NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - GlaxoSmithKline
   - Lupus UK
   - British Association of Dermatologists
   - British Health Professionals in Rheumatology
   - British Renal Society
   - British Society for Rheumatology
   - Primary Care Rheumatology Society
   - Renal Association
   - Royal College of Nursing
   - Royal College of Pathologists
   - NHS Bolton
   - Commissioning Support Appraisals Service

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Report summarising petition received following ACD consultation**

5. **Additional evidence submitted by GlaxoSmithKline**

6. **ERG critique of additional evidence**
   - ERG erratum and additional sensitivity analysis
   - ERG additional analysis

7. **Professor David Isenberg's Comments on manufacturer's additional analyses**

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

No comments were received on the ACD from the clinical specialists or patient experts.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

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 may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
GSK	**Executive Summary** We welcome the opportunity to respond to the Committee's initial conclusions regarding the evidence base to support the use of belimumab within the NHS. The ACD raised a number of issues arising from the modelling assumptions, the patient population and the disease scoring which drive the cost-effectiveness model. There were also concerns raised regarding the comparison with rituximab. We believe that we can address the main points raised by the Committee and the clinical specialists to support the use of belimumab within the NHS as a valuable, cost-effective treatment for SLE.	Comments noted. Please see responses below.
GSK	There is inevitably uncertainty when appraising the effect of a drug on a complex, chronic disease with severe long term outcomes such as SLE, where most of the evidence is based on relatively short randomised controlled trials (RCTs). Considering the concerns of the committee we have reviewed the way the medicine could be used within the NHS. We are proposing an approach which would more accurately reflect the way belimumab is likely to be used in clinical practice by restricting treatment to a maximum of six years and focussing on those patients demonstrating the greatest benefit. By restricting treatment in this way, some of the uncertainty around the cost effectiveness is reduced and the estimated cost effectiveness is now at a level that would be regarded an efficient use of NHS resources (see Table 1 below and further information in detailed response). **Table 1 not replicated*** The revised health economic modelling, incorporating our patient access scheme (PAS), results in a revised base case ICER of [redacted] per QALY gained, with further reductions in the ICERs from additional key scenarios presented in Table 1. Therefore, given we believe that the health effects discount rate of 3.5% used in the base case is too high for this technology appraisal, the true assessment of cost-effectiveness is likely to lie within the range of [redacted] per QALY gained.	Comment noted. The Committee has considered the additional data presented by the manufacturer, including the longer term data on reductions in steroid use and revised cost effectiveness analyses. See responses below and FAD sections 4.11, 4.14, 4.16, 4.17, 4.24, 4.25.

Consultee	Comment	Response
GSK	The committee has acknowledged in the ACD the serious nature of SLE and its impact on patients as well as the innovative nature of belimumab which is the first medication to be specifically designed and licensed for these patients for a number of years. The current NICE Methods Guide 2008, outlines additional factors to consider when appraising a technology. These include: "where the innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure". In this case there are aspects of value not fully accounted for in our estimate of cost-effectiveness. Specifically, the full benefit of belimumab on disease flares and chronic fatigue are not adequately captured in the quality adjusted life years (QALYs) derived from EQ-5D utility values. Also, recently available data from the open-label Phase II belimumab extension study (Petri et al. 2011) shows a mean reduction in steroid use of 4.7mg/day, an average of 34.4% from the baseline dose, by the end of six years of follow-up. This is an important finding, as not only does it have the potential to lead to improved quality of life for patients experiencing fewer steroid-related side effects, but future steroid related organ damage would also be reduced. The impact of this recent data is not fully reflected in our current estimates of cost effectiveness.	Comment noted. The Committee discussed whether any health-related quality-of-life benefits may not have been captured in the calculation of the QALY. It was aware that disease flares had not been included in the economic modelling. The Committee noted that in the BLISS trials that although differences in EQ-5D were demonstrated between treatment groups these were not statistically significant at 52 weeks. Further, there were no statistically significant differences at week 52 for FACIT-fatigue scores in the target population in people receiving belimumab compared with people receiving standard care. The Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life from belimumab had not been adequately captured. The Committee concluded that the issues identified around innovation did not change its conclusions about the cost effectiveness of belimumab. See FAD section 4.28.
GSK	Finally, we do not believe that the arguments presented in our submission regarding the comparison of belimumab with rituximab has been given sufficient consideration. Rituximab is unlicensed for SLE and is not supported by evidence from RCTs. [redacted] Moreover, in the absence of these biologics being available on the NHS, SLE patients may be admitted to hospital for alternative more expensive treatments such as intravenous immunoglobulin (IVIG).	Comments noted. The Committee did not consider that there was reliable data available to judge the relative efficacy of rituximab and belimumab, or that the costs of the treatments had been captured accurately. The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. See FAD sections 4.12 and 4.27.
GSK	For the reasons outlined above, and considering our revised assessment of cost-effectiveness, our specific target population, the proposed patient access scheme, and having addressed the committee's concerns regarding the relevance and uncertainty around some of the key assumptions in our health economic model, we would ask the committee to reconsider its decision and approve the use of belimumab in this group of severe patients.	Comments noted. Please see responses below.

Consultee	Comment	Response
GSK	1. Do you consider that all of the relevant evidence has been taken into account? Yes. However we believe that the Appraisal Committee and clinical specialists identified several areas of uncertainty that require further exploration and we would like the committee to consider a revised base case with supporting scenarios to address these. In addition, since submitting in April, there is new published data concerning the reduction of steroid use which is more reflective of clinical practice than observed in RCTs. The additional analyses we present have a considerable impact on improving the estimated cost-effectiveness for belimumab compared with the results presented in our original submission. After further consultation with lupus experts we also believe these revised assumptions are supported clinically. The detail of these analyses are provided in Appendix 1 of this document, however the rationale for the revised base case and other changes to the original assumptions are summarised in this section along with the updated cost-effectiveness results. Please note that all ICERs in this document incorporate the discount on price offered in our patient access scheme (PAS).	Comment noted. The Committee has considered the additional data presented by the manufacturer, including the longer term data on reductions in steroid use and revised cost effectiveness analyses. See responses below and FAD sections 4.11, 4.14, 4.16, 4.17, 4.24, 4.25.
GSK	Duration of treatment with belimumab – Revised Base Case The most important change we have made to our base case for health economic assessment concerns the expected duration of continuous treatment with belimumab. It is clear from the comments in the ACD (Section 4.13) that we needed to align this duration more closely with how clinicians would consider using belimumab to manage their eligible SLE patients in clinical practice. Although the duration of treatment in our original submission was based on the SmPC for belimumab which states that belimumab could be used continuously, the waxing and waning nature of SLE means that clinicians are unlikely to continue belimumab indefinitely, but instead use it as clinically indicated. The indefinite treatment duration assumed in the original model submitted to NICE does not therefore reflect likely real life use and will have therefore provided a very conservative estimate of cost-effectiveness.	Comment noted. The Committee understood that belimumab would not be used continuously over a lifetime. However, NICE can only make recommendations for belimumab within its marketing authorisation which describes continuous treatment, therefore the Committee is unable to make recommendations for intermittent treatment or alternative administration schedules outside of those described in the SPC. Further there is no evidence for the use of belimumab in this way. The Committee discussed the revised analyses presented by the manufacturer, which incorporated continuous treatment but limited the maximum treatment duration to 6 years. However, the Committee concluded that the rationale for the choice of continuous treatment with a maximum duration of 6 years could not be considered sufficiently robust to use it as the basis of decision making. See FAD sections 4.4 and 4.16.

Consultee	Comment	Response
GSK	Other standard of care treatments for SLE, such as immunosuppressants, are frequently prescribed for between two and five years depending on the level and type of disease activity patients' experience. Although there is a lack of direct evidence to identify an optimal treatment duration for belimumab, partly due to the heterogeneous nature of the disease, to date there are six years of efficacy and safety data for belimumab from the Phase II extension study (LBSL99) (Petri et al. 2011), which demonstrate, for the majority of patients in the study, a sustained response to belimumab without compromising safety. Supported by this evidence, and after discussion with clinicians, we propose a revised base case which incorporates a maximum six year treatment duration for belimumab. After this time all belimumab patients mirror the standard of care (SoC) treatments for the remainder of the model horizon and revert to the SoC level of disease activity. Although we do acknowledge that this duration of treatment could be considered arbitrary, it is believed that it is long enough for the benefits of belimumab on controlling high disease activity to have an important impact on reducing long-term morbidity while also being a realistic continuous treatment duration that clinicians would be comfortable with for patients who demonstrated a suitable sustained level of response. This treatment duration will also help to reduce some of the uncertainty around the modelled assumption of retaining the same level of benefit for belimumab as seen in the trials over long-term treatment. This revised base case yields an ICER of [redacted] per QALY gained. This provides a more cost-effective use of NHS resources compared with our original base case which assumed lifetime use. If shorter treatment durations with belimumab are considered, the cost-effectiveness is further improved, as the incremental costs, which are mainly driven by the drug acquisition cost, are reduced. However health benefits may also be reduced compared with the revised base case duration of six years as there is less estimated long-term benefit due to the shorter durations of reduced disease activity with belimumab. We believe the choice of a maximum treatment duration of six years is therefore an evidence-based and appropriate compromise for treatment with belimumab in our proposed target population. *Key Scenario Analyses* In addition to the revised base case analysis described above we have considered a number of scenario analyses which look at different treatment durations of belimumab, different discount rates and the inclusion and exclusion of treatment continuation. However there are two alternative scenarios which we consider the most important for consideration because of the impact they have on the assessment of cost-effectiveness and they are discussed below:	Comment noted. The Committee understood that belimumab would not be used continuously over a lifetime. However, NICE can only make recommendations for belimumab within its marketing authorisation which describes continuous treatment, therefore the Committee is unable to make recommendations for intermittent treatment or alternative administration schedules outside of those described in the SPC. Further there is no evidence for the use of belimumab in this way. The Committee discussed the revised analyses presented by the manufacturer, which incorporated continuous treatment but limited the maximum treatment duration to 6 years. However, the Committee concluded that the rationale for the choice of continuous treatment with a maximum duration of 6 years could not be considered sufficiently robust to use it as the basis of decision making. See FAD sections 4.4 and 4.16.

Consultee	Comment	Response
GSK	*1. Revised Discount Rate* After we had submitted in April 2011, NICE issued updated guidance, effective from July 2011, on the methods of technology appraisal with regards to the level of acceptable discounting for health effects (www.nice.org.uk/media/955/4F/Clarification_to section_5.6_of_the_Guide_to_Methods_of_Technology_Appraisals.pdf). This updated guidance specifies that for certain chronic diseases where treatment effects are both substantial in restoring health and sustained over a very long period, a rate of 1.5% for health effects and 3.5% for costs can be applied. SLE is often a lifelong, severely debilitating disease with significant morbidity which can lead to premature death. Belimumab specifically binds to soluble human B-lymphocyte stimulator (BLyS) and inhibits its biological activity. In Phase III clinical trials, belimumab demonstrated clinically important reductions in disease activity, and has the potential to provide important long-term benefits including reduced organ damage, reduced use of high dose steroids - along with their associated risks - and consequently, improved survival. Clinical experts also concur that reducing disease activity in the near-term has important benefits in the longer-term. We believe that belimumab should be appraised with this lower discount rate. Therefore for our revised base case which includes a maximum treatment duration of six years, and for our original base case which assumed lifetime treatment with belimumab, we have conducted a scenario analysis for the assessment of cost-effectiveness incorporating a health effects discount rate of 1.5%. For our original model, with lifetime treatment, incorporating this level of discount for health effects yielded an ICER of [redacted] per QALY gained. For our revised base case with a maximum treatment duration of six years, the corresponding ICER is [redacted] per QALY gained.	Comment noted. The Committee discussed the use of the alternative discount rate and noted that the sensitivity analysis provided by the manufacturer showed that the ICERs were sensitive to using discount rates of 3.5% for costs and 1.5% for benefits. The Committee considered that belimumab as it was currently modelled reflected a scenario where it was assumed there was continued treatment with continued benefit. This differed from the scenario that had led to the clarification of the methods guide, where there was limited duration of treatment with curative intent. Therefore the Committee concluded that belimumab does not meet the criteria for differential discounting of health benefits. See FAD, section 4.24.

Consultee	Comment	Response
GSK	*2. Treatment Continuation Criterion* In our original base case (and also our revised base case) we included a treatment continuation rule (stopping criterion) after six months. This rule was specifically included in the model to try and represent how patients could be managed on belimumab in clinical practice as recommended in the SmPC. The SmPC states that "Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment". For the health economic model an objective measure was required to determine for each patient whether belimumab should be continued or discontinued after six months treatment. Our continuation rule required patients to demonstrate a reduction of at least 4 points in SELENA-SLEDAI (SS) score. A minimum reduction of 4 points in SS score is accepted as a clinically relevant improvement in disease activity (Gladman et al. 2000). We are aware that the Committee felt this continuation rule was arbitrary and may not be adhered to in clinical practice (see ACD Section 4.12). An SS score reduction of 4 or more was a pre-specified component of the composite primary endpoint of the BLISS trials and the main driver of efficacy. The SELENA-SLEDAI is a validated, robust measure (Griffiths et al. 2005) and a decrease of 4 or more points relates to a clinically meaningful change in disease activity (Gladman et al. 2000). We have consulted with lupus experts and have been advised that incorporating a treatment continuation rule in clinical practice as part of the management of patients on belimumab would be easily achievable and acceptable if it was a stipulated requirement in NICE guidelines. As reflected by the clinicians at the Appraisal Committee Meeting, it would in fact be valuable to introduce objective assessment of SLE routinely in clinical practice. It is also worth considering that patients in our proposed target population will be managed in only a small number of specialist lupus centres. This will help ensure that clinicians adhere to any specific requirements for prescribing belimumab as detailed in the guidance that NICE issues. There is no other recommended, validated, objective treatment continuation criterion for any treatments currently used in the management of lupus patients in clinical practice. However, stopping rules are routinely used in clinical practice for assessing continuation of treatments for rheumatoid arthritis. For example, the NICE guidance on tumour necrosis factor (TNF) inhibitors in disease-modifying anti-rheumatic drug (DMARD) failures states that treatment should be continued only if there is an adequate response (defined as improvement of Disease Activity Score 28 (DAS28) by at least 1.2 points) at 6 months following initiation of therapy (TA130). There is no reason to believe there would be any difficulties in implementing a treatment continuation rule for lupus patients.	Comment noted. The Committee understood that the Summary of Product Characteristics for belimumab states that discontinuation of treatment should be considered if there is no improvement in disease control after 6 months of treatment. The Committee discussed the difference between the 4 and 6 point continuation rules and heard from the clinical specialists that they would prefer the lower stopping rule which required an improvement of 4 points in the SELENA-SLEDAI score and would be uneasy using the higher continuation rule of 6 points unless it reduced the base case ICER to an acceptable level On balance, the Committee was persuaded that the application of stopping rules was appropriate, but concluded, that it was not appropriate to consider using the more restrictive rule of a SELENA-SLEDAI score improvement of 6 or more as the base-case analysis for decision making. See FAD section 4.17.

Consultee	Comment	Response
GSK	In addition, being mindful of limited NHS resources, introducing a more stringent treatment continuation criterion, could allow for a more efficient use of NHS resources by ensuring that only those patients showing the greatest response to belimumab continue on this drug. We have therefore also modelled as a scenario, a more stringent criterion for allowing continued treatment with belimumab, which requires patients to have a decrease in SS score of at least 6 points after six months. This more stringent criterion improves the cost-effectiveness compared with the base case, as fewer patients will reach the level of reduction in SS score required for treatment continuation. For the revised base case, this analysis yields an ICER of [redacted] per QALY gained when incorporating a health effects discount rate of 3.5%. When a health effects discount rate of 1.5% is used in the model, the ICER is further reduced to [redacted] per QALY gained.	Comment noted. See response above.
GSK	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence There are some aspects of the interpretation of the clinical evidence that we believe require further clarification and consideration. The main issues that we would like the committee to consider further relate to: i) the representativeness of our target BLISS SLE population and their likelihood of developing significant long-term organ damage which has an impact on survival ii) the relevance of the SELENA-SLEDAI tool to patient selection and management iii) health effects being underestimated in the health economic model and iv) the cost and efficacy comparison with rituximab.	Comments noted. See responses below.
GSK	**i) Representativeness of our target BLISS SLE population and likelihood of developing significant long-term organ damage** • **The range of clinical manifestations seen in our RCTs, and our proposed target subgroup, is representative of those seen in SLE patients in the UK** • **Due to having both a high level of disease activity (SS score ≥10) and the presence of serological biomarkers indicative of systemic disease, these patients are likely to progress to serious long-term morbidity.**	Comments noted. See responses to detailed comments below.

Consultee	Comment	Response
GSK	ACD Section 3.5. The Committee states that “Most of the patients in the trials had a relatively narrow range of manifestations of systemic lupus erythematosus, mainly restricted to mucocutaneous, immunological and/or musculoskeletal damage.” This range of manifestations is not narrow. Involvement of these organ systems (mucocutaneous, immunological and musculoskeletal) represent significant disease activity. Specifically, immunological manifestations, such as serological changes (e.g. low complement and positive anti-dsDNA), is indicative of wider systemic disease activity.	Comments noted. Section 3 of the FAD describes the evidence submitted, rather than the Committee consideration of that evidence. The sentence in the evidence section has been amended to state that most of the patients had a range of manifestations of systemic lupus erythematosus, mainly involving mucocutaneous, immunological and/or musculoskeletal damage. See FAD section 3.5.
GSK	ACD Section 4.16 In their evidence to the Committee the clinical specialists stated that SLE patients with higher disease activity are more likely to have organ damage and die than people with lower disease activity. However, it was also stated by the specialists that this increased morbidity from high disease activity was likely to be dependent on the site of organ damage. For example, treatment for patients with mainly musculoskeletal or mucocutaneous damage was unlikely to result in a survival benefit. Our target population comprised patients with a SELENA-SLEDAI score of ≥10 (representative of high disease activity) and had low complement and positive anti-dsDNA; these are markers of systemic disease; patients with serologically active disease are more likely to flare (Petri et al. 2009; Tseng et al. 2006) and develop long term organ damage (Swaak et al. 1999) which can lead to premature death. Therefore by ensuring sustained suppression of disease activity it is plausible that the patients in our target population will have a survival benefit from treatment with belimumab, irrespective of the organs involved. Whilst the 52 and 76 week BLISS trials were not designed to demonstrate a reduction in mortality, the positive impact demonstrated by belimumab on reducing disease activity and the acknowledged link between high levels of disease activity and serious long-term organ damage (Stoll et al. 2004; Swaak et al. 1999), supports a beneficial effect of belimumab on survival. According to the NICE scope, modelling long-term benefits for chronic diseases is an appropriate approach to the assessment of cost-effectiveness, and we note that the ERG has commented positively on the methodology used to model the natural history of SLE and of the potential long-term benefits that may accrue.	Comments noted. The Committee concluded that the specified target population was relevant and that attempting to link short term outcomes with long term outcomes in the economic model was appropriate. The Committee discussed the survival gains observed from the economic modelling and accepted that a gain in survival was plausible. However, it concluded that there was considerable uncertainty as to the validity of the modelled gains in overall survival. See FAD sections 4.5, 4.13, 4.20.

Consultee	Comment	Response
GSK	It is acknowledged that patients with renal or cerebral involvement are most likely to die, however, according to the lupus experts we have consulted, it is not always evident which patients are likely to develop renal damage. Unlike in rheumatoid arthritis where disease progresses in a "step wise" manner, in SLE, patients can move from having no symptoms to a full blown disease flare in a short spate of time, irrespective of initial organ involvement. Patients do not die of disease activity directly. Uncontrolled disease activity increases mortality due to increased organ damage and increased risk from concomitant drugs, such as cardiovascular risk with high dose steroids, and risk of infection from immunosuppressants. By controlling disease activity and promoting longer remission, the negative impact of prolonged high disease activity and risk of flare in any organ will be decreased. This section in the ACD also discussed how survival time in the model was predicted to be longer in the high disease activity target population than in the overall trial population, (31.9 years in the standard care arm of the target group compared with 30.5 years in the overall standard care arm in the overall pooled BLISS populations), when the opposite would be expected as the target population had the more severe disease. Thus the Committee concluded that there was considerable uncertainty around the validity of the modelled gains in survival. We have investigated this further and can clarify that this is due mainly to the differences in age distribution, with patients in the target population within the trials being on average younger than those in the total population. When the same age distribution seen for the total BLISS population is included in the model for the target population, the life expectancy (life years undiscounted in the table) was reduced to 28.4 years for the SoC group, below that of the total population (see Table 2 below for the summary of the results for outcomes). This result demonstrates that the long-term modelling is robust and does provide expected comparative survival estimates for the different populations. **Table 2 not replicated**	Comments noted. The Committee concluded that attempting to link short term outcomes with long term outcomes in the economic model was appropriate. The Committee discussed the survival gains observed from the economic modelling and accepted that a gain in survival was plausible. However, it concluded that there was considerable uncertainty as to the validity of the modelled gains in overall survival. See FAD sections 4.13 and 4.20. Comment noted. The FAD has been amended to reflect this explanation. However, the Committee did not consider that this explanation reduced the uncertainty about the validity of the modelled gains in overall survival. See FAD section 4.20.
GSK	**ii) Relevance of SELENA-SLEDAI Instrument** • **The SELENA-SLEDAI Instrument is a valid, reliable tool that is easy to administer and suited for use in clinical practice.** • **A SELENA-SLEDAI score ≥10 is able to identify patients with the most serious disease activity.**	Comment noted. See responses to detailed comments below.

Consultee	Comment	Response
GSK	ACD Sections 4.4 and 4.5. The clinical specialists at the Appraisal Committee stated that the SELENA-SLEDAI disease activity instrument could be considered a relatively crude tool. The Committee was concerned that the specification of a SELENA-SLEDAI score of 10 or more may be considered an arbitrary cut-off value with which to identify a suitable target population. Like most disease specific instruments in SLE there are acknowledged limitations of the SELENA-SLEDAI. However, the SELENA-SLEDAI is widely used internationally, has been shown to be valid, reliable and sensitive to change (Griffiths et al. 2005), and is recognised by clinical experts as a useful instrument for identifying the various presentations of disease activity in patients with SLE. In addition it has been shown to correlate highly (coefficient ≥0.76) with other recognised tools such as British Isles Lupus Assessment Group (BILAG) index and European Consensus Lupus Activity Measurement (ECLAM) (Bencivelli et al. 1992). Unlike other instruments, the SELENA-SLEDAI instrument is relatively simple to use, easy to learn/teach, quick to administer, can be administered by trained nurses rather than being reliant solely on experienced physicians, and does not require a computer for generating a score; it can therefore be considered an appropriate tool for implementation in clinical practice. Indeed, many clinicians would welcome the introduction of the more routine use of objective disease scoring in SLE as historically this has been absent in this disease area. Comparisons can be drawn with rheumatoid arthritis where the (DAS) has been successfully implemented. GSK in conjunction with UK SLE experts would be prepared to support any necessary training for the SELENA-SLEDAI instrument for clinicians and nurses. We also note that SELENA-SLEDAI will be captured in the UK BILAG Biologics in Lupus Registry. With regards to the SELENA-SLEDAI score cut-off value of 10 as an eligibility criterion for our proposed high disease activity target population, this was a pre-specified criterion for subgroup analysis in the two Phase III randomised controlled trials (RCTs) and a stratification criterion for randomisation into the trials. Published evidence demonstrates that an SS score of 10 identifies patients with high disease activity (Griffiths et al. 2005), is likely to capture the majority of very ill patients, and is predictive of those likely to develop very poor, long-term morbidity (Swaak et al. 1999). In addition, consultation with lupus experts has supported this cut-off value as indicative of patients who have clinically serious disease.	Comment noted. The Committee understood that although the SELENA-SLEDAI score was not currently used in UK clinical practice to measure disease activity, a more routine use of the SELENA-SLEDAI score in clinical practice could improve the management of systemic lupus erythematosus. The Committee accepted that the specified target population is clinically relevant. See FAD section 4.5.

Consultee	Comment	Response
GSK	**iii) Health effects have been underestimated in the assessment of cost-effectiveness** ACD Section 4.22. In this section it is stated that the Committee was satisfied that all relevant benefits to HRQoL were captured in the cost-effectiveness assessment, noting in particular that FACIT-F scores were not statistically significantly better at week 52 in the target population in people receiving belimumab than in people receiving standard care. We maintain that some HRQoL benefits have been underestimated in the cost-effectiveness assessment for the reasons outlined below: Utilities for disease activity were obtained from the EQ-5D generic instrument which was completed by patients at pre-determined time-points during the trial. These time-points would not necessarily have coincided with when patients were feeling at their worst during a disease flare. Disease flares were not specifically included in the health economic model due to the additional complexity this would have introduced. Because of this the effect of flares on quality of life is likely to have been underestimated in the model and so too any benefit of belimumab had in reducing flare activity. This is supported by published evidence of poor correlation between disease activity (e.g. SLEDAI) and a number of QoL instruments (McElhone et al. 2006).	Comment noted. The Committee discussed whether any health-related quality-of-life benefits may not have been captured in the calculation of the QALY. It was aware that disease flares had not been included in the economic modelling. The Committee noted that in the BLISS trials that although differences in EQ-5D were demonstrated between treatment groups these were not statistically significant at 52 weeks. Further, there were no statistically significant differences at week 52 for FACIT-fatigue scores in the target population in people receiving belimumab compared with people receiving standard care. The Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life from belimumab had not been adequately captured. The Committee concluded that the issues identified around innovation did not change its conclusions about the cost effectiveness of belimumab. See FAD section 4.28.

Consultee	Comment	Response
GSK	ACD Section 4.9. In this section it is stated that the Committee noted the limited steroid sparing effect observed in the BLISS studies. It is very likely however, that a greater steroid sparing effect would in fact be seen with belimumab in clinical practice. Given the double-blind nature of the study it is highly probable that the BLISS trialists were cautious in reducing the steroid dose too much or too quickly in the RCTs due to concern of the impact this could have on inducing a flare. Indeed, in the BLISS trials only patients who had improving SLE disease activity for at least eight weeks could, at the investigator's discretion, reduce the steroid dose, targeting a reduction to 7.5 mg/day or lower after the Week 24 visit. Therefore in terms of steroid sparing effect, the benefits that belimumab could offer are likely to have been underestimated. This is supported by recent results from the Phase II belimumab extension study (LBSL99) (Petri et al. 2011) which showed that for patients remaining in the study with steroid data recorded, the dose of steroid gradually and significantly reduced over time (Figure 1). By the end of Year 6 the steroid dose had reduced by an average of 4.7mg/day, an average of 34.4% from the baseline dose (Petri et al. 2011). In this study there were no restrictions on steroid use and it was left to the physicians' discretion as to whether it was appropriate to reduce a patient's steroid dose. Therefore this reflects more accurately how steroid tapering would be managed in clinical practice for patients receiving belimumab. This is important when considering HRQoL, because, although there was a clear improvement in disease activity with belimumab in the trials, this benefit may not have been fully realised by the patients if they were still experiencing side effects from high dose steroid use. Additionally, reducing steroid use may have important long-term benefits with reducing future steroid -related organ damage. **Figure 1 not replicated**	Comment noted. The Committee discussed these long-term data for reductions in steroid dose. The Committee understood the importance of reductions in steroid dose for patients and recognised the positive indications of these findings. However, in the absence of any control group, the Committee concluded that these data suggested, but were not definitive proof of a reduction in steroids associated with belimumab treatment. See FAD section 4.11.

