacious for some time in this most variable of diseases) it would be stopped and the costs would disappear. But there are a group of patients who clearly gain long term benefit. Also likely to reduce renal flares (based on Lupus nephritis data) which would save a huge amount of money in the long term.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Absolutely - this is an entirely discriminatory appraisal; lupus predominantly affects younger women of colour - the ratio of women to men is 8:1 and it is much more common in people from non European non white backgrounds. To deny this already disadvantaged population a licensed proven treatment is simply wrong.

Name	[redacted]
Organisation	Louise Coote Lupus Unit, Guy's & St Thomas' NHS Foundation Trust
Conflict	N/A

Comments on the ACD:

Has all of the relevant evidence been taken into account?

No. Please see general comments in particular the recent FDA approval of belimumab for lupus nephritis (December 2020) and the need for a non-B cell depleting agent to treat active SLE given the ongoing COVID-19 pandemic. The lack of such an option places our SLE patients at high risk of severe and life threatening Covid-19 infection and therefore hospitalisation and death, which is unacceptable in our opinion. The risk of "long Covid-19" and its potential long term sequelae is also currently unknown in this patient cohort.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I cannot comment on the cost effectiveness calculations as this is outside my area of expertise.

I disagree with the summary of clinical effectiveness, however. A long term (> 12 months) head to head comparison is sought between treatment with belimumab and either standard of care or rituximab. This is difficult in the UK cohort due to the 2016 NICE / NHSE commissioning agreement. The 2016 NICE / NHSE guidance specified that patients fulfilling certain criteria (inc SLEDAI >10) should preferentially be treated with belimumab over rituximab hence there is no comparative real world data for this group. Our own data also show that 41% of our cohort of 48 currently active belimumab treated SLE patients failed to respond to prior treatment with rituximab. Many patients also failed treatment courses of highly cytotoxic drugs such as cyclophosphamide prior to being commenced on belimumab. The long term safety and benefit of belimumab in our patient cohort is clear.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Belimumab is a highly effective and safe drug for the treatment of patients with multisystem SLE who have failed standard of care. The drug is widely used both intravenously and subcutaneously throughout the world to great patient benefit.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Name	[redacted]
Organisation	Newcastle Upon Tyne NHS Trust
Conflict	

Comments on the ACD:

The team at Newcastle Upon Tyne NHS Trust do not agree with the NICE decision not to fund Belimumab for patients with SLE living in England.

Lupus is a life limiting and can be an organ or life threatening condition. There is a significant burden of disease and treatment related damage and toxicity.

In our unit in Newcastle Upon Tyne connective tissue disease specialist centre, we have a small but significant, select number of patients who have shown significant clinical response to Belimumab who have been refractory to disease modifying drugs, steroids and, in most cases, Rituximab. They have fulfilled current criteria for initiation of the drug following regional MDT discussion and continuation according to current NHS England guidelines. The use of the drug has been limited to patients with very severe, refractory, SLE.

Therapeutic options are limited in SLE. In sharp contrast to Rheumatoid arthritis which can be debilitating but is rarely life threatening. A large number of high cost drugs are licenced for RA. Belimumab is a useful alternative to Rituximab which has raised concerns about covid vaccination response.

It is likely that healthcare costs of patients who are currently being treated with Belimumab or are currently eligible for this will increase significantly if this drug is withdrawn. Patients will require increased hospital admissions, requirement for high dose steroids (with associated risks of diabetes, osteoporotic fractures, weight

gain, hypertension, glaucoma, skin thinning and muscle atrophy) and potential need for organ support e.g. dialysis.

Subcutaneous Belimumab has been of significant benefit to patients with fewer hospital attendances during the COVID-19 pandemic and less time off work.

I do not agree with the calculations of cost effectiveness stated which do not adequately reflect the health care costs of repeated hospital admissions and long term steroid morbidity. Belimumab met primary end points in the BLISS trials. SLE is a rare condition. Currently Belimumab is one of only three drugs licensed for use in SLE (prednisolone and hydroxychloroquine).

Withdrawing Belimumab would potentially be discriminatory towards childbearing women. In some cases Belimumab is the only alternative to IV cyclophosphamide treatment which can result in infertility.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

ADDENDUM: Critique of the company response to the ACD and revised PAS

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 17/08/2021

Critique of the company response to the ACD and revised PAS

Issue 1: As no new evidence has been presented, the ERG has no further comments.

The ERG incorporated the revised PAS in its analyses.

Issue 2-6: As no new evidence has been presented, the ERG has no further comments.