Consultee	Comment	Response
GSK	As detailed in our original submission, we believe that the EQ-5D underestimates the impact of SLE on HRQoL. Certain relevant dimensions of health are not directly included in the EQ-5D instrument, such as fatigue or sensory impairment. This has also been discussed by the NICE Decision Support Unit in their report 'The incorporation of health benefits in cost utility Analysis using the EQ-5D' (Wailoo et al. 2010). Chronic fatigue is one of the most prevalent clinical manifestations of SLE and severely affects HRQoL (Thumboo et al. 2007; Zonana-Nacach et al. 2000). It is nearly always a major factor in the life of a patient with SLE; it can be debilitating and difficult to treat. In the high disease activity subgroup, the pooled data from both studies showed that belimumab 10 mg/kg was associated with significantly improved fatigue scores compared with placebo at Weeks 8 and 12 ($p < 0.05$) and although at Week 52 a statistically significant difference with placebo was not seen, the mean change from baseline in the belimumab group (4.9 points) was superior to that seen in the placebo group (3.3 points). We further note that both clinical experts and patient groups at the first appraisal committee meeting specifically pointed to the significant impact of fatigue and sensory impairment on patients with SLE.	Comment noted. The Committee discussed whether any health-related quality-of-life benefits may not have been captured in the calculation of the QALY. It was aware that disease flares had not been included in the economic modelling. The Committee noted that in the BLISS trials that although differences in EQ-5D were demonstrated between treatment groups these were not statistically significant at 52 weeks. Further, there were no statistically significant differences at week 52 for FACIT-fatigue scores in the target population in people receiving belimumab compared with people receiving standard care. The Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life from belimumab had not been adequately captured. The Committee concluded that the issues identified around innovation did not change its conclusions about the cost effectiveness of belimumab. See FAD section 4.28.
GSK	**iv) Comparison with rituximab** • **The costs presented for rituximab based on the doses used in their clinical trial and presented in our original submission are appropriate and justifiable for comparison with belimumab costs.** • **The current available RCT evidence for both drugs demonstrates that belimumab met its primary endpoint whereas rituximab failed to do so. Thus our approach of assuming belimumab is at least as effective as rituximab is conservative**	Comments noted. See responses to detailed comments below.

Consultee	Comment	Response
GSK	ACD Section 4.20. It is stated in this section that the Committee are not convinced by the cost and efficacy arguments with rituximab which were presented in our original submission, and in particular, the Committee believes we may have overestimated the annual cost of rituximab used to treat SLE patients. Had the manufacturers of rituximab been successful in their clinical trial programme and successfully obtained a licence for use of this drug in SLE then the licensed dose would most likely have been reflective of the dose used in the clinical trials. The 52 week EXPLORER trial (Merrill et al. 2010) used a dose of 1000mg by infusion at days 1, 15, 168, 182, which based on 10mg/ml solution with a vial price of 50ml=£873.15 (Monthly Index of Medical Specialities (MIMS) 2011) gives an annual price of £6985.20, as detailed in our original submission. According to NICE methodology, as a stated comparator, the appropriate comparison to be made in any economic evaluation would be to use the comparative efficacy from the randomised controlled trials, with the corresponding doses and costs. Using estimated costs of how rituximab is currently used off licence in some specialist centres is inappropriate when making a comparison to belimumab, which currently has only been used in clinical trials. Both Phase 3 studies for belimumab (BLISS-52 and BLISS-76), successfully achieved their primary composite endpoint, SRI, at week 52. In the EXPLORER study, the only published RCT in non-lupus nephritis patients (Merrill et al. 2010), no difference was noted between the rituximab and SoC group and the placebo and SoC group at week 52 in their primary endpoint, which was based on BILAG scores, nor in any secondary endpoints. We acknowledge that the populations were very different between the rituximab and belimumab studies; in particular the patients enrolled in the EXPLORER trial had significant and acute disease and were on very high doses of steroid at study entry. In our original submission and during the clarification process we provided a clear justification of why indirect comparisons of efficacy were inappropriate and this was supported by the ERG in their report. However it still remains that efficacy with rituximab from RCTs has not been established and therefore we believe that we are taking a conservative approach by assuming at least comparable efficacy between the two drugs. Given that rituximab has been identified as a valid comparator for this appraisal and is used in our proposed target population, the available evidence suggests that concluding similar efficacy and costs is reasonable and therefore we reiterate the conclusion in our original submission that belimumab, with our proposed patient access scheme, would provide a [redacted] alternative in our target SLE population who would otherwise receive rituximab or some other more expensive, unlicensed treatment such as intravenous immunoglobulin (IVIG).	Comments noted. The NICE methods guide indicates that the Institute has a preference for head to head trial data and in the absence of head to head trial data mixed treatment comparisons may be presented. The methods guide states that in the absence of such comparisons the Appraisal Committee will be particularly cautious when reviewing the results of analyses. No formal comparison of the efficacy of rituximab and belimumab was submitted to the Committee. The Committee discussed the evidence available and concluded that there are no reliable data to show the relative efficacy of belimumab compared with rituximab. See FAD section 4.12. In the absence of any estimate of relative effectiveness, a comparison of the costs of the two products was provided in the manufacturer submission. A single analysis that accounted for both effects and costs was not submitted to the Committee. The NICE methods guide states that the comparator for an appraisal includes routine and standard NHS practice. The Committee accepted that rituximab was a relevant comparator, but heard from the clinical specialists that the regimen used in the EXPLORER trial did not constitute the regimen used in clinical practice. On this basis the Committee was not persuaded that the costs provided by the manufacturer accurately reflected the costs of providing rituximab in UK clinical practice. See FAD section 4.26.

Consultee	Comment	Response
GSK	ACD Section 3.29. The text in this section which states “The ERG highlighted that information on SLEDAI and SF-36 changes in the rituximab EXPLORER trial were available, and that randomised controlled trials for both rituximab and belimumab recorded BILAG changes, thus offering the potential for an indirect comparison” is inconsistent with the text in Section 4.10 which states “The Committee heard from the ERG that there were three outcomes for which an indirect comparison could be completed (that is, BILAG, SLEDAI, and SF-36 scores), but data were only available in the public domain for the SF-36. The ERG also highlighted the differences in the trial populations, which it considered meant that the results of an indirect comparison were not meaningful.” This latter text provides a more complete assessment of the ERG’s opinion as to the inappropriateness of conducting an indirect comparison of efficacy between belimumab and rituximab. Whereas the statement in Section 3.29 suggests that an indirect comparison would be valid.	Comment noted. The text in section 3.34 (previously 3.29) reflects what was submitted to the appraisal and is stated in the ERG report (page 37). The text in section FAD section 4.12 reflects what the Committee subsequently heard from the ERG at the Committee meeting. The text in 3.34 has been revised in light of these comments.
GSK	Other Points for Clarification of Interpretation of the Evidence ACD Sections 3.4 and 3.14. In these sections NICE makes a reference to the “marketing authorisation population”. Limited data for a subgroup of the licensed population, defined as patients with positive anti-dsDNA and low complement, was presented in our original submission but this does not include all patients with high disease activity eligible under the license for belimumab, and therefore should be referred to as a subgroup of the marketing authorisation population.	Comment noted. This comment has been taken into account in the drafting of the FAD. In the evidence section this group is referred to as the people enrolled in the BLISS trials that met the criteria of the marketing authorisation. This is to distinguish them from the target population which is a subgroup of the marketing authorisation population.

Consultee	Comment	Response
GSK	ACD Section 3.31. This section states that the ERG were unclear of the derivation of the 8% annual discontinuation rate among patients showing a response to belimumab at week 24, and of the reasonableness of extrapolation of this value in the health economic model. This annual discontinuation rate was estimated from the BLISS trials for patients defined as belimumab responders (SELENA-SLEDAI score decrease of ≥ 4) after 24 weeks of treatment based on a time to discontinuation analysis as detailed in our original submission. The latest available data from the Phase II belimumab extension study (LBSL99) summarised in Table 3 below (GlaxoSmithKline data on file 2011) also shows that our assumption to continue using an 8% annual discontinuation rate is reasonable, and indeed may have underestimated the cost-effectiveness in our original submission, as it shows from Year 2 onwards the rate ranged from 6.7% to 19.7% over six years, giving an average discontinuation rate of 13.0%. With our revised base case incorporating a shorter treatment duration, uncertainty is again reduced with regards to the discontinuation rate as we have clinical trial evidence to support our assumption. Higher rates of discontinuation lead to better cost-effectiveness due to drug acquisition cost being the main contributor to incremental costs. **Table 3 not replicated**	Comment noted. The Committee recognised that the original model assumed an 8% annual discontinuation rate after 24 weeks and that additional evidence provided after consultation, from the Petri study showed a higher discontinuation rate of 13%. The Committee concluded it was appropriate to use a higher annual discontinuation rate in the consideration of cost effectiveness. See FAD section 4.14.
GSK	ACD Section 4.8. The Committee concluded that there was uncertainty about the extent to which standard of care (SoC) in the BLISS trials was representative of UK clinical practice, with particular reference to the fact that approximately 50% of BLISS patients were receiving immunosuppressants as part of their SoC. There are no national guidelines for the management of SLE in the UK and the treatment pathway is not 'step-wise' as in other conditions such as rheumatoid arthritis. Hence there is considerable variability in standard of care treatment between SLE patients and across UK centres. The lupus experts we have consulted believe that the proportion of patients receiving immunosuppressants in the BLISS trials seems reasonable based on the level of variability in SoC currently evident in the UK. These trials included a variety of different combinations of SoC treatments, all of which could be observed in UK clinical practice and therefore it is reasonable to assume the results are applicable to the UK.	Comment noted. The Committee understood there was variability in standard of care in UK clinical practice. However, for the target population (that is, the subgroup of patients from the BLISS trials), clinical specialists considered that standard care would include an immunosuppressant. See FAD section 4.9.

Consultee	Comment	Response
GSK	ACD Section 4.14. The Committee suggested that the long-term benefits on disease activity assumed in the health economic model may have been overestimated as it has been observed that in other conditions such as rheumatoid arthritis, patients on biological treatments can experience a reduction in the response to treatment over time. The duration of response with belimumab in SLE cannot be compared with treatment with biologics in rheumatoid arthritis as this disease takes a very different course. The six years of data currently available for the Phase II extension study provides good evidence of a sustained response over this duration, so with our revised base case with a maximum six year treatment duration, we believe that the assumption of continued benefit can be supported. Consequently in our revised cost-effectiveness assessment we do not believe that the model has over-estimated the benefit of belimumab.	Comment noted. The ACD referenced what had been heard by the Committee from the clinical specialists. This paragraph has been amended to include further detail on the clinical experience of the use of rituximab in SLE. See FAD section 4.18.
GSK	3. Additional Considerations To our knowledge, this is the first cost-effectiveness model to be produced for SLE, a very complex disease to model. The analyses conducted on the Johns Hopkins database, a large SLE cohort with a long-term follow-up, produced a series of robust natural history models (NHMs) which represent the long-term course of the disease. We believe that including these NHMs into the health economic model to enable the link between the benefit observed with belimumab on the outcomes in the trials to the risk of long-term events, has resulted in a fair estimate of the cost-effectiveness of this medicine.	Comment noted. The Committee concluded that attempting to link short term outcomes with long term outcomes in the economic model was appropriate. See FAD section 4.13.
GSK	4. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We do not believe the provisional recommendations are sound and a suitable basis for guidance to the NHS for the following reasons: • Belimumab was specifically designed to treat a rare, severely debilitating disease with a significant unmet need where there has been little innovation for 50 years. It specifically binds to BLyS and inhibits its biological activity thus having a beneficial effect on reducing disease activity as demonstrated in two large RCTs.	Comments noted. The Committee specifically considered the innovative nature of belimumab including its development to target the underlying pathology of systemic lupus erythematosus. See FAD section 4.28.

Consultee	Comment	Response
GSK	• Our proposed target population, which we have identified as a cost-effective subgroup to receive belimumab, is considerably smaller than our licensed SLE population and targets treatment to patients with the most serious disease activity and who are likely to gain the most from belimumab. We would also ask the committee to consider the implications of a restricted treatment duration of six years and the implications of a lower discount rate and more stringent continuation rules.	Comments noted. The Committee concluded that the specified target population was relevant (see FAD section 4.5). The Committee has considered the revised analyses assuming continuous treatment for a maximum of 6 years, but concluded that the rationale for the choice of a maximum treatment duration of 6 years could not be considered sufficiently robust to use it as the basis of decision making. See FAD section 4.16.
GSK	• [redacted] Moreover, in the absence of these biologics being available on the NHS, SLE patients may be admitted to hospital for alternative more expensive treatments such as Intravenous immunoglobulin (IVIG).	Comments noted. The Committee did not consider that there was reliable data available to judge the relative efficacy of rituximab and belimumab, or that the costs of the treatments had been captured accurately. The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. See FAD sections 4.12 and 4.27.
GSK	• There are aspects of value not fully accounted for in our estimate of cost-effectiveness. Specifically, the full benefit of belimumab on disease flares and chronic fatigue are not adequately captured in the quality adjusted life years (QALYs) derived from EQ-5D utility values. In addition the implications of new evidence supporting a steroid sparing effect for belimumab have not been considered.	Comment noted. The Committee discussed whether any health-related quality-of-life benefits may not have been captured in the calculation of the QALY. It was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life from belimumab had not been adequately captured. The Committee concluded that the issues identified around innovation did not change its conclusions about the cost effectiveness of belimumab. See FAD sections 4.28
GSK	• There is no alternative NICE guidance for any other treatment in SLE. If this appraisal results in a negative recommendation for belimumab patients will continue to receive treatments that have not been rigorously assessed for either clinical or cost-effectiveness within the NHS. Specifically the use of rituximab will continue, which is unlicensed for SLE and has not demonstrated any efficacy benefit in RCTs or shown evidence of being a cost-effective medicine in SLE.	Comment noted. NICE was asked by the Department of Health to appraise the use of belimumab in systemic lupus erythematosus. NICE does not make recommendations about the use of comparators in an appraisal.

Consultee	Comment	Response
GSK	5. 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 gender, race, disability, age, sexual orientation, religion or belief? We have not identified any aspects of the recommendations that require particular consideration to ensure unlawful discrimination is avoided against any group of people.	Comment noted. No actions requested.
British Association of Dermatologists	1. The applicability of combining data from 2 studies in different patient groups from different geographical areas where the characteristics of the patient groups may be different. I agree that this is the case, and the more impressive results from South America etc may well be dependent upon the characteristics of the different patient cohorts. Whether this has relevance to multi-cultural UK is more difficult to say, since non-Caucasian patients are very well represented in most SLE clinic populations 2. The overall results largely depend on the non-white groups for their positivity, and if the BLISS 76 study is taken alone, there would be little benefit in having belimumab available.	Comments noted. The Committee considered whether the individual BLISS trials were representative of the population of UK patients with systemic lupus erythematosus. While the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52, it agreed that, on balance, data from BLISS-52, and therefore from the pooled analysis would be relevant. See FAD section 4.7.
British Association of Dermatologists	3. The standard of care chosen suggests that cyclophosphamide is not used except for the treatment of nephritis. This is incorrect; it is used for vasculitis and severe skin disease as well. As a consequence, the background therapy used for comparison is too limited. This has particular relevance since the major systems to be benefitted by belimumab in the trials included musculo-skeletal and muco-cutaneous	Comment noted. The Committee was aware that cyclophosphamide was included as a comparator in the scope, but accepted the manufacturer's justification that it was largely used for lupus nephritis, which was a different population to the one covered by the marketing authorisation for belimumab. Further, it heard from clinical specialists that cyclophosphamide is used infrequently because of side effects. The Committee has considered all the analyses presented in the submissions of evidence. See FAD section 4.3.

Consultee	Comment	Response
British Association of Dermatologists	4. The descriptive comparisons with rituximab are interesting and valuable, but serve to point out the difficulties of current practice, where clinical trials fail to demonstrate effectiveness of rituximab, but it is a drug still widely used in the management of patients with more severe and persistent disease activity, including vasculitis and particular types of skin involvement, based on a widely held perception that the trials were unreliable and do not reflect experience. In practice, drugs of this nature are funded where clinicians are suitably persuasive on their patients behalf, a situation NICE appraisal was meant to avoid. This leaves NICE with an interesting problem as far as belimumab is concerned, and suggests that their decision, in whichever direction, should be definitive.	Comment noted. The Committee did not consider that there were reliable data available to judge the relative efficacy of rituximab and belimumab, or that the costs of the treatments had been captured accurately. The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. The Committee concluded that belimumab had not been shown to be a cost-effective used of NHS resource in comparison with rituximab. See FAD sections 4.12 and 4.27
British Association of Dermatologists	5. Even allowing for PAS reductions, this is an expensive drug, and the assumptions made by the manufacturers are all in a direction favourable to its use. It is likely that the impact on additional years of life is less than that assumed, with similar smaller impacts on systems involvement. Against this, the effect on those systems e.g. skin, that do not affect survival, but have a significant effect on quality of life, is underrepresented by the NICE analysis, and from a dermatological point of view, this is an area for which there are few effective treatments. The available studies do not adequately define which forms of skin disease may respond, since it is unlikely to be all of them.	Comment noted. The Committee concluded that there was considerable uncertainty around the validity of the modelled gains in survival. The Committee also acknowledged that the manufacturer may have under-estimated some of the benefits associated with delaying certain types of organ damage. See FAD sections 4.20 and 4.23.
British Association of Dermatologists	6. The target group is a post-hoc selection, based on those patients who appeared to respond best. This really needs a further study. It would also be interesting to know if there is a dose response in the activity against skin disease, since if there is, and the 1mg dose was effective, there would be around a 10 fold reduction in cost which would bring the drug into more reasonable costing areas.	Comment noted. NICE can only make recommendations about a product within its marketing authorisation. For this reason the use of belimumab 1mg/kg could not be considered.
British Association of Dermatologists	7. For what it is worth, I personally doubt if there are currently sufficient supporting data, particularly on cost effectiveness, to justify belimumab's use.	Comment noted. No actions required.
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document and evaluation report for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.	Comment noted. No actions required.

Consultee	Comment	Response
NHS Bolton	NHS Bolton would agree with the proposed recommendation based on the presented clinical and cost-effectiveness data. The ICER for the drug without a patient access scheme in place is not a cost-effective use of resources compared to standard care (ICER of £64,410 - £71,000 per QALY gained). Although a patient access scheme has been submitted, the ICER still continues to be higher than that usually considered by NICE to be cost-effective use of NHS resources. The data presented did not provide a case for comparing belimumab against rituximab (current standard practice although unlicensed) in terms of cost-effectiveness again supporting the case that this is not a cost-effective use of NHS resources or affordable.	Comments noted. No actions required.
NHS Bolton	NHS Bolton agrees that the use of this drug should be in patients who have a high-degree of disease activity only (despite the wider marketing authorisation). With regard to dosing, more frequent doses are required for belimumab compared to rituximab which will lead to additional patient hospital attendances and hence cost. During the first 6 months of treatment (suggested review period) the patient will need to attend hospital on 7 occasions (more if additional monitoring is required), compared to current practice with rituximab this is a greater inconvenience for the patient. There is also the opportunity with rituximab to utilise homecare services, however NHS Bolton is not sure whether this option would be available to patients for belimumab infusions. NHS Bolton would support the manufacturers proposed PAS (a discount on the list price) being offered, as this ensures minimal administrative burden for provider, commissioner and manufacturer. The current level of discount in the PAS however would seem insufficient to meet the required levels of cost effectiveness required.	Comments noted. The Committee concluded that the manufacturer's target population was relevant. See FAD section 4.5. Comments noted. The Committee recognised that administration and pharmacy costs had not been included in the comparison of belimumab and rituximab costs provided by the manufacturer. See FAD section 4.26. Comments noted. No actions required.
NHS Bolton	There was no direct comparison of efficacy made between belimumab and rituximab (current, standard care for this group of patients a relevant comparator).	Comment noted. The Committee considered whether it was appropriate to complete an analysis of the relative efficacy of rituximab and belimumab. See FAD section 4.12.
NHS Bolton	No information in the trial data, identified if patients had received previous treatment with rituximab. In practice, patients who would fit the clinical criteria for belimumab may have previously received rituximab it is unknown whether safety or efficacy data is available to support any sequential use.	Comment noted. No evidence of clinical or cost effectiveness was provided to consider sequential use of belimumab and rituximab.

Consultee	Comment	Response
NHS Bolton	Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care (when considering functional assessment at week 52 comparing standard care and belimumab therapy).	Comment noted. The Committee was aware of the available health related quality of life data and took this into account when making recommendations. See FAD sections 4.10 and 4.28.
NHS Bolton	The costs presented in the model for administration costs of belimumab are felt to be underestimated in relation to practice. It is more likely that the tariff of day case admission will be used, which will increase the costs. Additional costs of making up the infusion per individual patient (as based on weight) in a pharmacy aseptic unit would also need to be considered.	Comments noted. The Committee recognised that administration and pharmacy costs may have been underestimated in the manufacturer's analysis. The Committee agreed that a value as had been used in previous appraisal of intravenous treatments of rheumatoid arthritis should be used in the base-case analysis. See FAD section 4.22.
NHS Bolton	Patient populations in the BLISS studies did not include patient participants from the UK hence it is difficult to determine if the patients in the trial are representative of patients with SLE and high-disease activity in the UK. This would include age, sex, gender, medicines management, criteria for diagnosis etc.	Comments noted. The Committee considered whether the individual BLISS trials were representative of the population of UK patients with systemic lupus erythematosus. While the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52, it agreed that, on balance, data from BLISS-52, and therefore from the pooled analysis would be relevant. See FAD section 4.7.
NHS Bolton	The review time for belimumab in the model was at 24 weeks, based on an assessment of the SELENA-SELEDAI score. Experts suggested that if the score was shown to be less than 4 points (i.e. some benefit of treatment) they may still continue with belimumab ? this would affect the % of patients stopping in practice when compared to the trial and costs would be higher than predicted, which could be an unexpected cost pressure to the payer.	Comment noted. The Committee took into account issues around continuation rules when making recommendations. See FAD section 4.17.

Consultee	Comment	Response
NHS Bolton	NHS Bolton supports the development of new, novel agents however they must be cost-effective and affordable to the NHS. Budgets are no longer increasing. To fund drugs that are less cost-effective (e.g. by analysis of ICERs/ QALYs) than NICE deems cost-effective would be very difficult to justify, when decisions are being made to refuse treatments which have greater clinical evidence in some cases. To fund this drug, other services may need to be decommissioned and taking into account the cost-differential of rituximab, the currently used standard of care, the difference in affordability is likely to be still too great to justify use. *[On implementation]:* These tools are useful when a technology is recommended for use.	Comments noted. No actions required.
British Renal Society	• **Has all of the relevant evidence been taken into account?** We cannot see any obvious omission. •**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes	Comments noted. No actions required.
British Renal Society	• **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The two BLISS trials show some modest benefit for mild / modestly active SLE despite significant treatment in the placebo arm. The concern however is that only 34% of the trial patients were in the category being targeted in the submission and only 52% in BLISS 72 and 42% of patients in BLISS 56 were on immunosuppressants in addition to oral steroids, so they are not the patients nephrologists would be putting forward for a biological agent. Cerebral and renal diseases were excluded from the two trials and this is almost always the group of patients that nephrologists are looking for additional treatment for.	Comment noted. The Committee understood there was variability in standard of care in UK clinical practice. It agreed that for the target population, standard care was likely to include an immunosuppressant. The Committee recognised that there was uncertainty as to the effect of belimumab on the full range of manifestations of systemic lupus erythematosus. See FAD sections 4.3 and 4.5.
British Renal Society	• **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 gender, race, disability, age, sexual orientation, religion or belief?** No • **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?** This has been covered in submission by other groups.	Comments noted. No actions required.

Consultee	Comment	Response
Lupus UK	**A) Has all the relevant evidence been taken into account?** As far as we were aware, although reference is made to ERG's consideration of an unpublished trial in para 3.38	Comments noted. No actions required.
Lupus UK	**B) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** 1) the results from 2 clinical trials were submitted, BLISS 52 and BLISS 76: the primary outcome was statistically significant in both trials (3.7). BLISS 76 showed a statistically significant difference in response rate between belimumab and standard care (3.7). We therefore find it difficult to know how the committee can reject the findings of the BLISS 76 trial.	Comments noted. The Committee did not reject the results of the BLISS 76 study. However, although this trial demonstrated a statistically significant result for the primary outcome. Differences between groups for secondary outcomes were not seen as consistently as for the BLISS 52 study. The Committee considered that evidence of effect had been shown with more consistency in the BLISS 52 study. See FAD section 4.10.
Lupus UK	2) the results from BLISS 52 trial (which gives clearer evidence of effect) was not considered so seriously by the committee because of the racial mix not being seen as generalisable to this country's population (3.28, 3.5). We did point out during the meeting that SLE affects all races, but is disproportionately higher and often more serious in certain racial groups; we also pointed out that the racial mix of the UK is now very diverse and wide, for example there is a large Asian population in many large cities in this country (4.6).	Comments noted. The Committee considered that although BLISS-76 was more representative of the population of England and Wales as a whole than BLISS-52, data from BLISS-52, and therefore from the pooled analysis would be relevant. The Committee understood that the UK is a multi-ethnic country and that systemic lupus erythematosus affects some racial groups more severely than white populations. See FAD section 4.7.
Lupus UK	The committee's consideration of the clinical evidence (4.6-4.10) seems to waver between acknowledging that BLISS 52 population may have some relevance to UK (4.6: 'pooled analysis could be considered relevant') and dismissing it (4.9: 'the relevance of both the pooled and unspooled data to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, nature of standard care and effects of belimumab on the full range of possible manifestations of SLE'). Whilst accepting that the numbers in each study, when pooled, give a greater weight to the findings of BLISS 52 as the sample size was bigger, we feel that more consideration of data from BLISS 52 should be given by the committee in reaching their decision.	Comments noted. The Committee has taken into account the results of the BLISS 52 study in making its recommendations, the data from both studies was included in the manufacturer's model.

Consultee	Comment	Response
Lupus UK	3) Evidence for secondary outcomes may not be so clear: lupus patients can have a multiplicity of symptoms (and their often fluctuating or flitting pattern) which make it very difficult for precise endpoints to be observed. For some patients improvement would be outside the remit of the specified secondary outcome measures, but could have given a positive effect during the trials.	Comments noted. The Committee has considered all evidence that has been submitted, including submissions from the manufacturer and from patient and professional groups. The Committee discussed whether any evidence was available that strongly indicated that the economic analysis had failed to capture the health benefits associated with belimumab. See FAD section 4.28.
Lupus UK	There was evidence of a reduction in steroid use, although this may have been insufficient to avoid side effects, lupus patients are always grateful for anything which reduces the need for steroids. It is a great milestone to come off steroids altogether, which unfortunately is very difficult for many people to pass, so any treatment which has some effect would be extremely welcome and a real boost to morale for those where other treatments have not managed to reduce the burden of steroids.	Comment noted. The Committee discussed the evidence submitted from the belimumab phase III trials and from the phase II extension study about steroid sparing. The Committee recognised the importance of reduction in steroid use. See FAD section 4.11.
Lupus UK	Trials were conducted on patients with a high level of disease activity (score of 10+ SLEDAI) (3.1, 4.4), mainly mucocutaneous, immunological and/or musculoskeletal damage (3.5). These systems may also not give such clear markers of improvement and be open to fluctuation.	Comments noted. The Committee has considered all evidence that has been submitted, including the submissions from the manufacturer and from patient and professional groups. The Committee discussed whether any evidence was available that strongly indicated that the economic analysis had failed to capture the health benefits associated with belimumab. See FAD section 4.28.
Lupus UK	Unlike many drug trials where subjects receive either drug or placebo, standard care was continued for all patients in the trials, therefore a clear improvement between those receiving the drug and those on placebo would be less easily observed.	Comments noted. The patients in the marketing authorisation and target population are those with high disease activity despite standard treatment. See FAD section 4.3.
Lupus UK	4) some results from BLISS 76 showed improvements early (some at week 24, many at week 52): this seems to have be taken by the committee as evidence that the 76 week trial was less effective, but this may be indicating that the drug has effect in a shorter period of time than 76 weeks. This information should not lead to dismissing its effectiveness as paras 2.3 and 3.32 states that the drug will be discontinued at 6 months if there is no improvement. This may have a bearing on the length of time the drug would need to be used and therefore the costings.	Comments noted. The Committee did not reject the results of the BLISS 76 study. However, although this trial demonstrated a statistically significant result for the primary outcome. Differences between groups for secondary outcomes were not seen as consistently as for the BLISS 52 study. See FAD section 4.10.

Consultee	Comment	Response
Lupus UK	**C) Are the provisional recommendations sound and a suitable basis for guidance in the NHS?** 1) Rituximab is given as a comparator within the appraisal document, but 3.13 notes that 'the EXPLORER trial showed no statistically significant differences in major or partial clinical responses between the rituximab group and the placebo group over 52 weeks'. In fact belimumab did meet its primary endpoint and showed some improvement in other symptoms: this would appear to be better 'evidence' for belimumab than for rituximab.	Comment noted. Comparators in a NICE appraisal are those that are used in UK clinical practice. At the Committee meeting the Committee heard from clinical specialists that rituximab would be an appropriate comparator for belimumab. The Committee explored the comparison of belimumab with rituximab and the evidence available to support the comparison, noting that head-to-head data comparing belimumab with rituximab were not available. The Committee concluded that there were no reliable data to show the relative efficacy of rituximab and belimumab. See FAD sections 4.3 and 4.12.
Lupus UK	2) What guidance is NICE giving to both lupus patients and their clinicians? It would appear that rituximab is preferred to belimumab by the Appraisal committee for lupus patients, but trials of rituximab were not conducted on lupus patients, so we are left with unclear guidance on prescribing, especially for patients where existing therapies have not been effective and the activity of the disease is out of control and likely to result in either very serious organ damage or death, not allowing time for special application to be made to local trusts for decision.	NICE has been asked by the Department of Health to appraise the clinical and cost effectiveness of belimumab for the treatment of systemic lupus erythematosus. It is outside the remit of this appraisal to consider treatment guidelines for systemic lupus erythematosus or the use of rituximab. This is more appropriately considered as part of a clinical guideline.
Lupus UK	**D) 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 gender, race, disability, age, sexual orientation, religion or belief?** 1) We stated that SLE affects many racial groups more severely than the Caucasian population. Many drug trials are conducted on white male populations: in the BLISS 52 trials we see that belimumab was shown to have better effect on certain racial populations, but the committee thought that this population was not generalisable to the UK population: we feel that this decision will disadvantage certain racial groups where the drug has been seen to be effective. 2) If NICE does not give clear guidance on funding for this drug, we feel that will disadvantage certain racial groups, where English may not be their first language, and they may not have the experience or confidence to challenge decisions made locally.	Comments noted. The Committee considered that although the patients enrolled in BLISS-76 were more representative of the population of England and Wales as a whole than BLISS-52, data from BLISS-52, and therefore from the pooled analysis would be relevant because the UK is a multi-ethnic country and that systemic lupus erythematosus affects some racial groups more severely than white populations. The Committee has taken into account the results of the BLISS 52 study in making its recommendations, the data from both studies was included in the manufacturer's model. See FAD section 4.7.

Consultee	Comment	Response
Royal College of Nursing	**Has the relevant evidence been taken into account?** No comments to add at this stage.	Comments noted. No actions required.
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** There is no doubt that the cost of Belimumab cannot be compared with that of conventional therapy and will of course, be at added cost to the NHS. An important issue is that the trial data reports that Belimumab helps to reduce steroid dosage and length of treatment with steroids. The use of long term steroids carry many potential side effects which can impact on quality of life and lead to numerous co-morbidities many of which will have cost and health implications for many years. Whilst Belimumab is not free of side effects, its comparators are greater and significantly impact on individuals' quality of life, capacity to work, mental health status, personal relationships and life aspirations.	Comments noted. The Committee discussed the evidence submitted from the belimumab phase III trials and also from the phase II extension study about steroid sparing. The Committee recognised the importance of reduction in steroid use. See FAD section 4.11.
Royal College of Nursing	Clinically, there is a concern about the choices of medication available to lupus teams in the group of patients who are steroid dependent and not responding to conventional therapies, including immunosuppression. Belimumab has met the primary endpoint in both of its pivotal Phase 3 trials, it is FDA approved and approved by European commissioners. This then is a very sensible option for treatment in a group not responding to conventional therapy.	Comments noted. The Committee recognised that there are few drugs licensed for systemic lupus erythematosus. See FAD section 4.28.
Royal College of Nursing	Rituximab did not meet its endpoint and therefore did not receive either a licence in lupus or NICE approval. Yet this document directly recommends a head to head trial between Belimumab which has met its primary endpoint and Rituximab which did not meet its endpoint. This will not realistically happen as drug companies would not consider it to be cost effective or in their best interests.	Comment noted. This has been amended in the FAD. The Committee acknowledges the manufacturer's post marketing commitment to investigate intermittent treatment with belimumab including time to flare from withdrawal of treatment and response to belimumab at retreatment, and considered that these studies would be of value. See FAD section 6.1.
Royal College of Nursing	The only drugs currently holding a licence for lupus are steroids, Hydroxychloroquine and Belimumab. All other drugs used are off licence and therefore without NICE approval, this will result in clinicians having to apply with IFRs which may be rejected, resulting in loss of clinical time to the NHS and patient care.	Comments noted. The Committee recognised that there are few drugs licensed for systemic lupus erythematosus. See FAD section 4.28.

Consultee	Comment	Response
Royal College of Nursing	Rituximab is widely used to treat lupus and every time this is planned, an IFR has to be completed. Patients understand that these drugs are off licence which does not provide them with any significant confidence in its effectiveness.	Comment noted. The Committee did not consider that there were reliable data available to judge the relative efficacy of rituximab and belimumab, or that the costs of the treatments had been captured accurately. The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. See FAD sections 4.12, 4.26, 4.27.
Royal College of Nursing	It is anticipated that following response to treatment with Belimumab that infusions can be reduced in frequency and even stopped when in remission. Costings should reflect this in the appraisal document and it is not clear that this has been considered in sufficient detail.	Comment noted. NICE can only make recommendations within the marketing authorisation of a product. The SPC describes continuous use with belimumab. See FAD section 4.15.
Royal College of Nursing	**Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** We consider that the NICE appraisal committee should review its decision regarding Belimumab. The opportunity to provide this as a reasonable treatment option for those with active auto-antibody positive muco-cutaneous and musculoskeletal complications of lupus has to be re-considered in the light that these patients are currently on long term steroids and immunosuppression with little potential for stopping these drugs over time. These cause a significant number of side effects, which cannot always be prevented and then impact on quality of life when co-morbidities develop.	Comments noted. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations (Social Value Judgements - Principles for the development of NICE guidance; principle 5). The Committee discussed the evidence submitted from the belimumab phase III trials and also from the phase II extension study about steroid sparing. The Committee recognised the importance of reduction in steroid use. See FAD section 4.11.
Royal College of Nursing	**Are there any equality related issues that need special consideration that are not covered in the ACD?** None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	Comments noted. The Committee has considered issues relating to equality. See FAD section 4.29.

Consultee	Comment	Response
Renal Association	• **Has all of the relevant evidence been taken into account?** The evidence has been well considered in particular the lack of availability of a direct comparison with Rituximab.	Comment noted. No actions required.
Renal Association	• **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries of clinical effectiveness have erred on the side of caution. a) The ACD highlights that the population in BLISS-76 reflects the England and Wales population more closely than that in BLISS-52. However, patients with lupus in England and Wales are not representative of the population as a whole as they tend to be much more ethnically varied and hence BLISS-52 may be as appropriate as BLISS-76. As the committee noted, more outcomes were significantly improved with Belimumab in BLISS-52 than BLISS-76.	Comments noted. The Committee considered that although the population enrolled in BLISS-76 was more representative of the population of England and Wales as a whole than BLISS-52, data from BLISS-52, and therefore from the pooled analysis would be relevant. The Committee understood that the UK is a multi-ethnic country and that systemic lupus erythematosus affects some racial groups more severely than white populations. See FAD section 4.7.
Renal Association	b) There are several comments about the arbitrary nature of a SELENA-SLEDAI score of >10 being significant and of stopping at 24 weeks if improvement in SELENA-SLEDAI score being not greater than 4. However, current clinical practice is much more arbitrary and scoring systems are not in routine use in most lupus clinics. Ensuring that responses are documented with scoring would be a huge improvement in the management of patients with lupus and the inclusion of the BILAG and PGA scores (as used in the SRI) would improve this further. The BLISS trials are to be commended for including formal scoring and the recommendation of a target population and the use of scoring to assess the benefit of therapy would be advantageous. Patients often remain on treatments that are ineffective for prolonged periods and responses are often poorly judged. Whilst a score of 10 is fairly arbitrary it does require significant clinical disease that would be noticeable to patients and therefore is meaningful.	Comment noted. The Committee noted that although the SELENA-SLEDAI score is not currently used in UK clinical practice to measure disease activity, a more routine use of the SELENA-SLEDAI score in clinical practice could improve the management of systemic lupus erythematosus. See FAD section 4.5.
Renal Association	c) Standard of care is not standard in England and Wales – treatment approaches vary by unit and individual clinician and reflect the lack of trial data in the “target” population described in the manufacturer’s submission. Patients could be on a range of treatments though for musculoskeletal and skin involvement are less likely to be on Rituximab but are likely to be on steroid sparing agents if severe. Hence the SOC treatments in both trials are reasonable representations of the SOC likely to be given to different lupus patients in England and Wales.	Comment noted. The Committee understood there was variability in standard of care in UK clinical practice. The analysis of cost effectiveness is based on the efficacy observed in the BLISS clinical trials for belimumab and standard of care. See FAD section 4.9.

Consultee	Comment	Response
Renal Association	*In the economic analysis more consideration should be given to:* a) consideration that in practice Belimumab is likely to be discontinued e.g. after a maximum of 2 years. The manufacturer's suggestion that it might be a lifelong treatment is surprising and not in keeping with current approaches to treatment, especially with biologicals. It is very likely that clinicians would plan a course of treatment and then either to increase dosage intervals or simply stop and see how patients fared. This would significantly reduce costs.	Comments noted. The Committee understood that belimumab would not be used continuously over a lifetime. However, the SPC describes continuous treatment, therefore the Committee is unable to make recommendations for intermittent treatment or alternative administration schedules. Further there is no evidence for the use of belimumab in this way. The Committee discussed the revised analyses presented by the manufacturer, which limited the maximum treatment duration to 6 years. However, it was noted that while some patients may be on treatment for less than six years, some patients may require treatment for more than six years. The Committee concluded that the rationale for the choice of a maximum treatment duration of 6 years could not be considered sufficiently robust to use it as the basis of decision making. See FAD sections 4.4 and 4.16.
Renal Association	b) If review at 6 months is mandated, the scoring could be more rigorous (though this is not based on the data available) and for instance insistence on an improvement of at least 6 rather than 4 in SELENA-SLEDAI score being a guide to stopping treatment (or a failure of trend to improvement might be clinically more meaningful). This would reduce the numbers of patients being treated and reduce costs.	Comment noted. The Committee discussed the difference between the 4 and 6 point continuation rules and heard from the clinical specialists that they would prefer the lower stopping rule which required an improvement of 4 points in the SELENA-SLEDAI score and would be uneasy using the higher continuation rule of 6 points unless it reduced the base case ICER to an acceptable level. The Committee was persuaded that the application of stopping rules was appropriate, but concluded, that it was not appropriate to consider using the more restrictive rule of a SELENA-SLEDAI score improvement of 6 or more as the base-case analysis for decision making. See FAD section 4.17.

Consultee	Comment	Response
Renal Association	c) Cost effectiveness based on mortality is not hugely relevant in the early phase of lupus as the mortality rates, although hugely elevated compared to a normal population, are not absolutely high. The clinical issues are those that allow maintenance of normal life (being able to work, look after children, have safe pregnancies) with minimum short and long term adverse events. Any drug which reduces the exposure to steroids is likely to be cost effective both to the individual and to the NHS.	Comments noted. The Committee discussed the evidence submitted from the belimumab phase III trials and from the phase II extension study about steroid sparing. The Committee recognised the importance of reduction in steroid use. The economic analysis submitted by the manufacturer includes steroid usage. See FAD section 4.11.
Renal Association	• **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** On the basis of the comments above, there is room to reconsider cost effectiveness. There is a desperate need for new licensed therapies for lupus and whilst Belimumab may not be a perfect agent, there is evidence for its effectiveness. Skin and musculoskeletal problems in lupus can be hugely debilitating and often require very large doses of steroids – abhorrent drugs for a young, predominantly female population and associated with increased damage and premature mortality in the long term. It is not clear that this has been adequately considered in the cost effectiveness appraisal and will be a major issue for patients.	Comments noted. The Committee discussed the evidence submitted from the belimumab phase III trials and the phase II extension study about steroid sparing. The Committee recognised the importance of reduction in steroid use. The economic analysis submitted by the manufacturer includes steroid usage. See FAD section 4.11.
Renal Association	• **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 gender, race, disability, age, sexual orientation, religion or belief?** Lupus predominantly affects women of child bearing age from ethnic minority groups – by failing to recommend Belimumab, it is these groups that will be predominantly affected.	Comments noted. The Committee recognised that systemic lupus erythematosus primarily affects younger women (see FAD section 4.2) and affects some ethnic groups more severely than white populations (see FAD section 4.7). The Committee also recognised that systemic lupus erythematosus predominantly affects women of child bearing age from ethnic minority groups. The Committee discussed equalities issues, but did not consider that the recommendations adversely impacted on access to treatment for one group more than for another. See FAD section 4.29.
Royal College of Pathologists	Please note that the Royal College of Pathologists agree with the key conclusions (1.1, 4.19 & 4.21)	Comment noted. No actions requested

Consultee	Comment	Response
British Health Professionals in Rheumatology	BHPR thank the appraisal committee for their examination of the evidence and their hard work in preparing this document but are very disappointed with the conclusions. 1. There is no doubt that Belimumab cannot be compared in comparison cost with conventional therapy and will, of course, be at added cost to the NHS. An important issue is that the trial data reports Belimumab helps to reduce steroid dosage and length of treatment with steroids. The use of long term steroids carry many potential side effects which can impact on quality of life and lead to numerous co-morbidities many of which will have cost and health implications for many years. Whilst Belimumab is not free of side effects, its comparators are greater and significantly impact on individuals' quality of life, capacity to work, mental health status, personal relationships and life aspirations.	Comments noted. The Committee discussed the evidence submitted from the belimumab phase III trials and from the phase II extension study about steroid sparing. The Committee recognised the importance of reduction in steroid use. See FAD section 4.11.
British Health Professionals in Rheumatology	2. Clinically, there is a concern about the choices of medication available to lupus teams in the group of patients who are steroid dependent and not responding to conventional therapies, including immunosuppression. Belimumab has met the primary endpoint in both of its pivotal Phase 3 trials, it is FDA approved and approved by European commissioners. This then is a very sensible option for treatment in a group not responding to conventional therapy.	Comments noted. The Committee recognised that there are few drugs licensed for systemic lupus erythematosus. See FAD section 4.28.
British Health Professionals in Rheumatology	3. Rituximab did not meet its endpoint and therefore did not receive either a licence in lupus or NICE approval. Yet this document directly recommends a head to head trial between Belimumab which has met its primary endpoint and Rituximab which did not meet its endpoint. This will not realistically happen as drug companies would not consider it to be cost effective or in their best interests.	Comment noted. This has been amended in the FAD. The Committee acknowledges the manufacturer's post marketing commitment to investigate intermittent treatment with belimumab including time to flare from withdrawal of treatment and response to belimumab at retreatment, and considered that these studies would be of value. See FAD section 6.1.
British Health Professionals in Rheumatology	4. The only drugs currently holding a licence for lupus are steroids, Hydroxychloroquine and Belimumab. All other drugs used are off licence and therefore without NICE approval, this will result in clinicians having to apply with IFRs which may be rejected, resulting in loss of clinical time to the NHS and patient care.	Comments noted. The Committee recognised that there are few drugs licensed for systemic lupus erythematosus. See FAD section 4.28.

Consultee	Comment	Response
British Health Professionals in Rheumatology	5. Rituximab is widely used to treat lupus and every time this is planned, an IFR has to be completed. Patients understand that these drugs are off license which does not provide them with any significant confidence in its effectiveness.	Comment noted. The Committee did not consider that there were reliable data available to judge the relative efficacy of rituximab and belimumab, or that the costs of the treatments had been captured accurately. The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. See FAD sections 4.12, 4.26, 4.27.
British Health Professionals in Rheumatology	6. It is anticipated that following response to treatment with Belimumab that infusions can be reduced in frequency and even stopped when in remission. Costings should reflect this in the appraisal document and it is not clear that this has been considered in sufficient detail.	Comment noted. NICE can only make recommendations within the marketing authorisation of a product. The SPC describes continuous use with belimumab. See FAD section 4.15.
British Health Professionals in Rheumatology	It is therefore our opinion that the NICE appraisal committee should review its decision regarding Belimumab. The opportunity to provide this as a reasonable treatment option for those with active auto-antibody positive muco-cutaneous and musculoskeletal complications of lupus has to be re-considered in the light that these patients are currently on long term steroids and immunosuppression with little potential for stopping these drugs over time. These cause a significant number of side effects, which cannot always be prevented and then impact on quality of life when co-morbidities develop.	Comments noted. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations (Social Value Judgements - Principles for the development of NICE guidance; principle 5). The Committee discussed the evidence submitted from the belimumab phase III trials and also from the phase II extension study about steroid sparing. The Committee recognised the importance of reduction in steroid use. See FAD section 4.11.
British Society for Rheumatology	• The NICE Committee have focused their attention on a sub-set of patients both clinically and serologically active as GSK had wished. They do seem to have considered the majority of the relevant evidence carefully before coming to their conclusions.	Comments noted. No actions requested.

Consultee	Comment	Response
British Society for Rheumatology	• BSR was not overly impressed by the nature of the presentation given by GSK to NICE in Manchester which was attended by Prof. David Isenberg. The notion the company put forward to bring the biologic treatment of SLE in line with that of patients with rheumatoid arthritis, is based on an unlikely premise, i.e. that as lupus patients suffer from sustained disease activity (like rheumatoid), there would be a continuing need for the use of belimumab for up to 40 years. This seems very unlikely in most cases. In addition (see page 8 of 45 in the appraisal consultation document), given that black patients in the pooled total trial population did better at meeting the primary endpoint in the control group compared to the belimumab group, it is surprising that much of the modelling produced by GSK utilised the John Hopkins cohort, which is known to have a high proportion of black lupus patients.	Comment noted. The Committee understood that belimumab would not be used continuously over a lifetime. However, in describing the likely use of belimumab, the clinical specialist explained that once a patient was in remission treatment would be stopped by reducing its frequency or dose. Serological activity would be monitored and treatment restarted if a patient became symptomatic or if the serological tests signalled that the patient was likely to become so. However, the SPC describes continuous treatment, therefore the Committee is unable to make recommendations for intermittent treatment or alternative administration schedules. Further there is no evidence for the use of belimumab in this way. See FAD section 4.4.
British Society for Rheumatology	• BSR broadly agrees with the NICE conclusion that GSK's attempts to demonstrate that belimumab will increase longevity in lupus patients is, at this point, not tenable given the relatively modest amount available about long term outcome on the drug.	Comments noted. No actions requested.
British Society for Rheumatology	• BSR agrees with the NICE Committee's view that the patients included in the BLISS 76 study are more likely to be similar to patients in England and Wales than those included in the BLISS 52 study.	Comments noted. No actions requested.

Consultee	Comment	Response
British Society for Rheumatology	• The critical issue which the NICE committee avoids is as follows:- a) Throughout the document, rituximab is frequently referred to as being the obvious comparator and in several places it is expressed that the disappointment that the GSK company have made little use of such data as are available to compare their drug i.e. BENLYSTA with rituximab. However, this is to ignore completely the fact that rituximab in two large trials, one of non-renal lupus and one of renal lupus, did not meet its endpoints. As a consequence, the Primary Care Trusts in the UK are increasingly unwilling to fund its use in patients with lupus. If NICE now block BENLYSTA (which has of course been approved for use in lupus patients (of the type considered in the document) by the FDA and the European commissioners, then what exactly are physicians looking after lupus patients, who have failed standard immunosuppressive therapy, supposed to do next? NICE is clearly concerned about restraining costs but following NICE's figures, let us assume that 15,000 lupus patients in the UK do exist and that approximately 25% are of an age (over 50) where significant flare becomes much less likely. Then around 11,000 lupus patients are left of whom some say 1200 only would come into the hard to treat category. Assuming that neither rituximab nor BENLYSTA were available to them, significant danger exists that these patients would have to be admitted to hospital and treated with a very high dose intravenous steroids (with many potential complications) intravenous immunoglobulin (very expensive) or go back to a drug such as intravenous cyclophosphamide/mycophenolate. Each of the options is expensive (by virtue of it having to be given intravenously in the case of cyclophosphamide or just the unit cost of the drug (in the case of mycophenolate and IvIg) which they may well have failed previously. These seem far from ideal options and in these circumstances the possibility of using BENLYSTA at a significantly reduced cost from the company for a modest period of time e.g. six months to see if it can help to stabilise the patient's disease and reduce concomitant steroid therapy seems both an attractive proposition clinically and financially.	Comment noted. NICE has been asked by the Department of Health to appraise the clinical and cost effectiveness of belimumab for the treatment of systemic lupus erythematosus. It is outside the remit of this appraisal to consider treatment guidelines for systemic lupus erythematosus or the use of rituximab. This is more appropriately considered as part of a clinical guideline. Rituximab has been considered as a comparator in this appraisal and the Committee was aware of the clinical trial evidence available for rituximab and particularly the EXPLORER trial completed in patients with non renal systemic lupus erythematosus. The Committee has considered all evidence submitted as part of this appraisal. This included comparisons of belimumab with rituximab and with standard of care. See FAD section 4.12. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3).

Consultee	Comment	Response
Primary Care Rheumatology Society	1. The Primary Care Rheumatology society (PCRS) are disappointed that NICE do not feel that Belimumab has an active part to play in the management of active SLE. 2. We feel that SLE is such a multi-factorial disease that trials have not been able to demonstrate a significant effect for any of the newer drugs which are used to treat it; for example Rituximab. 3. Rituximab is however used with excellent results to treat some patients with SLE. 4. We are concerned that a refusal to allow clinicians to use Belimumab will also jeopardise the use of Rituximab in patients with SLE. In the current times of financial constraints within PCTs, funding for Biologic drugs is already threatened. We feel that PCTs will start to refuse finding for Rituximab for SLE, as there is a lack of good evidence for its efficacy, but it does undoubtedly work in the correctly selected patients. 5. This will leave patients with active SLE, no option but to be treated with high dose steroids and immunosuppressive drugs, which are all potentially harmful.	Comments noted. NICE has been asked by the Department of Health to appraise the clinical and cost effectiveness of belimumab for the treatment of systemic lupus erythematosus. It is outside the remit of this appraisal to consider treatment guidelines for systemic lupus erythematosus or the use of rituximab. This is more appropriately considered as part of a clinical guideline. The Committee was aware of the clinical trial evidence available for rituximab and particularly the EXPLORER trial. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Evidence Review Group's economic analysis and the manufacturer submission. See FAD section 4.12.
Primary Care Rheumatology Society	6. We do not feel that patients with SLE have been allowed to comment sufficiently upon this decision.	Comment noted. For each appraisal a matrix of stakeholders is developed which include patient organisations as consultees, these organisations are invited to submit evidence and to comment on the draft guidance. In addition, the draft guidance is available for public consultation and anybody including patients may comment on the guidance. The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness. See FAD section 4.2.
Primary Care Rheumatology Society	7. We consider it inhumane to deprive patients of a drug which could be potentially curative for their disease, just because it is not economical to treat everyone with SLE.	Comment noted. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 5).

Consultee	Comment	Response
Primary Care Rheumatology Society	8. In calculating the economic data and QALYs, we are aware that no account has been taken of the financial effect of patients with SLE having to cease work and become dependent on benefits. 9. If the lifetime effect of being on state benefits was taken into account and the lack of economic productivity for that patient, we are certain that it would become cost-effective to use Belimumab. 10. We would like to ask NICE to look back upon the ACD for using anti-TNF drugs to treat Rheumatoid arthritis and its initial refusal on an economic basis. The National Audit Office have now produced a report which supports the use of Biologic drugs in RA (1) and clearly states that it is cost-effective to use Biologic drugs because of the lifetime positive effects of keeping these patients in work and preventing them from needing to use health and social care when they become dependent.	Comment noted. The reference case stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on cost should be that of the NHS and PSS. See section 5.3.3.1. of the Guide to the Methods of Technology Appraisal
Primary Care Rheumatology Society	11. The PCRS strongly feel that the evidence for Belimumab has yet to evolve and that given more time and a more specific economical analysis, this drug would be shown to be cost-effective.	Comment noted. Each piece of guidance published by NICE has a review date at which it will be considered whether the guidance should be reviewed in light of new clinical or cost effectiveness evidence. In addition, consultees may at any time request with rationale the consideration of an earlier review than the date specified in the guidance.