Issue 7: The ERG continues to believe that the propensity score-matched (PSM) analysis did not match on important, clinically relevant variables. Urowitz et al. (2019)[1] list the clinically relevant predictors found in the systematic literature review, and the following variables were not included as predictors in the PSM analysis:

- Household income
- Educational attainment
- History of lupus anticoagulant positivity
- History of anti-β2-glycoprotein I positivity
- History of anti-Ro positivity
- Disease activity over time
- SF-20 physical functioning

The company incorrectly states in the ACD response that household income and educational attainment were included in the PSM analysis and therefore social deprivation was accounted for through these proxy variables, however in Urowitz et al. (2019),[1] household income and educational attainment were not included in the PSM analysis. Therefore, social deprivation is not accounted for in the PSM analysis.

Additionally, while disease progression and disease activity over time are potential confounders, they are extremely important prognostic factors. In unanchored multiple adjusted indirect comparison (MAICs), as in this PSM analysis, all effect modifiers and prognostic factors need to be adjusted for to give an unbiased treatment comparison. As such, not including disease progression and disease activity over time biases the analysis, as the two populations may have had very different disease progressions independent of their respective treatments. This shows the fundamental limitations of using analyses of this type, as it is not possible to adjust for disease progression measured after baseline without removing treatment effects. Equally, not adjusting any of the variables listed above, and any other effect modifiers and prognostic factors not identified in the review, will bias the analysis in unknown directions.

This is particularly problematic as the degree of differences in the baseline characteristics in the US LTE study cohort and the TLC are so large. The sample size in the US LTE study cohort decreased from 195 to 99 in the PSM analysis, indicating that to achieve an acceptable level of similarity between variables included in the analysis almost half the population had to be excluded. This is indicative of large differences in the US LTE study cohort and the TLC (also noticeable in the pre-matching bias of the identified effect modifiers and prognostic factors), which likely extend beyond the included variables to all unknown and unmeasured effect modifiers and prognostic factors. Additionally, collapsing variables such as smoking, other diseases and drug use, which could represent a large range of underlying conditions and doses (especially smoking), into binary categories reduces the adjustment for these variables, and so potentially substantial bias may remain even for the variables adjusted for in the PSM analysis.

As such, while the LTE data were potentially *"important to clinical management in the UK and the more relevant data available to demonstrate the effectiveness of belimumab plus ST compared to ST alone on organ damage progression"*, this does not imply that the PSM analysis is unbiased, nor that

substantial bias does not remain after the adjustment of some relevant effect modifiers and prognostic factors.

It is impossible to know, without further data, to what extent the patients who stopped taking belimumab before 5 years are different to patients who continued taking belimumab beyond 5 years, and therefore the extent of the potential bias from only including patients who continued on belimumab beyond 5 years. A large percentage of patients withdrew from belimumab, and while lack of efficacy was the stated reason in a minority of these withdrawals, it is plausible that lack of efficacy would have been a factor in withdrawals for other stated reasons. While it is indeed conceivable that patients discontinuing from belimumab *"could have potentially continued to receive the benefits of belimumab until year 5"*, it remains the view of the ERG that there is the potential of substantial bias in favour of belimumab from analysing only patients continuing to receive belimumab beyond 5 years.

Issue 8: The company did not provide any additional information. Unfortunately, no further explanation has been provided on how the calibration factor was derived. The ERG understands that the calibration factor was only applied to belimumab responders, which is appropriate. However, the way the calibration factor was derived may be problematic. It remains unclear whether the calibration factor was derived by calibrating the organ damage progression of the overall belimumab arm to match that of the PSM study or whether only belimumab responders at a certain time point were used. In Table 64 of the CS it is stated that the responder rule was disabled for the calibration exercise, suggesting that all patients in the model may have been used to calibrate modelled SDI to PSM SDI (but the ERG is uncertain about it). If this were to be the case, the calibration factor would bias model outcomes in favour of belimumab.

This is because modelled SDI change was significantly above PSM SDI change (implying more organ damage in the modelled population than in the PSM). This is not surprising as the SDI from the PSM is based on responders (those that have continued treatment). So, in order to calibrate the SDI of all modelled patients in the belimumab arm to the SDI from the PSM, the proportional decrease in SDI change (as estimated by the calibration factor) would have likely been over-estimated.

To make this more tangible:

Figure 14 in the response to clarification (which was shown in the committee slides) shows the SDI change of all modelled patients in belimumab arm (if this is how the company did it, which remains unclear) as it is without calibration (calibration factor=1). To get the SDI scores of these patients to the levels of the PSM at 5 years, the calibration factor (CF) had to be as low as 0.491. But if only responders had been used, the CF=1 line would likely have been lower, and the calibration factor would have likely been above 0.491.