Comments received from commentators

Commentator	Comment	Response
Commissioning support appraisals service (CSAS)	We are in agreement with the recommendations in the ACD not to recommend belimumab for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective. • Belimumab is not a cost effective use of NHS resources compared to standard care. The ICER without the patient access scheme (PPRS) was between £64,400 and £71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. • Belimumab is not considered a cost effective use of NHS resources compared to rituximab. No sound case was presented on the cost effectiveness of belimumab compared to rituximab.	Comments noted. No actions requested.
Commissioning support appraisals service (CSAS)	• No direct comparison of efficacy was made between belimumab and rituximab. Rituximab is used increasingly in patients with severe disease and is therefore a relevant comparator which should have been considered.	Comment noted. The Committee considered whether it was appropriate to complete an analysis of the relative efficacy of rituximab and belimumab. See FAD section 4.12.
Commissioning support appraisals service (CSAS)	• Generalisability of findings from the BLISS studies to the UK population is uncertain. Approximately 50% of patients enrolled in both BLISS trials were receiving an immunosuppressant whereas standard therapy in the UK for most SLE patients would include an immunosuppressant. Patients enrolled in the BLISS-52 study were recruited from South America, Asia and Eastern Europe and so are not representative of a UK population. Most patients included in the BLISS trials had mucocutaneous and musculoskeletal manifestations of SLE. The effect of belimumab on the full range of possible manifestations of SLE is therefore unknown.	Comments noted. The Committee considered whether the patients enrolled in the BLISS clinical trials were representative of the population of patients with SLE in England and Wales. While the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52, it agreed that, on balance, data from BLISS-52, and therefore from the pooled analysis would be relevant. See FAD section 4.7.

Commentator	Comment	Response
Commissioning support appraisals service (CSAS)	• There were numerous uncertainties about the plausibility of assumptions in the manufacturer's economic model. The manufacturer's model may have underestimated the ICER: it was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population; the number of patients discontinuing treatment at 24 weeks may have been overestimated; it was assumed that treatment effect would be maintained over time; it was unclear whether the modelled gains survival were valid; and cost data was derived from various sources which may have given inconsistent estimates. • Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care. Functional assessment of chronic illness therapy (FACIT)-fatigue scores were not significantly better at week 52 in people receiving belimumab compared to standard care.	Comments noted. The Committee took account of the uncertainties in the economic modelling when making recommendations. See FAD section 4.25.

Comments received from members of the public

Role*	Section	Comment	Response
Other: patient advocacy organisation	1	The Lupus Foundation of America is concerned that your preliminary recommendation could have a devastating international impact. For more than a half-century, people with lupus have expressed a desire for more tolerable and safe alternatives to the damaging therapies currently available. Current therapies for lupus, some considered 'standard of care,' were never properly tested or approved for lupus. Many of these drugs come with short and long-term side effects that can be worse than the disease itself. An international study, which followed a large number of lupus patients over several decades, found that half of the physical damage experienced by patients was the result of the therapies used to manage the disease. The lower costs of existing drugs mask the simple fact that their significant side effects are associated with an egregious rise in disabilities, hospitalizations and extreme long-term medical expenditures. If your recommendation stands, the decision will have a chilling effect on global industry investment in the development of new treatments for lupus, denying physicians and patients appropriate options to treat this complex and underserved disease.	Comment noted. NICE has been asked by the Department of Health to appraise the clinical and cost effectiveness of belimumab for the treatment of systemic lupus erythematosus. It is outside the remit of this appraisal to consider treatment guidelines for systemic lupus erythematosus or the use of rituximab. This is more appropriately considered as part of a clinical guideline. Comments noted. The Committee discussed the evidence submitted from the belimumab phase III trials and from the phase II extension study about steroid sparing. The Committee recognised the importance of reduction in steroid use and that there are few licensed therapies for systemic lupus erythematosus. See FAD sections 4.11 and 4.28.
NHS Professional 1	1	The ICER without the patient access scheme (PPRS) was between £64,400 and £71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. No sound case was presented on the cost effectiveness of belimumab compared to rituximab. Should NICE reverse its decision to support its use any service redesign would require full commissioning input therefore it would be impossible to comment on which services, if any, would have to be reduced.	Comments noted. No actions requested

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 1	3	No direct comparison of efficacy was made between belimumab and rituximab which is considered standard treatment. Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care.	Comments noted. The Committee considered whether it was appropriate to complete an analysis of the relative efficacy of rituximab and belimumab. See FAD section 4.12. The Committee took account of the health-related quality of life data available for belimumab when making recommendations. See FAD sections 4.10 and 4.28.
NHS Professional 1	4	The generalisability of the findings from the BLISS studies to the UK population is uncertain as patients enrolled in the BLISS-52 study were recruited from South America, Asia and Eastern Europe, therefore are not representative of a UK population. The manufacturer's model may have underestimated the ICER: it was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population the number of patients discontinuing treatment at 24 weeks may have been overestimated it was assumed that treatment effect would be maintained over time it was unclear whether the modelled gains survival were valid and cost data was derived from various sources which may have given inconsistent estimates.	Comments noted. The Committee considered whether the patients enrolled in the BLISS clinical trials were representative of the population of patient with SLE in England and Wales. While the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52, it agreed that, on balance, data from BLISS-52, and therefore from the pooled analysis would be relevant. See FAD section 4.7. Comments noted. The Committee took account of the uncertainties in the economic modelling when making recommendations. See FAD section 4.25.
NHS Professional 2	1	We believe that NICEs appraisal is a reasonable representation of the effectiveness and cost-effectiveness of this drug for this indication, given the limited evidence (only 2 RCTs). We agree with NICE's assessment and any reversal of the decision (without further substantive evidence bring the conclusions into doubt) would result in resources having to be diverted from more cost-effective interventions, harming the overall health of our population.	Comments noted. No actions requested
NHS Professional 3	1	We agree with this recommendation. Belimumab is not a cost effective use of NHS resources compared to standard care. The ICER without the patient access scheme (PPRS) was between £64,400 and £71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. Belimumab is not considered a cost effective use of NHS resources compared to rituximab. No sound case was presented on the cost effectiveness of belimumab compared to rituximab.	Comments noted. No actions requested

Role*	Section	Comment	Response
NHS Professional 3	3	No direct comparison of efficacy was made between belimumab and rituximab. Rituximab is used increasingly in patients with severe disease and is therefore a relevant comparator which should have been considered. RTX IS a de facto comparator in that it is widely used in this context in the NHS, and many PCTs routinely fund RTX in this setting. Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care. Functional assessment of chronic illness therapy (FACIT)-fatigue scores were not significantly better at week 52 in people receiving belimumab compared to standard care.	Comments noted. The Committee considered whether it was appropriate to complete an analysis of the relative efficacy of rituximab and belimumab. See FAD section 4.12. The Committee took account of the health-related quality of life data available for belimumab when making recommendations. See FAD section 4.10 and 4.28.
NHS Professional 3	4	Generalisability of findings from the BLISS studies to the UK population is uncertain. Approximately 50% of patients enrolled in both BLISS trials were receiving an immunosuppressant whereas standard therapy in the UK for most SLE patients would include an immunosuppressant. Patients enrolled in the BLISS-52 study were recruited from South America, Asia and Eastern Europe and so are not representative of a UK population. Most patients included in the BLISS trials had mucocutaneous and musculoskeletal manifestations of SLE. The effect of belimumab on the full range of possible manifestations of SLE is therefore unknown. There were numerous uncertainties about the plausibility of assumptions in the manufacturer's economic model. The manufacturer's model may have underestimated the ICER: it was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population the number of patients discontinuing treatment at 24 weeks may have been overestimated it was assumed that treatment effect would be maintained over time it was unclear whether the modelled gains survival were valid	Comments noted. The Committee considered whether the patients enrolled in the BLISS clinical trials were representative of the population of patient with SLE in England and Wales. While the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52, it agreed that, on balance, data from BLISS-52, and therefore from the pooled analysis would be relevant. See FAD section 4.7. Comments noted. The Committee took account of the uncertainties in the economic modelling when making recommendations. See FAD section 4.25.
NHS Professional 3	5	Unit costs: Belimumab is given at a recommended dose of 10 mg/kg belimumab on days 0, 14 and 28, and at 4 week intervals thereafter, with discontinuation of treatment if there is no improvement after 6 months. The list price of belimumab is £121.50 for a 120mg vial and £405 for a 400mg vial, though costs may vary in different settings because of negotiated procurement discounts. The manufacturer has agreed a patient access scheme with the Department of Health, which gives a discount on the list price. The size of the discount is commercial-in-confidence.	Comments noted. No actions requested

Role*	Section	Comment	Response
NHS Professional 4	1	Belimumab is not a cost effective use of NHS resources compared to standard care. The ICER without the patient access scheme (PPRS) was between £64,400 and £71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. Belimumab is not considered a cost effective use of NHS resources compared to rituximab. No sound case was presented on the cost effectiveness of belimumab compared to rituximab.	Comments noted. No actions requested
NHS Professional 4	3	No direct comparison of efficacy was made between belimumab and rituximab. Rituximab is used increasingly in patients with severe disease and is therefore a relevant comparator which should have been considered Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care. Functional assessment of chronic illness therapy (FACIT)-fatigue scores were not significantly better at week 52 in people receiving belimumab compared to standard care.	Comments noted. The Committee considered whether it was appropriate to complete an analysis of the relative efficacy of rituximab and belimumab. See FAD section 4.12. The Committee took account of the health related quality of life data available for belimumab when making recommendations. See FAD sections 4.10 and 4.28.
NHS Professional 4	4	Generalisability of findings from the BLISS studies to the UK population is uncertain. Approximately 50% of patients enrolled in both BLISS trials were receiving an immunosuppressant whereas standard therapy in the UK for most SLE patients would include an immunosuppressant. Patients enrolled in the BLISS-52 study were recruited from South America, Asia and Eastern Europe and so are not representative of a UK population. Most patients included in the BLISS trials had mucocutaneous and musculoskeletal manifestations of SLE. The effect of belimumab on the full range of possible manifestations of SLE is therefore unknown. Manufacturer's model may have underestimated the ICER: was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population the number of patients discontinuing treatment at 24 weeks may have been overestimated assumed that treatment effect would be maintained over time was unclear whether the modelled gains survival were valid and cost data was derived from various sources which may have given inconsistent estimates	Comments noted. The Committee considered whether the patients enrolled in the BLISS clinical trials were representative of the population of patient with SLE in England and Wales. While the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52, it agreed that, on balance, data from BLISS-52, and therefore from the pooled analysis would be relevant. See FAD section 4.7. Comments noted. The Committee took account of the uncertainties in the economic modelling when making recommendations. See FAD section 4.25.
NHS Professional 4	5	PCT/ CCP would need to consider services we might be forced to reduce if this technology were to be funded.	Comment noted. No actions requested

Role*	Section	Comment	Response
NHS Professional 5	1	Belimumab is not a cost effective use of NHS resources compared to standard care. The ICER without the patient access scheme (PPRS) was between £64,400 and £71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. Belimumab is not considered a cost effective use of NHS resources compared to rituximab. No sound case was presented on the cost effectiveness of belimumab compared to rituximab.	Comment noted. No actions requested
NHS Professional 5	3	No direct comparison of efficacy was made between belimumab and rituximab. Rituximab is used increasingly in patients with severe disease and is therefore a relevant comparator which should have been considered. Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care. Functional assessment of chronic illness therapy (FACIT)-fatigue scores were not significantly better at week 52 in people receiving belimumab compared to standard care.	Comment noted. The Committee considered whether it was appropriate to complete an analysis of the relative efficacy of rituximab and belimumab. See FAD section 4.12. The Committee took account of the health related quality of life data available for belimumab when making recommendations. See FAD sections 4.10 and 4.28.
NHS Professional 5	4	Generalisability of findings from BLISS studies to UK population is uncertain. Approximately 50% of patients enrolled in BLISS trials were receiving an immunosuppressant whereas standard therapy in the UK would usually include an immunosuppressant. Patients enrolled in BLISS-52 study were recruited from South America, Asia and Eastern Europe and are not representative UK population. Most patients included in the BLISS trials had mucocutaneous and musculoskeletal manifestations of SLE. The effect of belimumab on the full range of possible manifestations of SLE is therefore unknown. There were numerous uncertainties about the plausibility of assumptions in the manufacturer's economic model. The manufacturer's model may have underestimated the ICER: it was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population the number of patients discontinuing treatment at 24 weeks may have been overestimated it was assumed that treatment effect would be maintained over time it was unclear whether the modelled gains survival were valid and cost data was derived from various sources which may have given inconsistent estimates	Comments noted. The Committee considered whether the patients enrolled in the BLISS clinical trials were representative of the population of patient with SLE in England and Wales. While the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52, it agreed that, on balance, data from BLISS-52, and therefore from the pooled analysis would be relevant. See FAD section 4.7. Comments noted. The Committee took account of the uncertainties in the economic modelling when making recommendations. See FAD section 4.25.

Role*	Section	Comment	Response
Patient	3	I don't believe you have taken into account the full cost of looking after a very poorly lupus patient. I am not even the most severe case of lupus and the amount of drug, GP and multi consultant time I have put into my management. If I had less organ damage and less consultants, less other medications and tests not only this I would be better, off benefits and able to work and not need social care. I am really disappointed to hear of your decision against the first drug really recognised as being effective in SLE for fifty years. We're not asking for it as a first line treatment just when all other options have failed. Please reconsider your decision and give lupus patients some hope. Many drugs have already failed the research and development stage for SLE because it's a hard disease to show up in blood results. My blood results rarely accurately reflect my disease activity. So you may well be underestimating the benefit to the individual.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Evidence Review Group's critique and the manufacturers' submissions.

Response to Appraisal Consultation Document (ACD)
Belimumab for the treatment of
active autoantibody-positive systemic lupus erythematosus (SLE)
GlaxoSmithKline 21 October 2011

Executive Summary

We welcome the opportunity to respond to the Committee's initial conclusions regarding the evidence base to support the use of belimumab within the NHS. The ACD raised a number of issues arising from the modelling assumptions, the patient population and the disease scoring which drive the cost-effectiveness model. There were also concerns raised regarding the comparison with rituximab. We believe that we can address the main points raised by the Committee and the clinical specialists to support the use of belimumab within the NHS as a valuable, cost-effective treatment for SLE.

There is inevitably uncertainty when appraising the effect of a drug on a complex, chronic disease with severe long term outcomes such as SLE, where most of the evidence is based on relatively short randomised controlled trials (RCTs). Considering the concerns of the committee we have reviewed the way the medicine could be used within the NHS. We are proposing an approach which would more accurately reflect the way belimumab is likely to be used in clinical practice by restricting treatment to a maximum of six years and focussing on those patients demonstrating the greatest benefit. By restricting treatment in this way, some of the uncertainty around the cost effectiveness is reduced and the estimated cost effectiveness is now at a level that would be regarded an efficient use of NHS resources (see Table 1 below and further information in detailed response).

Table 1. Summary of Incremental cost-effectiveness ratios based on the new assumptions applied to the health economic model and with the patient access scheme (PAS) incorporated.

Description of Scenario	Scenario Details	Incremental Cost per QALY
Revised Base Case: Same as original base case but with a six year maximum belimumab treatment duration	Time horizon = lifetime; 6 year maximum belimumab treatment duration; treatment continuation criterion at 24 weeks defined as SS score reduction ≥4 points; and health effects discount rate of 3.5%	[redacted]
More stringent treatment continuation criterion	As revised base case but with treatment continuation criterion at 24 weeks of SS score of ≥6 and health effects discount rate of 3.5%	[redacted]
Health effects discount rate of 1.5%	As revised base case but with health effects discounting rate of 1.5%.	[redacted]
More stringent treatment continuation criterion with discount rate of 1.5%	As revised base case but with treatment continuation criterion at 24 weeks defined as SS score of ≥6 points; and health effects discount rate of 1.5%	[redacted]

The revised health economic modelling, incorporating our patient access scheme (PAS), results in a revised base case ICER of [redacted] per QALY gained, with further reductions in the ICERs from

additional key scenarios presented in Table 1. Therefore, given we believe that the health effects discount rate of 3.5% used in the base case is too high for this technology appraisal, the true assessment of cost-effectiveness is likely to lie within the range of [redacted] per QALY gained.

The committee has acknowledged in the ACD the serious nature of SLE and its impact on patients as well as the innovative nature of belimumab which is the first medication to be specifically designed and licensed for these patients for a number of years. The current NICE Methods Guide 2008, outlines additional factors to consider when appraising a technology. These include: "where the innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure".

In this case there are aspects of value not fully accounted for in our estimate of cost-effectiveness. Specifically, the full benefit of belimumab on disease flares and chronic fatigue are not adequately captured in the quality adjusted life years (QALYs) derived from EQ-5D utility values.

Also, recently available data from the open-label Phase II belimumab extension study (Petri et al. 2011) shows a mean reduction in steroid use of 4.7mg/day, an average of 34.4% from the baseline dose, by the end of six years of follow-up. This is an important finding, as not only does it have the potential to lead to improved quality of life for patients experiencing fewer steroid-related side effects, but future steroid related organ damage would also be reduced. The impact of this recent data is not fully reflected in our current estimates of cost effectiveness.

Finally, we do not believe that the arguments presented in our submission regarding the comparison of belimumab with rituximab has been given sufficient consideration. Rituximab is unlicensed for SLE and is not supported by evidence from RCTs. [redacted] Moreover, in the absence of these biologics being available on the NHS, SLE patients may be admitted to hospital for alternative more expensive treatments such as intravenous immunoglobulin (IVIG).

For the reasons outlined above, and considering our revised assessment of cost-effectiveness, our specific target population, the proposed patient access scheme, and having addressed the committee's concerns regarding the relevance and uncertainty around some of the key assumptions in our health economic model, we would ask the committee to reconsider its decision and approve the use of belimumab in this group of severe patients.

GSK's Detailed Response to the Appraisal Consultation Document (ACD).

1. <u>Do you consider that all of the relevant evidence has been taken into account?</u>

Yes. However we believe that the Appraisal Committee and clinical specialists identified several areas of uncertainty that require further exploration and we would like the committee to consider a revised base case with supporting scenarios to address these. In addition, since submitting in April, there is new published data concerning the reduction of steroid use which is more reflective of clinical practice than observed in RCTs.

The additional analyses we present have a considerable impact on improving the estimated cost-effectiveness for belimumab compared with the results presented in our original submission. After further consultation with lupus experts we also believe these revised assumptions are supported clinically. The detail of these analyses are provided in Appendix 1 of this document, however the rationale for the revised base case and other changes to the original assumptions are summarised in this section along with the updated cost-effectiveness results. Please note that all ICERs in this document incorporate the discount on price offered in our patient access scheme (PAS).

Duration of treatment with belimumab – Revised Base Case

The most important change we have made to our base case for health economic assessment concerns the expected duration of continuous treatment with belimumab. It is clear from the comments in the ACD (Section 4.13) that we needed to align this duration more closely with how clinicians would consider using belimumab to manage their eligible SLE patients in clinical practice. Although the duration of treatment in our original submission was based on the SmPC for belimumab which states that belimumab could be used continuously, the waxing and waning nature of SLE means that clinicians are unlikely to continue belimumab indefinitely, but instead use it as clinically indicated. The indefinite treatment duration assumed in the original model submitted to NICE does not therefore reflect likely real life use and will have therefore provided a very conservative estimate of cost-effectiveness. Other standard of care treatments for SLE, such as immunosuppressants, are frequently prescribed for between two and five years depending on the level and type of disease activity patients' experience. Although there is a lack of direct evidence to identify an optimal treatment duration for belimumab, partly due to the heterogeneous nature of the disease, to date there are six years of efficacy and safety data for belimumab from the Phase II extension study (LBSL99) (Petri et al. 2011), which demonstrate, for the majority of patients in the study, a sustained response to belimumab without compromising safety. Supported by this evidence, and after discussion with clinicians, we propose a revised base case which incorporates a maximum six year treatment duration for belimumab. After this time all belimumab patients mirror the standard of care (SoC) treatments for the remainder of the model horizon and revert to the SoC level of disease activity. Although we do acknowledge that this duration of treatment could be considered arbitrary, it is believed that it is long enough for the benefits of belimumab on controlling high disease activity to have an important impact on reducing long-term morbidity while also being a realistic continuous treatment duration that clinicians would be comfortable with for patients who demonstrated a suitable sustained level of response. This treatment duration will also help to reduce some of the uncertainty around the modelled assumption of retaining the same level of benefit for belimumab as seen in the trials over long-term treatment. This revised base case yields an ICER of [redacted] per QALY gained. This provides a more cost-effective use of NHS resources compared with our original base case which assumed lifetime use. If shorter treatment durations

with belimumab are considered, the cost-effectiveness is further improved, as the incremental costs, which are mainly driven by the drug acquisition cost, are reduced. However health benefits may also be reduced compared with the revised base case duration of six years as there is less estimated long-term benefit due to the shorter durations of reduced disease activity with belimumab. We believe the choice of a maximum treatment duration of six years is therefore an evidence-based and appropriate compromise for treatment with belimumab in our proposed target population.

Key Scenario Analyses

In addition to the revised base case analysis described above we have considered a number of scenario analyses which look at different treatment durations of belimumab, different discount rates and the inclusion and exclusion of treatment continuation. However there are two alternative scenarios which we consider the most important for consideration because of the impact they have on the assessment of cost-effectiveness and they are discussed below:

1. **Revised Discount Rate**

   After we had submitted in April 2011, NICE issued updated guidance, effective from July 2011, on the methods of technology appraisal with regards to the level of acceptable discounting for health effects (***www.nice.org.uk/media/955/4F/Clarification_to_section_5.6_of_the_Guide_to_Methods_of_Technology_Appraisals.pdf***). This updated guidance specifies that for certain chronic diseases where treatment effects are both substantial in restoring health and sustained over a very long period, a rate of 1.5% for health effects and 3.5% for costs can be applied. SLE is often a lifelong, severely debilitating disease with significant morbidity which can lead to premature death. Belimumab specifically binds to soluble human B-lymphocyte stimulator (BLyS) and inhibits its biological activity. In Phase III clinical trials, belimumab demonstrated clinically important reductions in disease activity, and has the potential to provide important long-term benefits including reduced organ damage, reduced use of high dose steroids - along with their associated risks - and consequently, improved survival. Clinical experts also concur that reducing disease activity in the near-term has important benefits in the longer-term. We believe that belimumab should be appraised with this lower discount rate.

   Therefore for our revised base case which includes a maximum treatment duration of six years, and for our original base case which assumed lifetime treatment with belimumab, we have conducted a scenario analysis for the assessment of cost-effectiveness incorporating a health effects discount rate of 1.5%. For our original model, with lifetime treatment, incorporating this level of discount for health effects yielded an ICER of [redacted] per QALY gained. For our revised base case with a maximum treatment duration of six years, the corresponding ICER is [redacted] per QALY gained.

2. **Treatment Continuation Criterion**

   In our original base case (and also our revised base case) we included a treatment continuation rule (stopping criterion) after six months. This rule was specifically included in the model to try and represent how patients could be managed on belimumab in clinical practice as recommended in the SmPC. The SmPC states that "Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment". For the health economic model an objective measure was required to determine for each patient whether belimumab should be continued or discontinued after six months

treatment. Our continuation rule required patients to demonstrate a reduction of at least 4 points in SELENA-SLEDAI (SS) score. A minimum reduction of 4 points in SS score is accepted as a clinically relevant improvement in disease activity (Gladman et al. 2000). We are aware that the Committee felt this continuation rule was arbitrary and may not be adhered to in clinical practice (see ACD Section 4.12). An SS score reduction of 4 or more was a pre-specified component of the composite primary endpoint of the BLISS trials and the main driver of efficacy. The SELENA-SLEDAI is a validated, robust measure (Griffiths et al. 2005) and a decrease of 4 or more points relates to a clinically meaningful change in disease activity (Gladman et al. 2000). We have consulted with lupus experts and have been advised that incorporating a treatment continuation rule in clinical practice as part of the management of patients on belimumab would be easily achievable and acceptable if it was a stipulated requirement in NICE guidelines. As reflected by the clinicans at the Appraisal Committee Meeting, it would in fact be valuable to introduce objective assessment of SLE routinely in clinical practice. It is also worth considering that patients in our proposed target population will be managed in only a small number of specialist lupus centres. This will help ensure that clinicians adhere to any specific requirements for prescribing belimumab as detailed in the guidance that NICE issues.

There is no other recommended, validated, objective treatment continuation criterion for any treatments currently used in the management of lupus patients in clinical practice. However, stopping rules are routinely used in clinical practice for asssessing continuation of treatments for rheumatoid arthritis. For example, the NICE guidance on tumour necrosis factor (TNF) inhibitors in disease-modifying anti-rheumatic drug (DMARD) failures states that treatment should be continued only if there is an adequate response (defined as improvement of Disease Activity Score 28 (DAS28) by at least 1.2 points) at 6 months following initiation of therapy (TA130). There is no reason to believe there would be any difficulties in implementing a treatment continuation rule for lupus patients.

In addition, being mindful of limited NHS resources, introducing a more stringent treatment continuation criterion, could allow for a more efficient use of NHS resources by ensuring that only those patients showing the greatest response to belimumab continue on this drug. We have therefore also modelled as a scenario, a more stringent criterion for allowing continued treatment with belimumab, which requires patients to have a decrease in SS score of at least 6 points after six months. This more stringent criterion improves the cost-effectiveness compared with the base case, as fewer patients will reach the level of reduction in SS score required for treatment continuation.

For the revised base case, this analysis yields an ICER of [redacted] per QALY gained when incorporating a health effects discount rate of 3.5%. When a health effects discount rate of 1.5% is used in the model, the ICER is further reduced to [redacted] per QALY gained.

2. <u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence</u>

There are some aspects of the interpretation of the clinical evidence that we believe require further clarification and consideration. The main issues that we would like the committee to consider further relate to:

i) the representativeness of our target BLISS SLE population and their likelihood of developing significant long-term organ damage which has an impact on survival
ii) the relevance of the SELENA-SLEDAI tool to patient selection and management
iii) health effects being underestimated in the health economic model
and
iv) the cost and efficacy comparison with rituximab.

i) Representativeness of our target BLISS SLE population and likelihood of developing significant long-term organ damage

- **The range of clinical manifestations seen in our RCTs, and our proposed target subgroup, is representative of those seen in SLE patients in the UK**
- **Due to having both a high level of disease activity (SS score ≥10) and the presence of serological biomarkers indicative of systemic disease, these patients are likely to progress to serious long-term morbidity.**

ACD Section 3.5. The Committee states that "Most of the patients in the trials had a relatively narrow range of manifestations of systemic lupus erythematosus, mainly restricted to mucocutaneous, immunological and/or musculoskeletal damage."