This calibration factor is then applied to responders and their resulting SDI change may therefore be even lower than that of the PSM.

In conclusion: it is likely inappropriate to use the whole modelled cohort to derive the calibration factor and only responders should be used. Clarification is needed as to how the company derived the calibration factor. However, the caveats around the risk of bias of the PSM still apply in addition.

It may be helpful for the committee to see graphs of organ damage progression for modelled belimumab responders, belimumab non-responders and patients in the ST arm and the overall belimumab arm in the model (both with and without the use of the calibration factor), but bearing in mind the high risk of bias of the PSM study.

Issue 9: Issue 9 covers two issues:

1) A significant proportion of belimumab non-responders at 24 weeks become responders at 52 weeks.

The ERG appreciates the company's *"post-hoc analysis of the pooled 52/76 IV BLISS trial data which demonstrates that in the HDA-2 subgroup out of the 87 patients who were considered to be non-responders at week 24 (<4-point reduction in SS score), 30 (34.5%) of patients achieve a ≥4-point reduction in SS score at week 52"*. According to the company, 46.5% of all modelled belimumab non-responders had a ≥4-point reduction in SS score at week 52. This means that the model overestimates the reduction in SS score of belimumab non-responders. In addition, the appropriateness of the 24 week assessment could be questioned.

2) The company's assumption that belimumab non-responders have the same SS score at one year as patients treated with ST.

This assumption stands in contrast to the company's analysis of their BLISS trial data that was presented in the original submission. The company provided a scenario that attempts to capture the detriment of belimumab non-responders compared to patients treated with ST through an addition of costs in the first year, which has a small impact on model outcomes. The ERG continues to use the BLISS trial data that shows a detriment in the SS score at one year. This may also resolve above issue 9.1, i.e. it may lead to a proportion of modelled belimumab non-responders with ≥4-point reduction in SS score more in line with the trial data, although the ERG was unable to check.

Given the 24-week assessment time point, a model cycle of 24 weeks would indeed be preferable, as highlighted in the ACD. The ERG considers that it is unclear what additional advantages can be derived from using a longer (that is an annual) cycle length compared to a cycle length of 24 weeks, even in a chronic disease.

Issue 10: This relates to the same issue the company partially addressed in Issue 9, namely:

2) The company's assumption that belimumab non-responders have the same SS score at one year as patients treated with ST.

The company provided a new scenario where belimumab non-responders assumed the average SS score of ST patients by year 1.5 (Week 76) instead of at 52 weeks (company's base-case) and right after 52 weeks, i.e. for all of year 2 (ERG base-case). The company's scenario consequently resulted in slightly higher ICERs than the ERG's amendment (see Tables 1 and 2 Fixing errors 1). The ERG's clinical expert considered that belimumab non-responders were likely to have the same SS score as patients treated with ST after one year. Hence, the ERG prefers its own implementation over that of the company.

Issue 11: The company provided scenario analyses incorporating their new PAS. Given the above considerations, the ERG produced its own scenarios in its original model file. The ERG was able to reproduce the company's updated base-case with the new PAS.

Table 1: ERG base-case of IV analyses, with revised PAS

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (/QALY)
Company base-case						
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,952
Standard therapy	£160,470	16.900	9.809			
Fixing errors 1: 1st year: SS reduction for belimumab non-responders (conditional on company base-case)						
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,539
Standard therapy	£160,470	16.900	9.809			
Matter of judgement 2: Calibration factor removed (conditional on company base-case)						
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,951
Standard therapy	£160,470	16.900	9.809			
ERG base-case (changes 1 and 2)						
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,428
Standard therapy	£160,470	16.900	9.809			

Table 2: ERG base-case of SC analyses, with revised PAS

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (/QALY)
Company base-case						
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,041
Standard therapy	£151,999	17.122	10.056			
Fixing errors 1: 1st year: SS reduction for belimumab non-responders (conditional on company base-case)						
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,773

Standard therapy	£151,999	17.122	10.056			
Matter of judgement 2: Calibration factor removed (conditional on company base-case)						
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,913
Standard therapy	£151,999	17.122	10.056			
ERG base-case (changes 1 and 2)						
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,116
Standard therapy	£151,999	17.122	10.056			

References:

[1] Urowitz MB, Ohsfeldt RL, Wielage RC, Kelton KA, Asukai Y, Ramachandran S. Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. *Ann Rheum Dis* 2019;78(3):372-379.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