This range of manifestations is not narrow. Involvement of these organ systems (mucocutaneous, immunological and musculoskeletal) represent significant disease activity. Specifically, immunological manifestations, such as serological changes (e.g. low complement and positive anti-dsDNA), is indicative of wider systemic disease activity.

ACD Section 4.16 In their evidence to the Committee the clinical specialists stated that SLE patients with higher disease activity are more likely to have organ damage and die than people with lower disease activity. However, it was also stated by the specialists that this increased morbidity from high disease activity was likely to be dependent on the site of organ damage. For example, treatment for patients with mainly musculoskeletal or mucocutaneous damage was unlikely to result in a survival benefit.

Our target population comprised patients with a SELENA-SLEDAI score of ≥10 (representative of high disease activity) and had low complement and positive anti-dsDNA; these are markers of systemic disease; patients with serologically active disease are more likely to flare (Petri et al. 2009; Tseng et al. 2006) and develop long term organ damage (Swaak et al. 1999) which can lead to premature death. Therefore by ensuring sustained suppression of disease activity it is plausible that the patients in our target population will have a survival benefit from treatment with belimumab, irrespective of the organs involved.

Whilst the 52 and 76 week BLISS trials were not designed to demonstrate a reduction in mortality, the positive impact demonstrated by belimumab on reducing disease activity and the acknowledged link between high levels of disease activity and serious long-term organ damage (Stoll et al. 2004; Swaak et al. 1999), supports a beneficial effect of belimumab on survival. According to the NICE scope, modelling long-term benefits for chronic diseases is an appropriate approach to the assessment of cost-effectiveness, and we note that the ERG has commented positively on the

methodology used to model the natural history of SLE and of the potential long-term benefits that may accrue.

It is acknowledged that patients with renal or cerebral involvement are most likely to die, however, according to the lupus experts we have consulted, it is not always evident which patients are likely to develop renal damage. Unlike in rheumatoid arthritis where disease progresses in a "step wise" manner, in SLE, patients can move from having no symptoms to a full blown disease flare in a short spate of time, irrespective of initial organ involvement. Patients do not die of disease activity directly. Uncontrolled disease activity increases mortality due to increased organ damage and increased risk from concomitant drugs, such as cardiovascular risk with high dose steroids, and risk of infection from immunosuppressants. By controlling disease activity and promoting longer remission, the negative impact of prolonged high disease activity and risk of flare in any organ will be decreased**.**

This section in the ACD also discussed how survival time in the model was predicted to be longer in the high disease activity target population than in the overall trial population, (31.9 years in the standard care arm of the target group compared with 30.5 years in the overall standard care arm in the overall pooled BLISS populations), when the opposite would be expected as the target population had the more severe disease. Thus the Committee concluded that there was considerable uncertainty around the validity of the modelled gains in survival. We have investigated this further and can clarify that this is due mainly to the differences in age distribution, with patients in the target population within the trials being on average younger than those in the total population. When the same age distribution seen for the total BLISS population is included in the model for the target population, the life expectancy (life years undiscounted in the table) was reduced to 28.4 years for the SoC group, below that of the total population (see Table 2 below for the summary of the results for outcomes). This result demonstrates that the long-term modelling is robust and does provide expected comparative survival estimates for the different populations.

Table 2: Summary of outcomes from the economic model for the original base case with a lifetime treatment duration for belimumab – High disease activity subgroup (Target population).

	SoC	Belimumab	Difference
Age at Death (years)	66.3	69.3	3.0
SLICC at Death	3.9	3.9	-0.1
Average Mean SLEDAI	5.8	4.77	-1.0
Average Monthly Steroid (mgs)	235.3	213.2	-22.1
Life Years (undiscounted)	28.35	31.31	3.0
Life Years (discounted)	15.65	16.79	1.1
QALYs (undiscounted)	15.28	17.12	1.8
QALYs (discounted)	8.91	9.74	0.8

ii) Relevance of SELENA-SLEDAI Instrument

- **The SELENA-SLEDAI Instrument is a valid, reliable tool that is easy to administer and suited for use in clinical practice.**
- **A SELENA-SLEDAI score ≥10 is able to identify patients with the most serious disease activity.**

ACD Sections 4.4 and 4.5. The clinical specialists at the Appraisal Committee stated that the SELENA-SLEDAI disease activity instrument could be considered a relatively crude tool. The Committee was concerned that the specification of a SELENA-SLEDAI score of 10 or more may be considered an arbitrary cut-off value with which to identify a suitable target population.

Like most disease specific instruments in SLE there are acknowledged limitations of the SELENA-SLEDAI. However, the SELENA-SLEDAI is widely used internationally, has been shown to be valid, reliable and sensitive to change (Griffiths et al. 2005), and is recognised by clinical experts as a useful instrument for identifying the various presentations of disease activity in patients with SLE. In addition it has been shown to correlate highly (coefficient ≥0.76) with other recognised tools such as British Isles Lupus Assessment Group (BILAG) index and European Consensus Lupus Activity Measurement (ECLAM) (Bencivelli et al. 1992). Unlike other instruments, the SELENA-SLEDAI instrument is relatively simple to use, easy to learn/teach, quick to administer, can be administered by trained nurses rather than being reliant solely on experienced physicians, and does not require a computer for generating a score; it can therefore be considered an appropriate tool for implementation in clinical practice. Indeed, many clinicians would welcome the introduction of the more routine use of objective disease scoring in SLE as historically this has been absent in this disease area. Comparisons can be drawn with rheumatoid arthritis where the (DAS) has been successfully implemented. GSK in conjunction with UK SLE experts would be prepared to support any necessary training for the SELENA-SLEDAI instrument for clinicians and nurses. We also note that SELENA-SLEDAI will be captured in the UK BILAG Biologics in Lupus Registry.

With regards to the SELENA-SLEDAI score cut-off value of 10 as an eligibility criterion for our proposed high disease activity target population, this was a pre-specified criterion for subgroup analysis in the two Phase III randomised controlled trials (RCTs) and a stratification criterion for randomisation into the trials. Published evidence demonstrates that an SS score of 10 identifies patients with high disease activity (Griffiths et al. 2005), is likely to capture the majority of very ill patients, and is predictive of those likely to develop very poor, long-term morbidity (Swaak et al. 1999). In addition, consultation with lupus experts has supported this cut-off value as indicative of patients who have clinically serious disease.

iii) Health effects have been underestimated in the assessment of cost-effectiveness

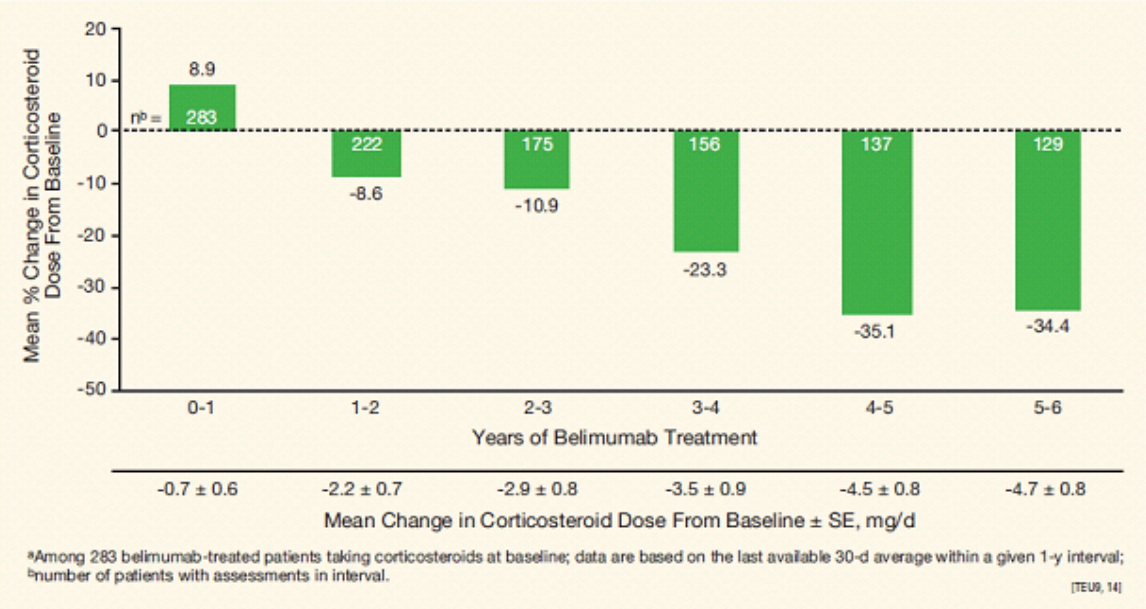
ACD Section 4.22. In this section it is stated that the Committee was satisfied that all relevant benefits to HRQoL were captured in the cost-effectiveness assessment, noting in particular that FACIT-F scores were not statistically significantly better at week 52 in the target population in people receiving belimumab than in people receiving standard care.

We maintain that some HRQoL benefits have been underestimated in the cost-effectiveness assessment for the reasons outlined below:

- Utilities for disease activity were obtained from the EQ-5D generic instrument which was completed by patients at pre-determined time-points during the trial. These time-points would not necessarily have coincided with when patients were feeling at their worst during a disease flare. Disease flares were not specifically included in the health economic model due to the additional complexity this would have introduced. Because of this the effect of flares on quality of life is likely to have been underestimated in the model and so too any benefit of belimumab had in reducing flare activity. This is supported by published evidence of poor correlation between disease activity (e.g. SLEDAI) and a number of QoL instruments (McElhone et al. 2006).

- **ACD Section 4.9.** In this section it is stated that the Committee noted the limited steroid sparing effect observed in the BLISS studies. It is very likely however, that a greater steroid sparing effect would in fact be seen with belimumab in clinical practice. Given the double-blind nature of the study it is highly probable that the BLISS trialists were cautious in reducing the steroid dose too much or too quickly in the RCTs due to concern of the impact this could have on inducing a flare. Indeed, in the BLISS trials only patients who had improving SLE disease activity for at least eight weeks could, at the investigator's discretion, reduce the steroid dose, targeting a reduction to 7.5 mg/day or lower after the Week 24 visit. Therefore in terms of steroid sparing effect, the benefits that belimumab could offer are likely to have been underestimated. This is supported by recent results from the Phase II belimumab extension study (LBSL99) (Petri et al. 2011) which showed that for patients remaining in the study with steroid data recorded, the dose of steroid gradually and significantly reduced over time (Figure 1). By the end of Year 6 the steroid dose had reduced by an average of 4.7mg/day, an average of 34.4% from the baseline dose (Petri et al. 2011). In this study there were no restrictions on steroid use and it was left to the physicians' discretion as to whether it was appropriate to reduce a patient's steroid dose. Therefore this reflects more accurately how steroid tapering would be managed in clinical practice for patients receiving belimumab. This is important when considering HRQoL, because, although there was a clear improvement in disease activity with belimumab in the trials, this benefit may not have been fully realised by the patients if they were still experiencing side effects from high dose steroid use. Additionally, reducing steroid use may have important long-term benefits with reducing future steroid -related organ damage.

Figure 1: Change in corticosteroid use over time in belimumab-treated patients taking corticosteroids at baseline



- As detailed in our original submission, we believe that the EQ-5D underestimates the impact of SLE on HRQoL. Certain relevant dimensions of health are not directly included in the EQ-5D instrument, such as fatigue or sensory impairment. This has also been discussed by the NICE Decision Support Unit in their report 'The incorporation of health benefits in cost utility Analysis using the EQ-5D' (Wailoo et al. 2010). Chronic fatigue is one of the most prevalent clinical manifestations of SLE and severely affects HRQoL (Thumboo et al. 2007; Zonana-Nacach et al. 2000). It is nearly always a major factor in the life of a patient with SLE; it can be debilitating and difficult to treat. In the high disease activity subgroup, the pooled data from both studies showed that belimumab 10 mg/kg was associated with significantly improved fatigue scores compared with placebo at Weeks 8 and 12 ($p < 0.05$) and although at Week 52 a statistically significant difference with placebo was not seen, the mean change from baseline in the belimumab group (4.9 points) was superior to that seen in the placebo group (3.3 points). We further note that both clinical experts and patient groups at the first appraisal committee meeting specifically pointed to the significant impact of fatigue and sensory impairment on patients with SLE.

iv) Comparison with rituximab

- **The costs presented for rituximab based on the doses used in their clinical trial and presented in our original submission are appropriate and justifiable for comparison with belimumab costs.**

- **The current available RCT evidence for both drugs demonstrates that belimumab met its primary endpoint whereas rituximab failed to do so. Thus our approach of assuming belimumab is at least as effective as rituximab is conservative**

ACD Section 4.20. It is stated in this section that the Committee are not convinced by the cost and efficacy arguments with rituximab which were presented in our original submission, and in particular, the Committee believes we may have overestimated the annual cost of rituximab used to treat SLE patients.

Had the manufacturers of rituximab been successful in their clinical trial programme and successfully obtained a licence for use of this drug in SLE then the licensed dose would most likely have been reflective of the dose used in the clinical trials. The 52 week EXPLORER trial (Merrill et al. 2010) used a dose of 1000mg by infusion at days 1, 15, 168, 182, which based on 10mg/ml solution with a vial price of 50ml=£873.15 (Monthly Index of Medical Specialities (MIMS) 2011) gives an annual price of £6985.20, as detailed in our original submission. According to NICE methodology, as a stated comparator, the appropriate comparison to be made in any economic evaluation would be to use the comparative efficacy from the randomised controlled trials, with the corresponding doses and costs. Using estimated costs of how rituximab is currently used off licence in some specialist centres is inappropriate when making a comparison to belimumab, which currently has only been used in clinical trials.

Both Phase 3 studies for belimumab (BLISS-52 and BLISS-76), successfully achieved their primary composite endpoint, SRI, at week 52. In the EXPLORER study, the only published RCT in non-lupus nephritis patients (Merrill et al. 2010), no difference was noted between the rituximab and SoC group and the placebo and SoC group at week 52 in their primary endpoint, which was based on BILAG scores, nor in any secondary endpoints. We acknowledge that the populations were very different between the rituximab and belimumab studies; in particular the patients enrolled in the EXPLORER trial had significant and acute disease and were on very high doses of steroid at study entry. In our original submission and during the clarification process we provided a clear justification of why indirect comparisons of efficacy were inappropriate and this was supported by the ERG in their report. However it still remains that efficacy with rituximab from RCTs has not been established and therefore we believe that we are taking a conservative approach by assuming at least comparable efficacy between the two drugs.

Given that rituximab has been identified as a valid comparator for this appraisal and is used in our proposed target population, the available evidence suggests that concluding similar efficacy and costs is reasonable and therefore we reiterate the conclusion in our original submission that belimumab, with our proposed patient access scheme, would provide a [redacted] alternative in our target SLE population who would otherwise receive rituximab or some other more expensive, unlicensed treatment such as intravenous immunoglobulin (IVIG).

ACD Section 3.29. The text in this section which states "The ERG highlighted that information on SLEDAI and SF-36 changes in the rituximab EXPLORER trial were available, and that randomised controlled trials for both rituximab and belimumab recorded BILAG changes, thus offering the potential for an indirect comparison" is inconsistent with the text in Section 4.10 which states "The Committee heard from the ERG that there were three outcomes for which an indirect comparison

could be completed (that is, BILAG, SLEDAI, and SF-36 scores), but data were only available in the public domain for the SF-36. The ERG also highlighted the differences in the trial populations, which it considered meant that the results of an indirect comparison were not meaningful." This latter text provides a more complete assessment of the ERG's opinion as to the inappropriateness of conducting an indirect comparison of efficacy between belimumab and rituximab. Whereas the statement in Section 3.29 suggests that an indirect comparison would be valid.

Other Points for Clarification of Interpretation of the Evidence

ACD Sections 3.4 and 3.14. In these sections NICE makes a reference to the "marketing authorisation population". Limited data for a subgroup of the licensed population, defined as patients with positive anti-dsDNA and low complement, was presented in our original submission but this does not include all patients with high disease activity eligible under the license for belimumab, and therefore should be referred to as **a subgroup** of the marketing authorisation population.

ACD Section 3.31. This section states that the ERG were unclear of the derivation of the 8% annual discontinuation rate among patients showing a response to belimumab at week 24, and of the reasonableness of extrapolation of this value in the health economic model. This annual discontinuation rate was estimated from the BLISS trials for patients defined as belimumab responders (SELENA-SLEDAI score decrease of ≥ 4) after 24 weeks of treatment based on a time to discontinuation analysis as detailed in our original submission. The latest available data from the Phase II belimumab extension study (LBSL99) summarised in Table 3 below (GlaxoSmithKline data on file 2011) also shows that our assumption to continue using an 8% annual discontinuation rate is reasonable, and indeed may have underestimated the cost-effectiveness in our original submission, as it shows from Year 2 onwards the rate ranged from 6.7% to 19.7% over six years, giving an average discontinuation rate of 13.0%. With our revised base case incorporating a shorter treatment duration, uncertainty is again reduced with regards to the discontinuation rate as we have clinical trial evidence to support our assumption. Higher rates of discontinuation lead to better cost-effectiveness due to drug acquisition cost being the main contributor to incremental costs.

Table 3: Summary of discontinuation from the Phase II Extension study LBSL99

	Years on belimumab				
	2	**3**	**4**	**5**	**6**
Number of patients starting year	339	274	248	223	208
% discontinued	19.2%	9.5%	10.1%	6.7%	19.7%

ACD Section 4.8. The Committee concluded that there was uncertainty about the extent to which standard of care (SoC) in the BLISS trials was representative of UK clinical practice, with particular reference to the fact that approximately 50% of BLISS patients were receiving immunosuppressants as part of their SoC.

There are no national guidelines for the management of SLE in the UK and the treatment pathway is not 'step-wise' as in other conditions such as rheumatoid arthritis. Hence there is considerable variability in standard of care treatment between SLE patients and across UK centres. The lupus experts we have consulted believe that the proportion of patients receiving immunosuppressants in the BLISS trials seems reasonable based on the level of variability in SoC currently evident in the UK. These trials included a variety of different combinations of SoC treatments, all of which could be observed in UK clinical practice and therefore it is reasonable to assume the results are applicable to the UK.

ACD Section 4.14. The Committee suggested that the long-term benefits on disease activity assumed in the health economic model may have been overestimated as it has been observed that in other conditions such as rheumatoid arthritis, patients on biological treatments can experience a reduction in the response to treatment over time.

The duration of response with belimumab in SLE cannot be compared with treatment with biologics in rheumatoid arthritis as this disease takes a very different course. The six years of data currently available for the Phase II extension study provides good evidence of a sustained response over this duration, so with our revised base case with a maximum six year treatment duration, we believe that the assumption of continued benefit can be supported. Consequently in our revised cost-effectiveness assessment we do not believe that the model has over-estimated the benefit of belimumab.

3. Additional Considerations

To our knowledge, this is the first cost-effectiveness model to be produced for SLE, a very complex disease to model. The analyses conducted on the Johns Hopkins database, a large SLE cohort with a long-term follow-up, produced a series of robust natural history models (NHMs) which represent the long-term course of the disease. We believe that including these NHMs into the health economic model to enable the link between the benefit observed with belimumab on the outcomes in the trials to the risk of long-term events, has resulted in a fair estimate of the cost-effectiveness of this medicine.

4. <u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>

We do not believe the provisional recommendations are sound and a suitable basis for guidance to the NHS for the following reasons:

- Belimumab was specifically designed to treat a rare, severely debilitating disease with a significant unmet need where there has been little innovation for 50 years. It specifically binds to BLyS and inhibits its biological activity thus having a beneficial effect on reducing disease activity as demonstrated in two large RCTs.
- Our proposed target population, which we have identified as a cost-effective subgroup to receive belimumab, is considerably smaller than our licensed SLE population and targets treatment to patients with the most serious disease activity and who are likely to gain the most from belimumab. We would also ask the committee to consider the implications of a restricted treatment duration of six years and the implications of a lower discount rate and more stringent continuation rules.
- [redacted]

[redacted] Moreover, in the absence of these biologics being available on the NHS, SLE patients may be admitted to hospital for alternative more expensive treatments such as Intravenous immunoglobulin (IVIG).

- There are aspects of value not fully accounted for in our estimate of cost-effectiveness. Specifically, the full benefit of belimumab on disease flares and chronic fatigue are not adequately captured in the quality adjusted life years (QALYs) derived from EQ-5D utility values. In addition the implications of new evidence supporting a steroid sparing effect for belimumab have not been considered.
- There is no alternative NICE guidance for any other treatment in SLE. If this appraisal results in a negative recommendation for belimumab patients will continue to receive treatments that have not been rigorously assessed for either clinical or cost-effectiveness within the NHS. Specifically the use of rituximab will continue, which is unlicensed for SLE and has not demonstrated any efficacy benefit in RCTs or shown evidence of being a cost-effective medicine in SLE.

5. 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 gender, race, disability, age, sexual orientation, religion or belief?

We have not identified any aspects of the recommendations that require particular consideration to ensure unlawful discrimination is avoided against any group of people.

References

Bencivelli, W., Vitali, C., Isenberg, D. A. et al. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. III. Development of a computerised clinical chart and its application to the comparison of different indices of disease activity. The European Consensus Study Group for Disease Activity in SLE. Clinical and Experimental Rheumatology 10[5], 549-554. 1992.

Gladman, D. D., Urowitz, M. B., Kagal, A. et al. Accurately describing changes in disease activity in Systemic Lupus Erythematosus. Journal of Rheumatology 27[2], 377-379. 2000.

GlaxoSmithKline data on file. 2011.

Griffiths, B., Mosca, M., & Gordon, C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. Best.Pract.Res.Clin Rheumatol. 19[5], 685-708. 2005.

McElhone, K., Abbott, J., & Teh, L. S. A review of health related quality of life in systemic lupus erythematosus. Lupus 15[10], 633-643. 2006.

Merrill, J. T., Neuwelt, C. M., Wallace, D. J. et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 62[1], 222-233. 2010.

Monthly Index of Medical Specialities (MIMS) 2011, Haymarket Medical Media.

Petri, M., Furie, R. A., Wallace, D. J. et al. Six-year experience with belimumab in patients with SLE. Ann Rheum Dis 70 (Suppl 3)[314]. 2011.

Petri, M., Singh, S., Tesfasyone, H. et al. Prevalence of flare and influence of demographic and serologic factors on flare risk in systemic lupus erythematosus: a prospective study. J Rheumatol. 36[11], 2476-2480. 2009.

Stoll, T., Sutcliffe, N., Mach, J. et al. Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus--a 5-yr prospective study. Rheumatology.(Oxford) 43[8], 1039-1044. 2004.

Swaak, A. J., van den Brink, H. G., Smeenk, R. J. et al. Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. Rheumatology.(Oxford) 38[10], 953-958. 1999.

Thumboo, J. & Strand, V. Health-related quality of life in patients with systemic lupus erythematosus: an update. Ann.Acad.Med Singapore 36[2], 115-122. 2007.

Tseng, C. E., Buyon, J. P., Kim, M. et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 54[11], 3623-3632. 2006.

Wailoo, A., Davis, S., & Tosh, J. The incorporation of health benefits in cost utility analysis using the EQ-5D. 15-11-2010.

Zonana-Nacach, A., Roseman, J. M., McGwin, G., Jr. et al. Systemic lupus erythematosus in three ethnic groups. VI: Factors associated with fatigue within 5 years of criteria diagnosis. LUMINA Study Group. LUpus in MInority populations: NAture vs Nurture. Lupus 9[2], 101-109. 2000.

NICE Belimumab response

A) Has all the relevant evidence been taken into account?
As far as we were aware, although reference is made to ERG's consideration of an unpublished trial in para 3.38

B) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
1) the results from 2 clinical trials were submitted, BLISS 52 and BLISS 76: the primary outcome was statistically significant in both trials (3.7). BLISS 76 showed a statistically significant difference in response rate between belimumab and standard care (3.7). We therefore find it difficult to know how the committee can reject the findings of the BLISS 76 trial.

2) the results from BLISS 52 trial (which gives clearer evidence of effect) was not considered so seriously by the committee because of the racial mix not being seen as generalisable to this country's population (3.28, 3.5). We did point out during the meeting that SLE affects all races, but is disproportionately higher and often more serious in certain racial groups; we also pointed out that the racial mix of the UK is now very diverse and wide, for example there is a large Asian population in many large cities in this country (4.6).

The committee's consideration of the clinical evidence (4.6-4.10) seems to waver between acknowledging that BLISS 52 population may have some relevance to UK (4.6: 'pooled analysis could be considered relevant') and dismissing it (4.9: 'the relevance of both the pooled and unspooled data to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, nature of standard care and effects of belimumab on the full range of possible manifestations of SLE'). Whilst accepting that the numbers in each study, when pooled, give a greater weight to the findings of BLISS 52 as the sample size was bigger, we feel that more consideration of data from BLISS 52 should be given by the committee in reaching their decision

3) Evidence for secondary outcomes may not be so clear: lupus patients can have a multiplicity of symptoms (and their often fluctuating or flitting pattern) which make it very difficult for precise endpoints to be observed. For some patients improvement would be outside the remit of the specified secondary outcome measures, but could have given a positive effect during the trials.

There was evidence of a reduction in steroid use, although this may have been insufficient to avoid side effects, lupus patients are always grateful for anything which reduces the need for steroids. It is a great milestone to come off steroids altogether, which unfortunately is very difficult for many people to pass, so any treatment which has some effect would be extremely welcome and a real boost to morale for those where other treatments have not managed to reduce the burden of steroids.

Trials were conducted on patients with a high level of disease activity (score of 10+ SLEDAI) (3.1, 4.4), mainly mucocutaneous, immunological and/or musculoskeletal damage (3.5). These systems may also not give such clear markers of improvement and be open to fluctuation.

Unlike many drug trials where subjects receive either drug or placebo, standard care was continued for all patients in the trials, therefore a clear improvement between those receiving the drug and those on placebo would be less easily observed.

4) some results from BLISS 76 showed improvements early (some at week 24, many at week 52): this seems to have be taken by the committee as evidence that the 76 week trial was less effective,

but this may be indicating that the drug has effect in a shorter period of time than 76 weeks. This information should not lead to dismissing its effectiveness as paras 2.3 and 3.32 states that the drug will be discontinued at 6 months if there is no improvement. This may have a bearing on the length of time the drug would need to be used and therefore the costings.

C) Are the provisional recommendations sound and a suitable basis for guidance in the NHS?
1) Rituximab is given as a comparator within the appraisal document, but 3.13 notes that 'the EXPLORER trial showed no statistically significant differences in major or partial clinical responses between the rituximab group and the placebo group over 52 weeks'. In fact belimumab did meet its primary endpoint and showed some improvement in other symptoms: this would appear to be better 'evidence' for belimumab than for rituximab.