ADDENDUM: ERG PSA results in response to the ACD and revised PAS

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 02/09/2021

Table 1: PSA results for ERG base-case after ACD response

	Incremental costs belimumab vs ST	Incremental QALYs belimumab vs ST	ICER (£/QALY)
IV formulation	[redacted]	[redacted]	£47,927
SC formulation	[redacted]	[redacted]	£51,442

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

ADDENDUM: ERG comments on company's additional clarifications dated 6th September 2021

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Date completed	09/09/2021

The company provided additional clarifications regarding the derivation of the calibration factor. The company confirmed the ERG's assumption that the calibration factor was derived using the entire modelled belimumab cohort (i.e. composed of both responders and non-responders). Since the calibration factor is based on the PSM data, which includes patients that are treated long-term, thus having lost non-responders, this approach lacks face and clinical validity.

The ERG would prefer the use of only responders in the belimumab cohort to derive the calibration factor. The company provided results from this analysis in a scenario. As was expected, the new calibration factor lies above the old one, although the difference is slightly smaller than the ERG expected (new CF=0.536 vs original CF=0.491). This means that removing non-responders has only altered the SDI progression of all patients treated with belimumab to a limited extent, meaning that the SDI progression of non-responders did not substantially affect the SDI progression of all belimumab-treated patients at 5 years. The ERG does not have evidence to help explain this and can only speculate: perhaps the SDI progression of belimumab non-responders may be under-estimated in the model (that is non-responders do better than they should). It is currently unclear whether the company's model setting where the 52-week belimumab non-responders do as well in terms of disease activity as their counterparts who received standard therapy (whilst evidence from BLISS shows that they did worse) had any impact on the derivation of the calibration factor. The ERG would prefer using the corrected model to derive the calibration factor in order to rule that out. Furthermore, as was highlighted before, the calibration factor is estimated for the 5-year time point, and therefore leads to underestimation of SDI progression in years 2, 3 and 4. This has not been addressed in this updated model.

It remains unclear to the ERG whether the calibration factor should be used, given the significant doubts over the appropriateness of the PSM for this purpose. If it is used, the ERG prefers the new calibration factor over the original one. However, this was not fully validated and it is likely that this calibration factor continues to overestimate the impact belimumab has on the reduction of organ damage.

NICE National Institute for Health and Care Excellence

Patient expert statement

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Abbie Thomas**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Lupus UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your	☒ I have personal experience of the condition

statement? (please tick all that apply)	☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with Lupus in 2008 when I was 19. I was fortunate to have a GP with an interest in Rheumatology and was diagnosed within a year of symptoms becoming persistent and unmanageable. I also have antiphospholipid syndrome and Raynaud's associated with my Lupus. Whilst I know it is not a definitive marker / indicator, my DsDNA has decreased from over 700 when I was first diagnosed to being consistently around 35 with most of that decrease happening in the last few years and while on Belimumab. Lupus is an incredibly difficult condition to live with for many reasons. There is no cure, the disease pathway is unknown (and varies so much from patient to patient), the level of disease activity is unpredictable, and it is invisible to those around you. I have faced discrimination at work because of this and have lost friendships because of it. My physical symptoms have been wide ranging but most commonly have featured: Severe joint pain and swelling (at the worst times this was affecting my movement, ability to use my hands fully etc.), intermittent rashes, persistent headaches, serositis, episodes of pericarditis, extreme costochondritis that resulted in having steroid injections into my sternum to ease the pain, nerve / muscle pain, persistent dry cough, debilitating fatigue, intermittent abnormal urinalysis. It is hard to describe what it is like to live with Lupus. To not being able to sleep because you are in pain no matter how tired you are. To feel completely exhausted just by getting up in the morning and having a shower. To feel like your body is stuck in treacle and every movement takes more effort. Forgetting things unless you write them down, never really feeling present in a conversation or moment because you are so tired and/or in pain. Putting on weight because you can't exercise the way you used to. Never knowing how you're going to be the next day or the next week. Feeling low, hopeless, and helpless. It is a lot for anyone to deal with but especially for someone moving through their 20s and 30s with many hopes of things they could have done. I am 33 years old, and I hate that I must ask my family for help to keep on top of jobs around the house and other 'normal' everyday tasks because I am in pain or too exhausted to manage it, but I don't have a choice. I live on my own and must try and save as much 'good' energy for work so that I can maintain my income and a level of independence.