2) What guidance is NICE giving to both lupus patients and their clinicians? It would appear that rituximab is preferred to belimumab by the Appraisal committee for lupus patients, but trials of rituximab were not conducted on lupus patients, so we are left with unclear guidance on prescribing, especially for patients where existing therapies have not been effective and the activity of the disease is out of control and likely to result in either very serious organ damage or death, not allowing time for special application to be made to local trusts for decision.

D) *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 gender, race, disability, age, sexual orientation, religion or belief?*
1) We stated that SLE affects many racial groups more severely than the Caucasian population. Many drug trials are conducted on white male populations: in the BLISS 52 trials we see that belimumab was shown to have better effect on certain racial populations, but the committee thought that this population was not generalisable to the UK population: we feel that this decision will disadvantage certain racial groups where the drug has been seen to be effective.

2) If NICE does not give clear guidance on funding for this drug, we feel that will disadvantage certain racial groups, where English may not be their first language, and they may not have the experience or confidence to challenge decisions made locally.

[redacted]
LUPUS UK 21st October 2011

British Association of Dermatologists

Comments on the appraisal consultation document and evaluation report relating to the use of belimumab for antibody positive systemic lupus erythematosus.

Belimumab, a BlyS specific inhibitor, is licensed in the US for use in antibody positive SLE. A European license has been applied for, and this NICE appraisal is examining the potential role of belimumab in a sub-group of SLE with higher disease activity. I have the following comments:

1. The applicability of combining data from 2 studies in different patient groups from different geographical areas where the characteristics of the patient groups may be different. I agree that this is the case, and the more impressive results from South America etc may well be dependent upon the characteristics of the different patient cohorts. Whether this has relevance to multi-cultural UK is more difficult to say, since non-caucasian patients are very well represented in most LE clinic populations
2. The overall results largely depend on the non-white groups for their positivity, and if the BLISS 76 study is taken alone, there would be little benefit in having belimumab available.
3. The standard of care chosen suggests that cyclophosphamide is not used except for the treatment of nephritis. This is incorrect; it is used for vasculitis and severe skin disease as well. As a consequence, the background therapy used for comparison is too limited. This has particular relevance since the major systems to be benefitted by belimumab in the trials included musculo-skeletal and muco-cutaneous.
4. The descriptive comparisons with rituximab are interesting and valuable, but serve to point out the difficulties of current practice, where clinical trials fail to demonstrate effectiveness of rituximab, but it is a drug still widely used in the management of patients with more severe and persistent disease activity, including vasculitis and particular types of skin involvement, based on a widely held perception that the trials were unreliable and do not reflect experience. In practice, drugs of this nature are funded where clinicians are suitably persuasive on their patients behalf, a situation NICE appraisal was meant to avoid. This leaves NICE with an interesting problem as far as belimumab is concerned, and suggests that their decision, in whichever direction, should be definitive.
5. Even allowing for PAS reductions, this is an expensive drug, and the assumptions made by the manufacturers are all in a direction favourable to its use. It is likely that the impact on additional years of life is less than that assumed, with similar smaller impacts on systems involvement. Against this, the effect on those systems e.g. skin, that do not affect survival, but have a significant effect on quality of life, is under-represented by the NICE analysis, and from a dermatological point of view, this is an area for which there are few effective treatments. The available studies do not adequately define which forms of skin disease may respond, since it is unlikely to be all of them
6. The target group is a post-hoc selection, based on those patients who appeared to respond best. This really needs a further study. It would also be interesting to know if there is a dose response in the activity against skin disease, since if there is, and the 1mg dose was effective, there would be around a 10 fold reduction in cost which would bring the drug into more reasonable costing areas.

7. For what it is worth, I personally doubt if there are currently sufficient supporting data, particularly on cost effectiveness, to justify belimumab's use.

[redacted]
On behalf of the British Association of Dermatologists

Belimumab for Single Technology Appraisal (STA)

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

Response from British Health Professionals in Rheumatology

BHPR thank the appraisal committee for their examination of the evidence and their hard work in preparing this document but are very disappointed with the conclusions.

The NICE appraisal consultation document relating to the use of Belimumab for the treatment of active auto-antibody positive systemic lupus erythematosus has not recommended this treatment as add-on therapy. This response is prepared on behalf of the BHPR and makes the following points in relation to this decision:

1. There is no doubt that Belimumab cannot be compared in comparison cost with conventional therapy and will, of course, be at added cost to the NHS. An important issue is that the trial data reports Belimumab helps to reduce steroid dosage and length of treatment with steroids. The use of long term steroids carry many potential side effects which can impact on quality of life and lead to numerous co-morbidities many of which will have cost and health implications for many years. Whilst Belimumab is not free of side effects, its comparators are greater and significantly impact on individuals' quality of life, capacity to work, mental health status, personal relationships and life aspirations.
2. Clinically, there is a concern about the choices of medication available to lupus teams in the group of patients who are steroid dependent and not responding to conventional therapies, including immunosuppression. Belimumab has met the primary endpoint in both of its pivotal Phase 3 trials, it is FDA approved and approved by European commissioners. This then is a very sensible option for treatment in a group not responding to conventional therapy.
3. Rituximab did not meet its endpoint and therefore did not receive either a licence in lupus or NICE approval. Yet this document directly recommends a head to head trial between Belimumab which has met its primary endpoint and Rituximab which did not meet its endpoint. This will not realistically happen as drug companies would not consider it to be cost effective or in their best interests.
4. The only drugs currently holding a licence for lupus are steroids, Hydroxychloroquine and Belimumab. All other drugs used are off licence and therefore without NICE approval, this will result in clinicians

having to apply with IFRs which may be rejected, resulting in loss of clinical time to the NHS and patient care.

5. Rituximab is widely used to treat lupus and every time this is planned, an IFR has to be completed. Patients understand that these drugs are off license which does not provide them with any significant confidence in its effectiveness.
6. It is anticipated that following response to treatment with Belimumab that infusions can be reduced in frequency and even stopped when in remission. Costings should reflect this in the appraisal document and it is not clear that this has been considered in sufficient detail.

It is therefore our opinion that the NICE appraisal committee should review its decision regarding Belimumab. The opportunity to provide this as a reasonable treatment option for those with active auto-antibody positive muco-cutaneous and musculoskeletal complications of lupus has to be re-considered in the light that these patients are currently on long term steroids and immunosuppression with little potential for stopping these drugs over time. These cause a significant number of side effects, which cannot always be prevented and then impact on quality of life when co-morbidities develop.

British Renal Society's comments on STA on Belimumab for the treatment of SLE

- Has all of the relevant evidence been taken into account?

  We cannot see any obvious omission.

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

  Yes

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

  The two BLISS trials show some modest benefit for mild / modestly active SLE despite significant treatment in the placebo arm. The concern however is that only 34% of the trial patients were in the category being targeted in the submission and only 52% in BLISS 72 and 42% of patients in BLISS 56 were on immunosuppressants in addition to oral steroids, so they are not the patients nephrologists would be putting forward for a biological agent. Cerebral and renal diseases were excluded from the two trials and this is almost always the group of patients that nephrologists are looking for additional treatment for.

- 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 gender, race, disability, age, sexual orientation, religion or belief?

  No

- Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?

  This has been covered in submission by other groups.

The British Society for Rheumatology

Kate Moore
Technology Appraisal Project Manager
National Institute of Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

17th October 2011

Dear Kate

Re: BSR comments of ACD - Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus

- The NICE Committee have focused their attention on a sub-set of patients both clinically and serologically active as GSK had wished. They do seem to have considered the majority of the relevant evidence carefully before coming to their conclusions.
- BSR was not overly impressed by the nature of the presentation given by GSK to NICE in Manchester which was attended by Prof. David Isenberg. The notion the company put forward to bring the biologic treatment of SLE in line with that of patients with rheumatoid arthritis, is based on an unlikely premise, i.e. that as lupus patients suffer from sustained disease activity (like rheumatoid), there would be a continuing need for the use of belimumab for up to 40 years. This seems very unlikely in most cases. In addition (see page 8 of 45 in the appraisal consultation document), given that black patients in the pooled total trial population did better at meeting the primary endpoint in the control group compared to the belimumab group, it is surprising that much of the modelling produced by GSK utilised the John Hopkins cohort, which is known to have a high proportion of black lupus patients.
- BSR broadly agrees with the NICE conclusion that GSK's attempts to demonstrate that belimumab will increase longevity in lupus patients is, at this point, not tenable given the relatively modest amount available about long term outcome on the drug.
- BSR agrees with the NICE Committee's view that the patients included in the BLISS 76 study are more likely to be similar to patients in England and Wales than those included in the BLISS 52 study.
- The critical issue which the NICE committee avoids is as follows:-

  a) Throughout the document, rituximab is frequently referred to as being the obvious comparator and in several places it is expressed that the disappointment that the GSK company have made little use of such data as are available to compare their drug i.e. BENLYSTA with rituximab. However, this is to ignore completely the fact that rituximab in two large trials, one of non-renal lupus and one of renal lupus, did not meet its endpoints. As a consequence, the Primary Care Trusts in the UK are increasingly unwilling to fund its use in patients with lupus. If NICE now block BENLYSTA (which has of course been approved for use in lupus patients (of the type considered in the document) by the FDA and the European commissioners, then what exactly are physicians looking after lupus patients, who have failed standard immunosuppressive

therapy, supposed to do next? NICE is clearly concerned about restraining costs but following NICE's figures, let us assume that 15,000 lupus patients in the UK do exist and that approximately 25% are of an age (over 50) where significant flare becomes much less likely. Then around 11,000 lupus patients are left of whom some say 1200 only would come into the hard to treat category. Assuming that neither rituximab nor BENLYSTA were available to them, significant danger exists that these patients would have to be admitted to hospital and treated with a very high dose intravenous steroids (with many potential complications) intravenous immunoglobulin (very expensive) or go back to a drug such as intravenous cyclophosphamide/mycophenolate. Each of the options is expensive (by virtue of it having to be given intravenously in the case of cyclophosphamide or just the unit cost of the drug (in the case of mycophenolate and IvIg) which they may well have failed previously. These seem far from ideal options and in these circumstances the possibility of using BENLYSTA at a significantly reduced cost from the company for a modest period of time e.g. six months to see if it can help to stabilise the patient's disease and reduce concomitant steroid therapy seems both an attractive proposition clinically and financially.

Yours sincerely,

[redacted]

[redacted]

The British Society for Rheumatology
Bride House, 18-20 Bride Lane
London EC4Y 8EE
Tel + 44 (0) 20 7842 0900
Fax + 44 (0) 20 7842 0901

Email bsr@rheumatology.org.uk
Web www.rheumatology.org.uk
Subscriptions & Membership:
Tel +44 (0) 1952 214061
Email subscriptions@rheumatology.org.uk

PRIMARY CARE RHEUMATOLOGY RESPONSE TO THE ACD on BELIMUMAB

1. The Primary Care Rheumatology society (PCRS) are disappointed that NICE do not feel that Belimumab has an active part to play in the management of active SLE.
2. We feel that SLE is such a multi-factorial disease that trials have not been able to demonstrate a significant effect for any of the newer drugs which are used to treat it; for example Rituximab.
3. Rituximab is however used with excellent results to treat some patients with SLE.
4. We are concerned that a refusal to allow clinicians to use Belimumab will also jeapordise the use of Rituximab in patients with SLE. In the current times of financial constraints within PCTs, funding for Biologic drugs is already threatened. We feel that PCTs will start to refuse finding for Rituximab for SLE, as there is a lack of good evidence for its efficacy, but it does undoubtedly work in the correctly selected patients.
5. This will leave patients with active SLE, no option but to be treated with high dose steroids and immunosuppressive drugs, which are all potentially harmful.
6. We do not feel that patients with SLE have been allowed to comment sufficiently upon this decision.
7. We consider it inhumane to deprive patients of a drug which could be potentially curative for their disease, just because it is not economical to treat everyone with SLE.
8. In calculating the economic data and QALYs, we are aware that no account has been taken of the financial effect of patients with SLE having to cease work and become dependent on benefits.
9. If the lifetime effect of being on state benefits was taken into account and the lack of economic productivity for that patient, we are certain that it would become cost-effective to use Belimumab.
10. We would like to ask NICE to look back upon the ACD for using anti-TNF drugs to treat Rheumatoid arthritis and its initial refusal on an economic basis. The National Audit Office have now produced a report which supports the use of Biologic drugs in RA (1) and clearly states that it is cost-effective to use Biologic drugs because of the lifetime positive effects of keeping these patients in work and preventing them from needing to use health and social care when they become dependent.
11. The PCRS strongly feel that the evidence for Belimumab has yet to evolve and that given more time and a more specific economical analysis, this drug would be shown to be cost-effective.

Refs. 1.

1.. Services for people with rheumatoid arthritis; National audit Office

- Publication date: **15 July 2009**

ACD on Belimumab for the Treatment of active autoantibody-positive systemic lupus erythematosus
Response by [redacted] on behalf of the Renal Association

- **Has all of the relevant evidence been taken into account?**
  The evidence has been well considered in particular the lack of availability of a direct comparison with Rituximab.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
  The summaries of clinical effectiveness have erred on the side of caution.
  a) The ACD highlights that the population in BLISS-76 reflects the England and Wales population more closely than that in BLISS-52. However, patients with lupus in England and Wales are not representative of the population as a whole as they tend to be much more ethnically varied and hence BLISS-52 may be as appropriate as BLISS-76. As the committee noted, more outcomes were significantly improved with Belimumab in BLISS-52 than BLISS-76.
  b) There are several comments about the arbitrary nature of a SELENA-SLEDAI score of >10 being significant and of stopping at 24 weeks if improvement in SELENA-SLEDAI score being not greater than 4. However, current clinical practice is much more arbitrary and scoring systems are not in routine use in most lupus clinics. Ensuring that responses are documented with scoring would be a huge improvement in the management of patients with lupus and the inclusion of the BILAG and PGA scores (as used in the SRI) would improve this further. The BLISS trials are to be commended for including formal scoring and the recommendation of a target population and the use of scoring to asses the benefit of therapy would be advantageous. Patients often remain on treatments that are ineffective for prolonged periods and responses are often poorly judged. Whilst a score of 10 is fairly arbitrary it does require significant clinical disease that would be noticeable to patients and therefore is meaningful.
  c) Standard of care is not standard in England and Wales – treatment approaches vary by unit and individual clinician and reflect the lack of trial data in the "target" population described in the manufacturer's submission. Patients could be on a range of treatments though for musculoskeletal and skin involvement are less likely to be on Rituximab but are likely to be on steroid sparing agents if severe. Hence the SOC treatments in both trials are reasonable representations of the SOC likely to be given to different lupus patients in England and Wales.

  In the economic analysis more consideration should be given to:
  a) consideration that in practice Belimumab is likely to be discontinued e.g. after a maximum of 2 years. The manufacturer's suggestion that it might be a lifelong treatment is surprising and not in keeping with current approaches to treatment, especially with biologicals. It is very

likely that clinicians would plan a course of treatment and then either to increase dosage intervals or simply stop and see how patients fared. This would significantly reduce costs.

b) If review at 6 months is mandated, the scoring could be more rigorous (though this is not based on the data available) and for instance insistence on an improvement of at least 6 rather than 4 in SELENA-SLEDAI score being a guide to stopping treatment (or a failure of trend to improvement might be clinically more meaningful). This would reduce the numbers of patients being treated and reduce costs.

c) Cost effectiveness based on mortality is not hugely relevant in the early phase of lupus as the mortality rates, although hugely elevated compared to a normal population, are not absolutely high. The clinical issues are those that allow maintenance of normal life (being able to work, look after children, have safe pregnancies) with minimum short and long term adverse events. Any drug which reduces the exposure to steroids is likely to be cost effective both to the individual and to the NHS.

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**
  On the basis of the comments above, there is room to reconsider cost effectiveness. There is a desperate need for new licensed therapies for lupus and whilst Belimumab may not be a perfect agent, there is evidence for its effectiveness. Skin and musculoskeletal problems in lupus can be hugely debilitating and often require very large doses of steroids – abhorrent drugs for a young, predominantly female population and associated with increased damage and premature mortality in the long term. It is not clear that this has been adequately considered in the cost effectiveness appraisal and will be a major issue for patients.

- **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 gender, race, disability, age, sexual orientation, religion or belief?**
  Lupus predominantly affects women of child bearing age from ethnic minority groups – by failing to recommend Belimumab, it is these groups that will be predominantly affected.

[redacted]
21/10/2011

National Institute for Health and Clinical Excellence

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

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus.

Nurses caring for people with lupus were invited to review the consultation document on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus. We note that the Appraisal Consultation Document has not recommended this treatment as add-on therapy.

The RCN's response to the four questions on which comments were requested is set out below:

i) **Has the relevant evidence been taken into account?**
No comments to add at this stage.

ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?**

There is no doubt that the cost of Belimumab cannot be compared with that of conventional therapy and will of course, be at added cost to the NHS. An important issue is that the trial data reports that Belimumab helps to reduce steroid dosage and length of treatment with steroids. The use of long term steroids carry many potential side effects which can impact on quality of life and lead to numerous co-morbidities many of which will have cost and health implications for many years. Whilst Belimumab is not free of side effects, its comparators are greater and significantly impact on individuals' quality of life, capacity to work, mental health status, personal relationships and life aspirations.

Clinically, there is a concern about the choices of medication available to lupus teams in the group of patients who are steroid dependent and not responding to conventional therapies, including immunosuppression. Belimumab has met the primary endpoint in both of its pivotal Phase 3 trials, it is FDA approved and approved by European commissioners. This then is a very sensible option for treatment in a group not responding to conventional therapy.

Rituximab did not meet its endpoint and therefore did not receive either a licence in lupus or NICE approval. Yet this document directly recommends a head to head trial between Belimumab which has met its primary endpoint and Rituximab which did not meet its endpoint. This will not realistically happen as drug companies would not consider it to be cost effective or in their best interests.

The only drugs currently holding a licence for lupus are steroids, Hydroxychloroquine and Belimumab. All other drugs used are off licence and therefore without NICE approval, this will result in clinicians having to apply with IFRs which may be rejected, resulting in loss of clinical time to the NHS and patient care.

Rituximab is widely used to treat lupus and every time this is planned, an IFR has to be completed. Patients understand that these drugs are off licence which does not provide them with any significant confidence in its effectiveness.

It is anticipated that following response to treatment with Belimumab that infusions can be reduced in frequency and even stopped when in remission. Costings should reflect this in the appraisal document and it is not clear that this has been considered in sufficient detail.

iii) **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?**

We consider that the NICE appraisal committee should review its decision regarding Belimumab. The opportunity to provide this as a reasonable treatment option for those with active auto-antibody positive muco-cutaneous and musculoskeletal complications of lupus has to be re-considered in the light that these patients are currently on long term steroids and immunosuppression with little potential for stopping these drugs over time. These cause a significant number of side effects, which cannot always be prevented and then impact on quality of life when co-morbidities develop.

iv) **Are there any equality related issues that need special consideration that are not covered in the ACD?**

None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.

Response to the Appraisal Consultation Document from the Royal College of Pathologists

Please note that the Royal College of Pathologists agree with the key conclusions (1.1, 4.19 & 4.21)

Regards

[redacted]

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	NHS Bolton are one of the official consultees for this technology appraisal. Responses are representative of the organisation not from myself as an individual.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	NHS Bolton would agree with the proposed recommendation based on the presented clinical and cost-effectiveness data. The ICER for the drug without a patient access scheme in place is not a cost-effective use of resources compared to standard care (ICER of Â£64,410 - Â£71,000 per QALY gained). Although a patient access scheme has been submitted, the ICER still continues to be higher than that usually considered by NICE to be cost-effective use of NHS resources. The data presented did not provide a case for comparing belimumab against rituximab (current standard practice although unlicensed) in terms of cost-effectiveness again supporting the case that this is not a cost-effective use of NHS resources or affordable.
Section 2 (The technology)	NHS Bolton agrees that the use of this drug should be in patients who have a high-degree of disease activity only (despite the wider marketing authorisation). With regard to dosing, more frequent doses are required for belimumab compared to rituximab which will lead to additional patient hospital attendances and hence cost. During the first 6 months of treatment (suggested review period) the patient will need to attend hospital on 7 occasions (more if additional monitoring is required), compared to current practice with rituximab this is a greater inconvenience for the patient. There is also the opportunity with rituximab to utilise homecare services, however NHS Bolton is not sure whether this option would be available to patients for belimumab infusions. NHS Bolton would support the manufacturers proposed PAS (a discount on the list price) being offered, as this ensures minimal administrative burden for provider, commissioner and manufacturer. The current level of discount in the PAS however would seem insufficient to meet the required levels of cost effectiveness required.
Section 3 (The manufacturer's submission)	There was no direct comparison of efficacy made between belimumab and rituximab (current, standard care for this group of patients a relevant comparator). No information in the trial data, identified if patients had received previous treatment with rituximab. In practice, patients who would fit the clinical criteria for belimumab may have previously received rituximab it is unknown whether safety or efficacy data is available to support any sequential use. Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care (when considering

	functional assessment at week 52 comparing standard care and belimumab therapy). The costs presented in the model for administration costs of belimumab are felt to be underestimated in relation to practice. It is more likely that the tariff of day case admission will be used, which will increase the costs. Additional costs of making up the infusion per individual patient (as based on weight) in a pharmacy aseptic unit would also need to be considered.
Section 4 (Consideration of the evidence)	Patient populations in the BLISS studies did not include patient participants from the UK hence it is difficult to determine if the patients in the trial are representative of patients with SLE and high-disease activity in the UK. This would include age, sex, gender, medicines management, criteria for diagnosis etc. The review time for belimumab in the model was at 24 weeks, based on an assessment of the SELENA-SELEDAI score. Experts suggested that if the score was shown to be less than 4 points (i.e. some benefit of treatment) they may still continue with belimumab ? this would affect the % of patients stopping in practice when compared to the trial and costs would be higher than predicted, which could be an unexpected cost pressure to the payer. NHS Bolton supports the development of new, novel agents however they must be cost-effective and affordable to the NHS. Budgets are no longer increasing. To fund drugs that are less cost-effective (e.g. by analysis of ICERs/ QALYs) than NICE deems cost-effective would be very difficult to justify, when decisions are being made to refuse treatments which have greater clinical evidence in some cases. To fund this drug, other services may need to be decommissioned and taking into account the cost-differential of rituximab, the currently used standard of care, Â the difference in affordability is likely to be still too great to justify use.
Section 5 (Implementation)	These tools are useful when a technology is recommended for use.
Section 6 (Proposed recommendations for further research)	No comments
Section 7 (Related NICE guidance)	No comments
Section 8 (Proposed date of review of guidance)	No comments
Date	10/21/2011 9:57:00 AM

csas
Commissioning Support
Appraisals Service

www.sph.nhs.uk/appraisals
Tel: +44 (0)1865 334787
Email: askappraisals@sph.nhs.uk

10th October 2011

National Institute for Health and Clinical Excellence

Dear Ms Moore

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

On behalf of Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus.

We are in agreement with the recommendations in the ACD not to recommend belimumab for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective.

- **Belimumab is not a cost effective use of NHS resources compared to standard care.** The ICER without the patient access scheme (PPRS) was between £64,400 and £71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources.
- **Belimumab is not considered a cost effective use of NHS resources compared to rituximab.** No sound case was presented on the cost effectiveness of belimumab compared to rituximab.
- **No direct comparison of efficacy was made between belimumab and rituximab.** Rituximab is used increasingly in patients with severe disease and is therefore a relevant comparator which should have been considered.
- **Generalisability of findings from the BLISS studies to the UK population is uncertain.** Approximately 50% of patients enrolled in both BLISS trials were receiving an immunosuppressant whereas standard therapy in the UK for most SLE patients would include an immunosuppressant. Patients enrolled in the BLISS-52 study were recruited from South America, Asia and Eastern Europe and so are not representative of a UK population. Most patients included in the BLISS trials had mucocutaneous and musculoskeletal manifestations of SLE. The effect of belimumab on the full range of possible manifestations of SLE is therefore unknown.
- **There were numerous uncertainties about the plausibility of assumptions in the manufacturer's economic model.** The manufacturer's model may have underestimated the ICER: it was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population; the number of patients discontinuing treatment at 24 weeks may have been overestimated; it was assumed that treatment effect would be maintained over time; it was unclear whether the modelled gains survival were valid; and cost

www.sph.nhs.uk/appraisals
Tel: +44 (0)1865 334787
Email: askappraisals@sph.nhs.uk

data was derived from various sources which may have given inconsistent estimates.

- **Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care.** Functional assessment of chronic illness therapy (FACIT)-fatigue scores were not significantly better at week 52 in people receiving belimumab compared to standard care.

If you require any further information please contact me directly.