	My social life is restricted and my friends, very kindly, adapt the things we do together so that I can manage as much as possible. But again, I am 33 years old. I became very despondent over a period of 2-3 years before starting Belimumab as it took a long time to find a drug treatment plan that was managing and improving my Lupus. I have taken hydroxychloroquine as standard since I was diagnosed. I had some success with Azathioprine initially however as my disease activity increased it was ineffective and I had to stop taking it due to abnormal liver function results. I tried Mycophenolate which was ineffective. I take Methotrexate injections, but they aren't sufficient on their own to keep my Lupus under control. I tried two courses of Rituximab and there was no measurable benefit. It was at that point I started on Belimumab in 2019. Prior to starting on Belimumab I would usually be on regularly recurring short courses of steroids too. Belimumab has been a lifeline for me and the thought of not having this drug available to me is a huge source of anxiety as I'm sure it is for the many others who had exhausted all other treatment options. I don't say this for dramatic effect, but I honestly don't know what life I would have without this treatment. I would be back to facing the difficult decisions I was starting to have to consider such as giving up work or going part time and how that would affect being able to afford to stay in my own home. How could I have any hope or positivity at going back on to a previous treatment that didn't work for me?
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The NHS offers all standard treatments for Lupus. However, generally for Lupus there are a limited number of treatments and Belimumab is the first created specifically for Lupus in decades. If you don't respond to the 'standard' treatments, your treatment options are very limited. The challenge with most of the treatments for Lupus is they take a while to become established in your system, which as a patient is very frustrating when you are feeling terrible but having to wait 3-6 months or so before a Dr will take a view on its effectiveness. I also find it very frustrating there is still a lack of acceptance that sometimes the patient won't fit the data criteria you are expecting. I have, on many occasions, just felt like I wasn't being seen. Result X said one thing, I said another but result X was the information used to make my treatment plan. I of course understand that there needs to be a level of data as a guide but with such a complex condition that can vary so widely from patient to patient what the patient is experiencing must have some weight too. There is also a lack of broader support e.g., other therapies, my Rheumatology department gets no mental health funding to support patients who are dealing with such complex, lifelong conditions.

10. Is there an unmet need for patients with this condition?	Generally, yes, and the NHS does need to keep up with the new treatments that are emerging and Belimumab should be part of that. Rheumatology Departments should also get more funding for mental health support and other holistic therapies.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Belimumab has given me the longest period without significant absence from work. It has given me the lowest use of steroids in years. I experience no side effects from the infusions (unlike when I was on Rituximab). The time commitment of the infusion is much easier to manage around work or other commitments (also unlike rituximab where I would miss a whole day of work and then would quite often feel unwell the following day). Belimumab has greatly improved the amount of joint inflammation and pain that I experience and has generally helped to keep my disease as stable as possible. It is hard to convey what my life was like before I started Belimumab in 2019, I was barely coping at work. I had no social life; every day was just as bad or worse than the day before. At that point I wasn't even 30. My Lupus can still be hard to manage / deal with and the fatigue is still one of the most difficult aspects to manage. But Belimumab has given me confidence in my treatment plan and the feeling that at least I know bad periods will settle back down and I feel more able to plan for things in the future knowing there is a good chance I'll be feeling well enough for them.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	None.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I think Belimumab could be of great benefit to many Lupus patients and may hopefully help prevent their disease advancing to a point of organ damage etc. However, if it can't be used for wider / more general treatment then it is a critical option to have for those who have had no result from the other approved standard treatments.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	It is recognised that Lupus predominantly impacts more women than men. Women, largely, still have the most care-giving responsibilities. Therefore, a medication that can be delivered via a shorter infusion time is advantageous to allow them to continue to maintain work and/or caring responsibilities.
Other issues	
15. Are there any other issues that you would like the committee to consider?	I would like to committee to recognise the period of high anxiety immunosuppressed patients have had by having to shield through the pandemic and with the additional uncertainty of COVID vaccine efficacy in immunosuppressed patients. This is also particularly relevant given the concern around Rituximab and its seemingly heightened detrimental impact on vaccine efficacy. I would like the committee to recognise that with poor disease control and a lack of effective treatment options it could lead to far greater and more costly medical treatments being needed e.g., if my disease worsens due poor treatment options that could result in kidney disease > dialysis > transplant.

Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • Belimumab is an effective treatment. • Lupus is highly unpredictable and does not follow one uniform path for disease progression or disease treatment. • Belimumab is a lifeline to patients who have proven resistant to other therapies. • Lupus is a life limiting and life affecting condition. • Lupus is a hidden disease and is generally poorly understood.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.