Yours sincerely

[redacted]

[redacted]

[redacted]

[redacted]

Email: [redacted]

[redacted]

[redacted]

[redacted]

Email: [redacted]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	other
Other role	Patient Advocacy Organization
Location	US
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The Lupus Foundation of America is concerned that your preliminary recommendation could have a devastating international impact. Â For more than a half-century, people with lupus have expressed a desire for more tolerable and safe alternatives to the damaging therapies currently available. Â Current therapies for lupus, some considered ?standard of care,? were never properly tested or approved for lupus. Â Many of these drugs come with short and long-term side effects that can be worse than the disease itself. Â An international study, which followed a large number of lupus patients over several decades, found that half of the physical damage experienced by patients was the result of the therapies used to manage the disease. Â The lower costs of existing drugs mask the simple fact that their significant side effects are associated with an egregious rise in disabilities, hospitalizations and extreme long-term medical expenditures. Â If your recommendation stands, the decision will have a chilling effect on global industry investment in the development of new treatments for lupus, denying physicians and patients appropriate options to treat this complex and underserved disease.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	10/21/2011 2:38:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The ICER without the patient access scheme (PPRS) was between Â£64,400 and Â£71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. No sound case was presented on the cost effectiveness of belimumab compared to rituximab. Should NICE reverse its decision to support its use any service redesign would require full commissioning input therefore it would be impossible to comment on which services, if any, would have to be reduced.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	No direct comparison of efficacy was made between belimumab and rituximab which is considered standard treatment. Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care.
Section 4 (Consideration of the evidence)	The generalisability of the findings from the BLISS studies to the UK population is uncertain as patients enrolled in the BLISS-52 study were recruited from South America, Asia and Eastern Europe, therefore are not representative of a UK population. The manufacturer?s model may have underestimated the ICER: it was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population the number of patients discontinuing treatment at 24 weeks may have been overestimated it was assumed that treatment effect would be maintained over time it was unclear whether the modelled gains survival were valid and cost data was derived from various sources which may have given inconsistent estimates.
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	10/20/2011 4:49:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	

Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We believe that NICEs appraisal is a reasonable representation of the effectiveness and cost-effectiveness of this drug for this indication, given the limited evidence (only 2 RCTs). We agree with NICE?s assessment and any reversal of the decision (wihout further substantive evidence bring the conclusions into doubt) would result in resources having to be diverted from more cost-effective interventions, harming the overall health of our population.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	10/20/2011 3:34:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	no conflicts
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We agree with this recomendation. Belimumab is not a cost effective use of NHS resources compared to standard care. The ICER without the patient access scheme (PPRS) was between Â£64,400 and Â£71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. Belimumab is not considered a cost effective use of NHS resources compared to rituximab. Â No sound case was presented on the cost effectiveness of belimumab compared to rituximab.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	No direct comparison of efficacy was made between belimumab and rituximab. Rituximab is used increasingly in patients with severe disease and is therefore a relevant comparator which should have been considered. RTX IS a de facto comparator in that it is widely used in this context in the NHS, and many PCTs routinely fund RTX in this setting. Belimumab did not demonstrate improved health-related quality

	of life benefits compared to standard care. Functional assessment of chronic illness therapy (FACIT)-fatigue scores were not significantly better at week 52 in people receiving belimumab compared to standard care.
Section 4 (Consideration of the evidence)	Generalisability of findings from the BLISS studies to the UK population is uncertain. Â Approximately 50% of patients enrolled in both BLISS trials were receiving an immunosuppressant whereas standard therapy in the UK for most SLE patients would include an immunosuppressant. Patients enrolled in the BLISS-52 study were recruited from South America, Asia and Eastern Europe and so are not representative of a UK population. Â Most patients included in the BLISS trials had mucocutaneous and musculoskeletal manifestations of SLE. Â The effect of belimumab on the full range of possible manifestations of SLE is therefore unknown. There were numerous uncertainties about the plausibility of assumptions in the manufacturer?s economic model. The manufacturer?s model may have underestimated the ICER: it was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population the number of patients discontinuing treatment at 24 weeks may have been overestimated it was assumed that treatment effect would be maintained over time it was unclear whether the modelled gains survival were valid
Section 5 (Implementation)	Unit costs: Belimumab is given at a recommended dose of 10 mg/kg belimumab on days 0, 14 and 28, and at 4 week intervals thereafter, with discontinuation of treatment if there is no improvement after 6 months. The list price of belimumab is Â£121.50 for a 120mg vial and Â£405 for a 400mg vial, though costs may vary in different settings because of negotiated procurement discounts. The manufacturer has agreed a patient access scheme with the Department of Health, which gives a discount on the list price. The size of the discount is commercial-in-confidence.
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	10/17/2011 3:22:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Belimumab is not a cost effective use of NHS resources compared to standard care. The ICER without the patient access scheme (PPRS) was between Â£64,400 and Â£71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. Belimumab is not considered a cost effective use of NHS resources compared to rituximab. Â No sound case was presented on the cost effectiveness of belimumab compared to rituximab.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	No direct comparison of efficacy was made between belimumab and rituximab. Rituximab is used increasingly in patients with severe disease and is therefore a relevant comparator which should have been considered Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care. Functional assessment of chronic illness therapy (FACIT)-fatigue scores were not significantly better at week 52 in people receiving belimumab compared to standard care.
Section 4 (Consideration of the evidence)	Generalisability of findings from the BLISS studies to the UK population is uncertain. Â Approximately 50% of patients enrolled in both BLISS trials were receiving an immunosuppressant whereas standard therapy in the UK for most SLE patients would include an immunosuppressant. Patients enrolled in the BLISS-52 study were recruited from South America, Asia and Eastern Europe and so are not representative of a UK population. Â Most patients included in the BLISS trials had mucocutaneous and musculoskeletal manifestations of SLE. Â The effect of belimumab on the full range of possible manifestations of SLE is therefore unknown. Manufacturer?s model may have underestimated the ICER: was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population the number of patients discontinuing treatment at 24 weeks may have been overestimated assumed that treatment effect would be maintained over timewas unclear whether the modelled gains survival were valid and cost data was derived from various sources which may have given inconsistent estimates
Section 5 (Implementation)	PCT/ CCP would need to consider services we might be forced to reduce if this technology were to be funded.
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	

Section 8 (Proposed date of review of guidance)	
Date	10/17/2011 12:34:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Belimumab is not a cost effective use of NHS resources compared to standard care. The ICER without the patient access scheme (PPRS) was between Â£64,400 and Â£71,000 per QALY, and with the PPRS applied the ICER still remained above the threshold range usually considered an acceptable use of NHS resources. Belimumab is not considered a cost effective use of NHS resources compared to rituximab. Â No sound case was presented on the cost effectiveness of belimumab compared to rituximab.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	No direct comparison of efficacy was made between belimumab and rituximab. Rituximab is used increasingly in patients with severe disease and is therefore a relevant comparator which should have been considered. Belimumab did not demonstrate improved health-related quality of life benefits compared to standard care. Functional assessment of chronic illness therapy (FACIT)-fatigue scores were not significantly better at week 52 in people receiving belimumab compared to standard care.
Section 4 (Consideration of the evidence)	Generalisability of findings from BLISS studies to UK population is uncertain. Â Approximately 50% of patients enrolled in BLISS trials were receiving an immunosuppressant whereas standard therapy in the UK would usually include an immunosuppressant. Patients enrolled in BLISS-52 study were recruited from South America, Asia and Eastern Europe and are not representative UK population. Â Most patients included in the BLISS trials had mucocutaneous and musculoskeletal manifestations of SLE. Â The effect of belimumab on the full range of possible manifestations of SLE is therefore unknown. There were numerous uncertainties about the plausibility of assumptions in the manufacturer?s economic model. The manufacturer?s model may have underestimated the ICER: it was uncertain whether the equations derived from a longer term cohort of patients with less active disease could be applied to the trial population the number of patients discontinuing treatment at 24 weeks may have been overestimated it was assumed that treatment effect would be maintained over time it was unclear whether the modelled gains survival were valid and

	cost data was derived from various sources which may have given inconsistent estimates
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	10/12/2011 3:38:00 PM

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	10/11/2011 8:43:00 PM

Name	[redacted]
Role	Patient
Other role	nurse
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	I dont believe you have taken into account the full cost of looking after a very poorly lupus patient. I am not even the most sever case of lupus and the amount of drug gp and multi consultant time i have put into my management. if i had less organ damage and less consultants less other medications and tests. not only this i would be better, off benefits and able to work and not need social care. i am really dissapointed to hear of your decsion against the first drug really recognised as being effective in SLE for Fifty years. were not asking for it as a first line treatment just when all other options have failed. please recondiser your decsion and give lupus patients some hope. many drugs have already failed the research and development stage for SLE because its a hard disease to shoe up in blood results. My blood results rarely accuratly reflect my disease activity. so you may well be underestimating the benefit to the individual.
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	10/11/2011 7:01:00 PM

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Should be recommended
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	drug has been specifically developed like no other, reduce need for other drug with bad side effects, lupus is extremely dehabilitating .i.e. ruins lives!!
Section 5 (Implementation)	should NOT be a postcode lottery
Section 6 (Proposed recommendations for further research)	agreed
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	10/6/2011 1:40:00 AM

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
SPECIAL HEALTH AUTHORITY

Single Technology Appraisal (STA)

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

Report to the Appraisal Committee following receipt of a petition during the Appraisal Consultation in September 2011

Lupus Europe, Lupus Foundation of America, and St. Thomas' Lupus Trust UK submitted on behalf of the International Lupus Patient Community a petition to NICE regarding the consultation on the draft guidance for the appraisal of belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus.

The petition was sent with a covering letter, which is shown below in Appendix one, and which was signed on behalf of many international lupus organisations.

The paper copy of the petition that we received had 3169 signatories on it, some of whom had included personal stories or comments. An example of this has been included below as Appendix Two.

The petition had been set up online and the full responses can be seen here - http://www.thepetitionsite.com/1/cover-Benlysta/

Appendix One – Cover letter received with the International Lupus Patient Community petition

International Lupus Patient Community Urges NICE to Cover Benlysta®

Lupus Europe • Lupus Foundation of America • St. Thomas' Lupus Trust, U.K.

October 21, 2011

Sir Andrew Dillon
Chief Executive
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

24 OCT 2011

Dear Sir Andrew:

The undersigned international lupus organizations, representing millions of people affected by lupus worldwide, are deeply concerned about the United Kingdom's National Institute for Health and Clinical Excellence (NICE) preliminary appraisal recommendation that Benlysta® not be covered through the publicly funded National Health Service. We believe that this decision could have a devastating international impact on the survival of this treatment and ask that the Institute consider the comments of the worldwide patient community as it prepares the final appraisal determination (FAD) for use of Benlysta®.

The advent of Benlysta® represents several significant firsts for lupus, a life threatening and disabling disease with few approved treatments. Benlysta® is the first therapy specifically developed for lupus since the disease was first recognized in the mid 1800's. It is the first to specifically address an important underlying pathology of this disease. In addition, it is the first to successfully complete two international Phase III clinical studies, which are the largest ever conducted for lupus.

These firsts are in contrast to current therapies for lupus, some considered "*standard of care,*" that were never properly tested or approved for lupus. Many of these drugs come with short and long-term side effects that can be worse than the disease itself, including bone loss, osteoporotic fractures, infertility, serious and sometimes fatal infections, obesity, depression, cardiovascular complications, vision loss and more.

An international study, which followed a large number of lupus patients over several decades, found that half of the physical damage experienced by these patients was the result of the therapies used to manage the disease.[i] The lower costs of existing drugs mask the simple fact that their significant side effects are associated with an egregious rise in disabilities, hospitalizations and extreme long-term medical expenditures. These include, over the lifetime of the disease, costs for joint replacements, hospitalizations, rehabilitation, long term home care, and many additional medications which become necessary to mitigate the consequences of the toxic and disabling treatments which are deemed to be so "cost-effective." This is

without even considering the human and economic toll on families and other caregivers as our patients battle this chronic lifelong illness with the toxic and inadequate available treatments.

For more than a half-century, people with lupus and their doctors have expressed a desire for more tolerable and safe alternatives to the damaging therapies currently available. The preliminary appraisal recommendation by NICE dashes the new hope in our lupus community, including patients, their families and physicians, that new treatments will finally become available.

Lupus is the prototypical autoimmune disease that affects more than five million people worldwide. If the preliminary appraisal recommendation from the UK stands, the decision will have a chilling effect on global industry investment in the development of new treatments for lupus, denying physicians and patients appropriate options to treat this complex and underserved disease.

Given the diversity in the way lupus affects patients, it is implausible to believe one therapy will be effective for all patients. The heterogeneity of lupus dictates the need for a full arsenal of therapies. Quixotically, this makes it harder to demonstrate efficacy for any one agent. Added to this is the requirement by regulatory agencies that patients stay in these trials for an entire year, which led most experts to conclude that the only ethical and safe way to conduct these trials would be to allow aggressive background treatments during the study, and to even allow these treatments to be increased if patients were not doing well.

The modest differences seen between those treated with Benlysta® and those who were not can be easily understood by the limited number of patients who could be expected to respond to any single targeted treatment and the relatively robust number who are likely to respond, over a year's time with the background medications that were allowed. The odds of any treatment succeeding under these dual restrictions seem poor at best.

Benlysta® has already beaten these odds to successfully demonstrate effectiveness in two large, international clinical trials, but by denying its availability to patients, there will be little incentive for companies to invest any further in new therapies for lupus. Therefore, we urge NICE to reconsider its preliminary appraisal recommendation and approve Benlysta® for coverage.

Yours faithfully,

Arthritis Victoria (Australia)
Asociación de Lupicos de Asturias (Spain)
Asociación Galega de Lupus (Spain)
Asociacion Leonesa de Lupus y Sindrome Antifosfolipido (Spain)
Asociación Lupus Argentina (Argentina)
Asociación Lupus de Cantabria (Spain)
Associació Catalana de Lupus E.G (Spain)
Association Lupus érythémateux, asbl (Belgium)
Asociacion Lupus Sonora IAP (Mexico)

Sir Andrew Dillon
October 21, 2011

Federación Española de Lupus (Spain)
Lupus Cyprus (Cyprus)
Lupus Canada (Canada)
Lupus Europe; Representing:
- *Belgium*
- *Cyprus*
- *Denmark*
- *Finland*
- *France*
- *Germany*
- *Hungary*
- *Iceland*
- *Ireland*
- *Italy*
- *Malta GC*
- *Netherlands*
- *Norway*
- *Portugal*
- *Romania*
- *Slovenia*
- *Spain*
- *Sweden*
- *Switzerland*
- *United Kingdom*

Lupus Foreningen i NRF (Norway)
Lupus Foundation of America, Inc. (United States)
Lupus Foundation of Jamaica (Jamaica)
Lupus Foundation of Ontario (Canada)
Lupus Foundation of the Philippines, Inc. (Philippines)
Lupus France (France)
Lupus Inspired Advocacy/Rheumatology Educational Trust Foundation, Inc (Philippines)
Lupus New Brunswick (New Brunswick, Canada)
Lupus Patienten Groep (The Netherlands)
Lupus Society of Alberta (Alberta, Canada)
Lupus SK Society Inc. (Saskatchewan, Canada)
St. Thomas' Lupus Trust, UK (United Kingdom)
Syamsi Dhuha Foundation (Indonesia)

---

[i] Gladman DD, Urowitz MB. Accrual of Organ Damage Over Time in Patients with Systemic Lupus Erythematosus, The Journal of Rheumatology 2003; 30:9

Appendix Two - International Lupus Patient Community Petition text and examples of responses

Sir Andrew Dillon, Chief Executive, National Institute of Health and Clinical Excellence (NICE), UK

We, the undersigned, band together to urge the National Institute for Health and Clinical Excellence's (NICE) to reverse their preliminary recommendation that Benlysta, a new safe and effective treatment for systemic lupus erythematosus, not be covered through the National Health Service. Your preliminary recommendation could have a devastating international impact on the survival of this important new treatment, and it may have a chilling effect on the future development of new lupus drugs thereby denying physicians and patients appropriate treatment options.

Lupus is a prototypical autoimmune disease that affects more than five million people worldwide. For more than a half century, people with lupus and their doctors have expressed a desire for more tolerable and safe alternatives to the damaging therapies currently available.

A large-scale international study found that half of the physical damage experienced by lupus patients was the result of existing therapies used to manage their disease. The short-term lower costs of existing drugs mask the simple fact that their significant side effects are associated with an egregious rise in disabilities, hospitalizations and extreme long-term medical expenditures. This is without even considering the human and economic toll on families and other caregivers as patients battle this chronic lifelong illness with the toxic and inadequate available treatments.

Therefore, we call on NICE to recommend the National Health Service provide coverage of Benlysta.

	Name	From	Comments
1.	[redacted]	Chelmsford, Essex, United Kingdom	
2.	[redacted]	Silver Spring, MD	
3.	[redacted]	Lympne, United Kingdom	
4.	[redacted]	Newcastle, United Kingdom	14 years ago when I was 14 my mum died aged 45 from lupus. I wish with all my heart that this treatment had been around and available to her back then as she may still have been with us now. I cannot believe that there is a ray of hope for lupus sufferers and their families in the form of this new treatment yet they are to be denied the opportunity for life due to funding. Please reconsider this decision which effectively puts a monetary value on the life of lupus sufferers.
5.	[redacted]	Washington, DC	
6.	[redacted]	Silver Spring, MD	
7.	[redacted]	Arlington, VA	
8.	[redacted]	Washington, DC	

	Name	From	Comments
1,503.	[redacted]	Widnes, United Kingdom	
1,504.	[redacted]	cornwlll, United Kingdom	
1,505.	[redacted]	Rickmansworth, United Kingdom	
1,506.	[redacted]	Atlanta, GA	
1,507.	[redacted]	Sydney, Australia	
1,508.	[redacted]	Thetford, United Kingdom	please help make my wife better
1,509.	[redacted]	Bondi Junction NSW, Australia	Please give SLE sufferers like me a chance to have a better life.
1,510.	[redacted]	Ennis, TX	
1,511.	[redacted]	South Coogee, Australia	My sister has Lupus
1,512.	[redacted]	Barcelona, Spain	My Lupus was diagnosed 20 years ago and it has been treated with Cortisone since then . So far is estabilized with some rashes and other kind of outbreak. I think that if in the UK is not covered by the NHS neither will do other countries.
1,513.	[redacted]	South Coogee, Australia	My sister in law has Lupus
1,514.	[redacted]	Sydney, Australia	
1,515.	[redacted]	Sydney, Australia	
1,516.	[redacted]	Purcellville, VA	My daughter contraced Lupus when she was 19 and has struggled with it for all of her adult life. She is now 46 and has just begin the new tretments and we are hoping for the best.
1,517.	[redacted]	Horicon, WI	I will be starting Benlysa soon. I am thankful that I have the opportunity to try a treatment that could help me.
1,518.	[redacted]	Hitchin, United Kingdom	I have had Lupus since I was 10 and it really upsets me that we have a new life saving drug but apparently its not worth paying for. This doesn't make sense at all. Surely if theres a drug that could save your life you should be entitled to have it.
1,519.	[redacted]	Hamilton, NJ	
1,520.	[redacted]	Surry Hills, Australia	
1,521.	[redacted]	Cheshire, United Kingdom	
1,522.	[redacted]	Pittsburgh, PA	
1,523.	[redacted]	farum, Denmark	

	Name	From	Comments
2,186.	[redacted]	Sulzbach, Germany	
2,187.	[redacted]	Granite Falls, MN	
2,188.	[redacted]	Berlin, NJ	
2,189.	[redacted]	Havertown, PA	People should be givin the option for treatment. I also have friends who suffer from Lupus.
2,190.	[redacted]	isle of wight, United Kingdom	
2,191.	[redacted]	stockport, United Kingdom	
2,192.	[redacted]	Greater Manchester, United Kingdom	
2,193.	[redacted]	Carneys Point, NJ	
2,194.	[redacted]	chicago ridge, IL	
2,195.	[redacted]	Taunton, United Kingdom	
2,196.	[redacted]	Miami, FL	
2,197.	[redacted]	Shawnee, OK	I have many friends who suffer from Lupus. Treatment options should be made available to every person.
2,198.	[redacted]	Omagh, United Kingdom	I have had lupus symptoms since I was 10, I have gone on a roller coaster ride just getting a diagnosis in my 30's being told it was growing pains, hormonal, in my head, so much pain, I think the day that I waken up without something sore is the day I will think there is something wrong but I believe I could adapt to a normal life lol- I hope this drug becomes available worldwide. I live in N. Ireland a friend of mine in USA is having a great result being on this drug... I know it may not help us all but it is brilliant that it is helping some. I am 46 now and I would love to know what feeling normal is actually like...
2,199.	[redacted]	Asheville, NC	
2,200.	[redacted]	port st lucie, FL	My 18 year old daughter has lupus and it has ruined her life. Please give this medicine a chance.
2,201.	[redacted]	Merced, CA	I was diagnosed with lupus 5 months ago and my life has drastically changed in so many ways. I am please asking you to please give us a chance to live a life with a possible treatment that targets the lupus. I hope to one day be able to live a normal productive life again, give us that chance please.
2,202.	[redacted]	dubai, United Arab Emirates	
2,203.	[redacted]	Raleigh, NC	
2,204.	[redacted]	Woodbury, CT	

Appendix 1
Additional cost-effectiveness analyses relevant to this Single Technology Appraisal

Provided below are the results from the health economic analysis for our proposed target (high disease activity) SLE subgroup incorporating our revised base case with a maximum treatment duration of six years and a treatment continuation criterion (SS score decrease of ≥4) after six months treatment. All ICERs quoted in this appendix incorporate the drug acquisition cost discount detailed in our proposed patient access scheme.

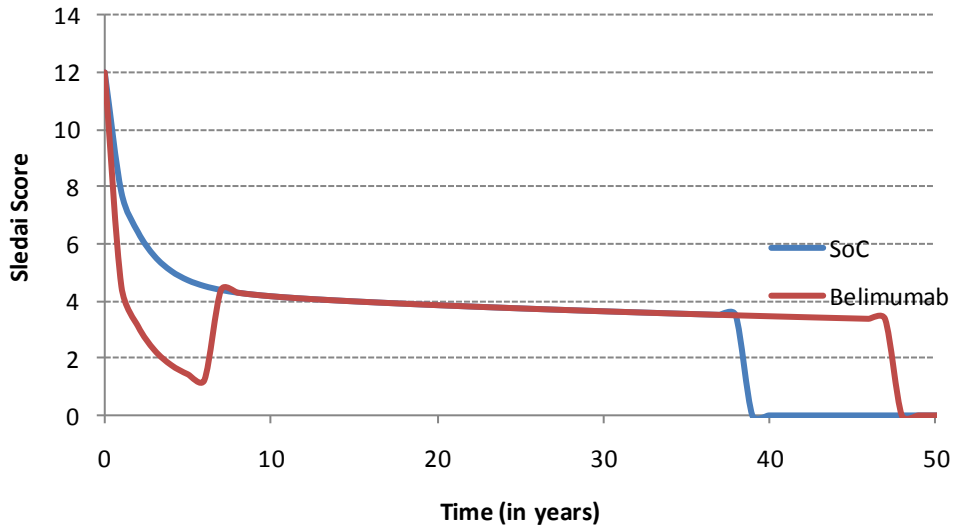
Methodology

All analyses described in this appendix relate to the health economic model supplied to NICE with our original submission in April 2011. The same key assumptions described for our original base case still apply for our revised base case except that a maximum treatment duration of six years for belimumab is now applied; the original base case had allowed up to a lifetime duration. The need to reconsider a treatment duration for belimumab, more in line with how it was likely to be used in clinical practice, was identified after reviewing the comments made in the ACD by the clinical specialists consulted for this appraisal. Our choice for a maximum treatment duration of six years as the revised base case duration was based on a number of considerations. Firstly, there is now long-term efficacy and safety trial data from the Phase II extension study (LBSL99) (Petri et al. 2011) for belimumab which demonstrates continued efficacy with belimumab without compromising safety over a six year follow-up duration. Secondly, other treatments for lupus, such as immunosuppressants, are frequently prescribed for between two and five years to maintain suppression of disease activity. It is through sustained suppression of disease activity that, in addition to improving patients' quality of life, and for some patients enabling steroid dose reductions with a lessening of their associated side effects, there is likely to be a benefit on reducing long term organ damage and on improving survival. Finally, we discussed our proposed treatment duration with a number of lupus specialists to ensure it was considered an acceptable duration for belimumab in the management of their eligible patients.

The methodology for the analysis of the BLISS study SELENA-SLEDAI scores, and the Johns Hopkins disease activity, steroid dose and natural history mortality and organ damage models is identical to that presented in our original submission. However detailed below is an explanation of the impact in the model of the incorporation of a maximum treatment duration of six years.

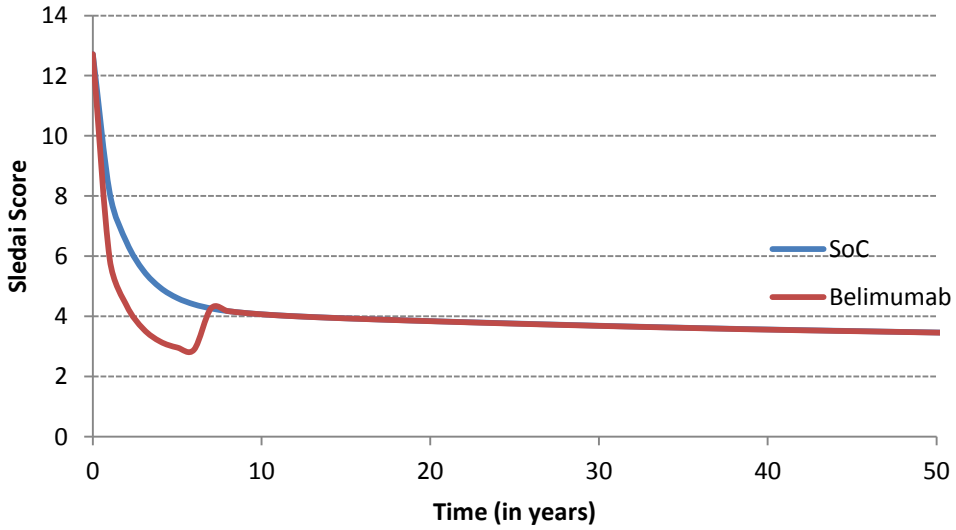
A patient who has not withdrawn early due to reasons related to natural discontinuation, and who successfully completes six years of belimumab treatment, is switched to continue to receive standard of care (SoC) treatments only from the start of the seventh year. This directly affects SLEDAI score in the belimumab arm of the model as it applies a SoC disease activity score for each belimumab patient from the end of Year 6 for the remaining duration of the model horizon, using the same simulation methodology used to generate SLEDAI scores for the patients allocated to the SoC arm in the model. This is graphically illustrated for SLEDAI score in Figure A1.

Figure A1. Example of SLEDAI score for a SoC patient and for a patient discontinuing belimumab treatment after year 6.



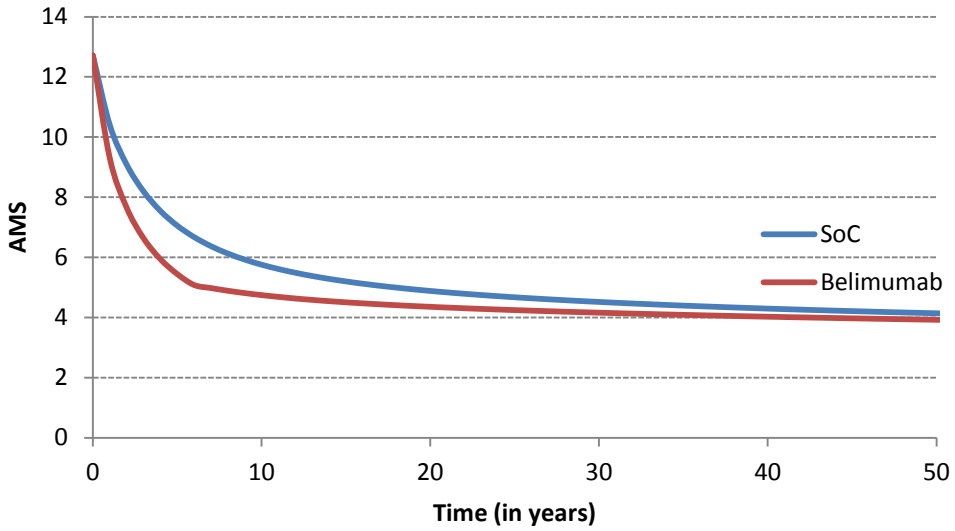
The adjusted (average) SLEDAI score (AMS) for 50,000 simulated patients is shown in Figure A2 over time for those patients who remain alive. It is clear from the graph that patients who are treated with belimumab (in addition to SoC) have a larger reduction in SS score than patients who are treated with SoC alone over the first six years.

Figure A2. SLEDAI Score over time for 50,000 patients simulated – High disease activity (Target) population.



Although the level of disease activity after discontinuation of belimumab returns to SoC levels, a beneficial effect from belimumab treatment is kept through a decreased average disease activity score over time (Figure A3).

Figure A3. Adjusted Mean SLEDAI (AMS) over time censored for death - Target population.



The average disease activity score is an important predictor of organ damage in the cardiovascular, renal, pulmonary and peripheral vascular systems (Table A1).

The lower disease activity for belimumab patients over six years of treatment will lead to a decreased steroid dose over this time period and a decreased risk for organ damage. The average disease activity (AMS) over lifetime, cumulative average prednisone dose and certain types of organ damage, contribute to the mortality risk (Table A2).

Table A1. Organ damage time to event models and corresponding covariates from Johns Hopkins cohort analysis

	CV	**Diabetes**	**GI**	**Malignancy**	**MSK**	**NP**	**Ocular**	**PV**	**GF**	**Pulmonary**	**Renal**	**Skin**
Survival model	Loglog	Exp	Exp	Exp	Loglog	Weibull	LogLog	Exp	Exp	Gompertz	Exp	LogLog
Covariates												
Male				0.4981								
Black		0.7805										
Age at diagnosis	-0.054			0.0229	-0.0354							
Past smoker								0.6066				-1.5658
Cholesterol				-0.0088		0.0047			0.005		0.008	
Hypertension	-1.089					0.5167		1.0051				
AAP										1.0132		
LAP								1.3705				
Log of age		2.2481				0.607	-2.97	1.1608		1.2316		
Log of disease duration	-0.741			0.3082	-0.6747							
AMS	-0.209		-0.0606		-0.0407	0.044	-0.045	0.1702		0.1388	0.3234	-0.0466
CAPD	-0.001	0.0019	0.0011		-0.0018		-0.002		0.0022			-0.0025
SLICC/ACR score				0.1467	-0.1448	0.0954				0.1039		
Renal damage	-0.834											
Diabetes at previous visit	-1.067											
Constant	10.123	-14.6564	-4.8419	-4.8106	7.0495	-7.3961	15.993	-11.695	-7.6433	-9.265	-8.293	9.651
Parametric par	1.2164				1.1421	0.8161	1.084			-0.0382		1.5938

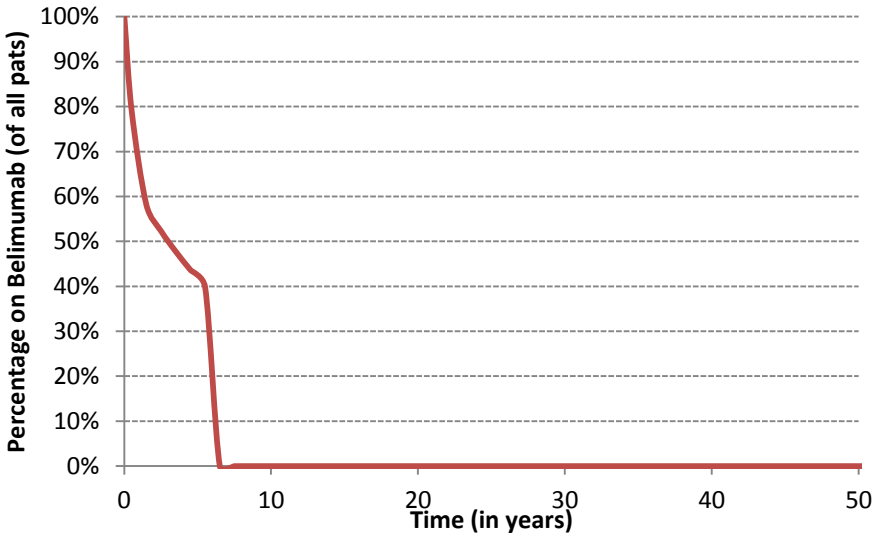
CV = cardiovascular, MSK = musculoskeletal, NP = neuropsychatric, PV = peripheral vascular, GI = gastrointestinal, GF = Gonadal Failure, Loglog = loglogistic, Exp = exponential, AAP = Anticardiolipid antibodies, LAP = Lupus anticoagulant positive, AMS = average mean SLEDAI up to current time, CAPD = cumulative average prednisone dose up to current time, Seros = serositis, Paramteric par = additional parametric distribution parameter for non-exponential survival models.

Table A2. Weibull survival model explaining risk of death with AMS included and item involvement effects removed – Johns Hopkins (JH) cohort

Covariates	Model coefficient
Constant	-10.366
Black ethnicity	0.7814
Age at diagnosis	0.0321
Cholesterol	0.0044
AMS over lifetime	0.2135
Cumulative Average Prednisone Dose (mg/month)	0.0012
Renal damage	0.652
Musculoskeletal damage at previous visit	0.415
Peripheral vascular damage at previous visit	0.9783
Gastrointestinal damage at previous visit	0.4684
Diabetes at previous visit	0.6764
Malignancy at previous visit	1.1489
Any infection at time of death at current visit	0.7409
Parametric distribution parameter for Weibull	1.6799

The discontinuation of patients on belimumab is shown in Figure A4. The steep fall in patients continuing with belimumab in the first year is caused by those patients not satisfying the treatment continuation criterion at 24 weeks and hence moving to SoC in the model. After six years all patients have switched to receiving SoC treatments only.

Figure A4. Discontinuation from belimumab (includes death) – Target population.



The survival over time is therefore improved for belimumab patients compared with patients on SoC due to the benefits of belimumab on these components. (Figure A5). The relatively steep decline in survival in the first year for both arms is caused by the relatively high standardised mortality ratio for patients younger than 24 years (see Table A3).

Figure A5. Survival of patients over time – Target population

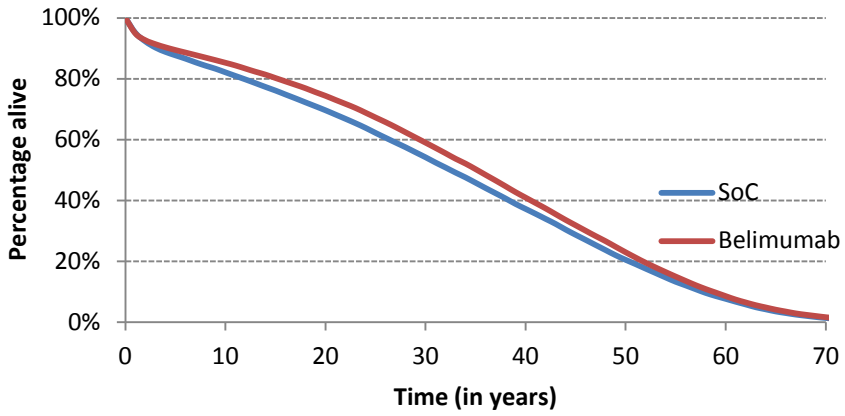


Table A3. Standardised Mortality Ratios for SLE patients stratified by age groups according to Bernatsky et al (2006).

Age	Standardized Mortality Ratio	95% CI
16-24	19.2	14.7, 24.7
25-39	8.0	7.0, 9.1
40-59	3.7	3.3, 4
>60	1.4	1.3, 1.5

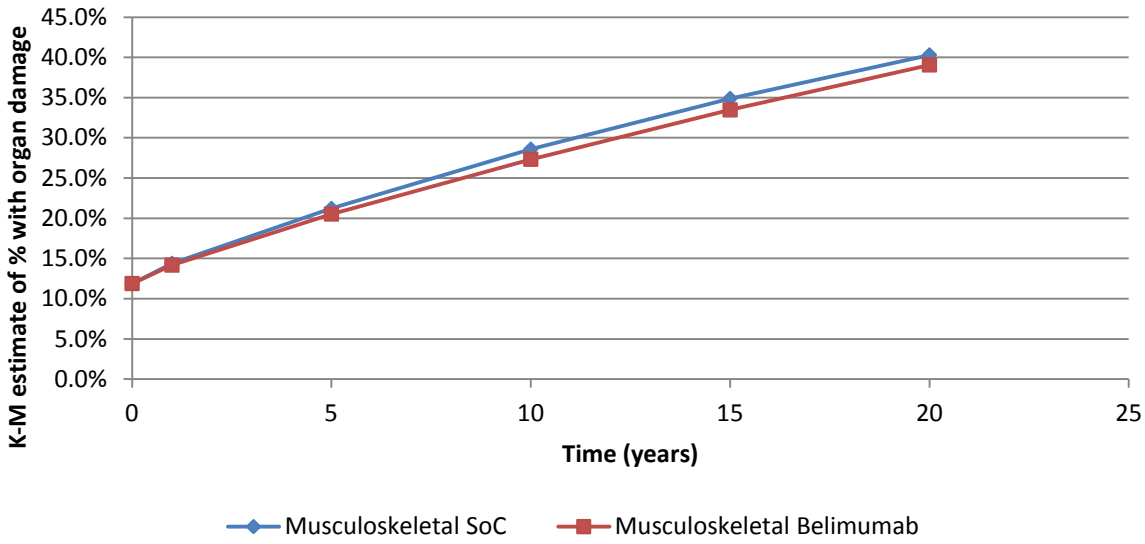
As belimumab patients have an estimated longer life expectancy, the exposure to the risk of organ damage is increased for belimumab patients, hence, for eight of the organs (diabetes, gastrointestinal, malignancy, musculoskeletal, neuropsychiatric and ocular, premature gonadal failure, and skin), the percentage of damage occurrence is similar or higher than for SoC (see Table A4). However, for cardiovascular, peripheral vascular, pulmonary and renal systems, fewer patients on belimumab develop damage compared to SoC. This is due to the dependence of damage risk on disease activity and steroid use which is lower for patients receiving belimumab.

Table A4. Organ damage occurrence for SLE patients until death - Target population

	SoC	Belimumab	Difference
Cardiovascular	23.9%	21.8%	-2.1%
Diabetes	17.9%	19.0%	1.0%
Gastrointestinal	22.1%	24.2%	2.2%
Malignancy	32.0%	33.4%	1.4%
Musculoskeletal	48.5%	49.0%	0.5%
Neuropsychiatric	44.7%	45.6%	0.9%
Ocular	35.1%	35.7%	0.5%
Peripheral vascular	21.5%	20.8%	-0.7%
Premature gonadal failure	7.2%	7.4%	0.1%
Pulmonary	39.9%	37.5%	-2.4%
Renal	24.3%	19.9%	-4.4%
Skin	7.9%	7.9%	0.0%

As belimumab is estimated to reduce the risk of organ damage for the cardiovascular, peripheral vascular, pulmonary and renal organ systems, this damage will occur later in belimumab patients; organ damage is irreversible and lasts until death. The duration of the organ damage therefore depends on the remaining lifespan of the patient. As discussed above, the occurrence of damage in the remaining organ systems is higher or similar in the belimumab arm compared with the SoC arm, due mainly by the increased life expectancy with belimumab. However, for the patients still alive, the proportion with organ damage is lower. This is illustrated in a Kaplan-Meier plot of musculoskeletal damage censoring for death (Figure A6).

Figure A6. Kaplan-Meier plot of the proportion of patients alive with musculoskeletal damage – Target population



The effect of belimumab on the duration of organ damage is thus a product of the decreased risk, delayed onset of organ damage and the prolonged life expectancy of these patients. Although a decreased duration of damage is shown for the cardiovascular, pulmonary and renal organ system, the duration of damage for most other organ systems is increased due to the prolonged life-expectancy (Table A5).

Table A5. Average duration (yrs) of organ damage – Target Population

	SoC	Belimumab	Difference
Cardiovascular	5.60	5.24	-0.36
Diabetes	2.64	2.92	0.28
Gastrointestinal	4.62	5.30	0.68
Malignancy	4.39	4.79	0.40
Musculoskeletal	11.24	11.90	0.66
Neuropsychiatric	11.17	11.76	0.60
Ocular	7.88	8.18	0.30
Peripheral vascular	3.66	3.65	-0.02
Premature gonadal failure	1.77	1.85	0.07
Pulmonary	9.87	9.44	-0.43
Renal	5.38	4.49	-0.89
Skin	2.47	2.62	0.15

Table A6 summarises the main outcome results for the revised base case including a maximum treatment duration of six years. As demonstrated previously in Figure A5, belimumab patients have an estimated increased life-expectancy. The model predicts that belimumab-treated patients, in the subgroup with high disease activity, live on average 2.0 years longer, have a reduction in average mean SLEDAI score of -0.6, and a similar total SLICC organ damage score at death compared with SoC patients (Table A5). Treatment with belimumab in this Target population provides an estimated additional 0.8 life years and 0.7 QALYs (discounted at 3.5%).

Table A6. Summary of health economic outcomes – Target population

	SoC	Belimumab	Difference
Age at Death	66.2	68.2	2.0
SLICC at Death	4.1	4.0	-0.1
AMS	5.5	4.89	-0.6
Average monthly steroid cumulative dose	228.1	215.4	-12.7
Life Years (undiscounted)	31.93	33.98	2.0
Life Years (discounted at 3.5%)	17.05	17.87	0.8
QALYs (undiscounted)	17.31	18.60	1.3
QALYs (discounted at 3.5%)	9.81	10.42	0.6

All the additional cost effectiveness analyses discussed in this appendix incorporate the discount on vial price offered in our proposed patient access scheme. Yearly drug acquisition costs for belimumab when the PAS drug discount scheme is considered are presented in the Table A7 below.

Table A7. Unit costs associated with the new technology in the economic model

Unit Costs	Belimumab 10mg/kg	Description
Mean cost of technology treatment based on an average weight of 65.4 kg as seen in the pooled BLISS study Target population	Year 1 annual cost = [redacted] Year 2 annual cost = [redacted]	The list price vial costs are [redacted] and [redacted] for the 120 mcg and 400 mcg vials respectively. For each weight, the optimal vial combination is chosen and costs for waste are added. Weight distribution according to the trials is used to determine average yearly belimumab costs.
Administration cost per infusion	[redacted] (Year 1) [redacted] (Year 2+)	£126 per infusion (14 in Year 1 and 13 in Year 2 onwards)
Monitoring and test costs	£0	No additional monitoring or tests are required for implementation of this technology
Total Year 1 costs	[redacted]	
Total Subsequent Year costs	[redacted]	

Table A8 below summarises disaggregated costs from the model. The total costs for patients consist of resource costs related to disease activity, belimumab acquisition and administration costs, and longer-term costs incurred by organ damage. For both treatment groups, the organ damage costs

are the highest component of the total costs. These costs are influenced by the duration of the organ damage shown in Table A5, the onset of organ damage through the discount rate, and the increase of costs over time. For the cardiovascular, peripheral vascular, pulmonary and renal organs, the costs are lower since the estimated duration was shorter. In total, the organ damage costs are slightly lower for belimumab-treated patients due to the benefits on the pulmonary and renal systems. The costs related to disease activity are slightly higher in the belimumab arms. Although belimumab patients have less disease activity and consequently lower direct resource costs per year on average, the costs increase due to the estimated increased life expectancy. Overall, the main difference in costs is caused by belimumab acquisition and administration, amounting to [redacted] of the total absolute cost difference of [redacted]

Table A8. Summary of (discounted) costs over a lifetime model horizon incorporating the PAS - Target population

Discounted	SoC	Belimumab	Difference	Absolute difference	% absolute difference
Disease activity related costs	£27,882	£28,537	£655	£655	[redacted]
Belimumab drug acquisition	£0	[redacted]	[redacted]	[redacted]	[redacted]
Belimumab administration	£0	[redacted]	[redacted]	[redacted]	[redacted]
Organ damage costs					
Cardiovascular	£1,838	£1,660	-£179	£179	[redacted]
Diabetes	£2,493	£2,693	£201	£201	[redacted]
Gastrointestinal	£359	£391	£32	£32	[redacted]
Malignancy	£998	£1,019	£21	£21	[redacted]
Musculoskeletal	£9,758	£10,060	£302	£302	[redacted]
Neuropsychiatric	£6,434	£6,644	£211	£211	[redacted]
Ocular	£392	£390	-£2	£2	[redacted]
Peripheral vascular	£1,380	£1,327	-£53	£53	[redacted]
Premature gonadal failure	£0	£0	£0	£0	[redacted]
Pulmonary	£42,692	£39,727	-£2,966	£2,966	[redacted]
Renal	£11,139	£9,102	-£2,037	£2,037	[redacted]
Skin	£0	£0	£0	£0	[redacted]
Sum of organ damage costs	£77,483	£73,013	-£4,470	-	
Total direct costs	£105,366	[redacted]	[redacted]	[redacted]	[redacted]

Table A9 summarises the results for the revised base case analysis incorporating the PAS. Belimumab-treated patients are estimated to live longer, however, due to their increased life expectancy and due to belimumab acquisition and administration costs, the total costs of managing SLE patients with high disease activity are higher than for SoC patients. The incremental costs are [redacted], with 0.8 added life years, or 0.6 added QALYs, discounted at 3.5%, resulting in an ICER of [redacted] per QALY gained.

Table A9. Discounted revised base case results with the PAS – Target population

	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
SoC	£105,366	17.05	9.81	-			
Belimumab	[redacted]	17.87	10.42	[redacted]	0.8	0.6	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity Analyses

Identical deterministic sensitivity analyses and PSA were conducted for this revised base case as documented in our original submission with our base case which included a lifetime duration of belimumab treatment.

Results of the Univariate Sensitivity Analyses

Tornado diagrams for the ICERs, QALYs and Costs resulting from the univariate sensitivity analyses are presented in Figures A7, A8, A9 and Tables A10, A11, and A12 respectively.

The main drivers of cost-effectiveness in our revised base case modelling, are similar to those specified in our original submission. The most important model driver is the treatment effect regression to estimate the effect on SS score of belimumab after 52 weeks; the smaller the benefit seen with belimumab compared to SoC, the lower the incremental QALY and hence the higher the ICER.

The effect of the AMS on mortality is also an important driver of the model results. The greater the reduction in AMS with belimumab, the greater the increase in life expectancy with belimumab compared with SoC and consequently the higher the QALY gain leading to more favourable ICERs.

The constant and effect of log age in the utility regression also have an important effect on the incremental effects and the ICER. However for these particular parameters, a univariate analysis is conditional on keeping the other parameters fixed, which in this case is not very likely due to the dependence between both coefficients. As discussed in our original submission there is substantial negative correlation between the constant and the effect of log age in the utility regression). As such, changing one parameter to the upper limit implies that the other parameter would likely be lower and hence they will (partly) cancel each other out. This also applies to the effect of log age and the constant in some of the organ damage models. This explains why the lower values for some of the latter analyses are above the base case value (e.g. for the natural history pulmonary model). In summary, caution should be used when interpreting the univariate results due to the correlation between several model parameters. As explained in our original submission, the PSA acknowledges this correlation by drawing from multivariate normal distributions with covariance matrices.

The ICERs yielded from the univariate sensitivity analyses ranged from [redacted] to [redacted] per QALY gained.

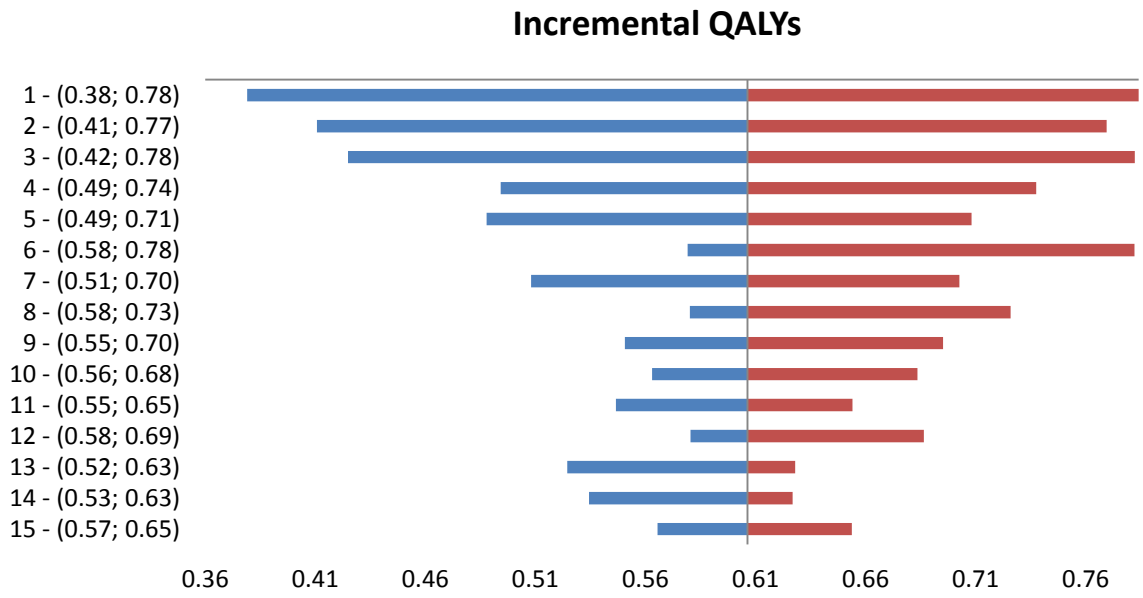
Figure A7. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on ICERs Incorporating the PAS – Target population

Note: Table A10 below details the variables identified as numbers in this tournado plot.

Table A10. Description of key variables with the largest impact on the ICER incorporating the PAS

Variable ID	Variable Name	Base Value	Lower bound	Upper bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
4	Coefficient of Log of age from the "clean utility" regression	0.15	-0.18	-0.10
5	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
6	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
7	Adjusted Mean SLEDAI coefficient at current visit from the natural history renal model	0.31	0.23	0.39
8	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
9	Log of age at current visit coefficient from the natural history neuropsychiatric model	0.61	0.03	1.23
10	Constant coefficient from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
11	Constant coefficient from the natural history renal model	-8.29	-9.01	-7.56
12	Coefficient of log of age at current visit from the natural history pulmonary model	1.23	0.59	1.92
13	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history cardiovascular model	-0.21	-0.34	-0.07
14	Coefficient of log of age at current visit from the natural history diabetes model	2.25	1.16	3.35
15	Constant coefficient from the natural history pulmonary model	-9.17	-11.41	-6.54

Figure A8 Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental QALYs – Target population



Note: Table A11 below details the variables identified as numbers in this tournado plot.

Table A11. Description of key variables with the largest Impact on Incremental QALYs

Variable ID	Variable	Base Value	Lower Bound	Upper Bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
4	Coefficient of Log of age from the "clean utility" regression	-0.15	-0.18	-0.10
5	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
6	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
7	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
8	Coefficient Log of age at current visit in natural history peripheral vascular model	1.16	0.43	1.89
9	Annual Discontinuation rate year 2 onwards for belimumab patients who were defined as “responders”	0.92	0.86	0.98
10	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history renal model	0.32	0.23	0.41
11	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history pulmonary model	0.14	0.06	0.22
12	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
13	Coefficient constant from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
14	Coefficient for log of age at current visit in natural history peripheral vascular model	1.16	0.03	1.23
15	Coefficient for renal damage at previous visit in the natural history mortality model	0.65	0.16	1.19

Figure A9. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental costs with PAS – Target population

Note: Table A12 below details the variables identified as numbers in this tournado plot.

Table A12. Description of key variables with the largest impact on Incremental costs

Variable ID	Variable	Base value	Lower Bound	Upper Bound
1	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
2	Annual Discontinuation rate year 2 onwards for belimumab patients who were defined as "responders"	0.92	0.86	0.98
3	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
4	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
5	Constant coefficient in the natural history diabetes model	-14.66	-19.14	-10.29
6	Log of age coefficient at current visit in natural history diabetes model	2.25	1.16	3.35
7	Log of age at current visit coefficient in natural history pulmonary model	1.23	0.59	1.92
8	Log of age at current visit coefficient in natural history peripheral vascular model	31.23	0.43	1.89
9	Constant coefficient from the natural history pulmonary model	-9.27	-11.78	-6.86
10	Coefficient for renal damage at previous visit from the mortality model	0.65	0.16	1.19
11	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
12	Adjusted Mean SLEDAI at current visit coefficient from the renal model	0.32	0.23	0.41
13	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
14	Adjusted Constant coefficient in the natural history Disease Activity Model	3.0	2.20	3.93
15	Constant coefficient from the natural history malignancy model	-4.81	-6.05	-3.53

Probabilistic Sensitivity Analyses (PSA)

The results for the probabilistic sensitivity analyses are presented in the form of a scatter plot (Figure A10) and a cost-effectiveness acceptability curve (Figure A11) below.

Figure A10. Scatter plot of the PSA with PAS - Target population

Figure A11. Acceptability curve of PSA with PAS - Target population

The PSA results show that at a willingness to pay of £30,000 per QALY gained, there is a [redacted] probability that belimumab is cost-effective compared to SoC. With a willingness to pay of £40,000 per QALY gained, there is an [redacted] probability that belimumab is cost-effective compared to SoC.

Scenario Analyses

The following two key scenario analyses have been considered for this revised base case:

1. As detailed in Point 1 on Page 4 of this response, we believe a discount rate for health effects of 1.5% is justified for this technology appraisal and therefore consider this a key alternative scenario for consideration by the Appraisal Committee.

2. As detailed in Point 2 on Page 4 of this response, being mindful of the annual cost to the NHS of treating patients with belimumab and of limited NHS resources, introducing a more stringent treatment continuation criterion after six months treatment would help to target belimumab to those patients believed to gain the greatest continued benefit with this treatment. In order to continue treatment with belimumab after six months patients would need to show a reduction in SELENA-SLEDAI (SS) score of at least 6 points.

Other scenario analyses considered are detailed below:

- Alternative maximum treatment durations for belimumab of 3, 5 and 10 years have also been examined to demonstrate the effect on the assessment of cost-effectiveness of shorter and longer maximum treatment durations compared with the base case. A maximum of 5 years is consistent with the maximum treatment duration used by clinicians for immunosuppressants currently used to treat SLE.

- The effect of excluding the treatment continuation criterion in the model has been examined to demonstrate the impact on estimated cost-effectiveness of not reviewing patient response in terms of reduced SS score after six months of treatment with belimumab.

- A different administration cost of £159 has been used in a scenario analysis, as this was suggested by the ERG who reviewed the STA appraisal for tocilizumab, a human monoclonal antibody for the treatment of rheumatoid arthritis, which also requires administration over one hour.

The results of the scenario analyses are presented in Table A13 below.

Table A13. Summary of Scenario Results with PAS - Target population

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised Base Case: 6 year maximum belimumab treatment duration	Time horizon = lifetime; 6 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; and health effects discount rate of 3.5%	[redacted]	0.81	0.606	[redacted]
Health effects discount rate of 1.5%	As revised base case but with discounting for benefits set to 1.5%.	[redacted]	1.33	0.897	[redacted]
More stringent treatment continuation criterion	As revised base case but with treatment continuation criterion at 24 weeks of SS score of ≥6 and health effects discount rate of 3.5%	[redacted]	0.68	0.508	[redacted]
More stringent treatment continuation criterion and health effects discount rate of 1.5%	As revised base case but with treatment continuation criterion at 24 weeks of SS score of ≥6 and health effects discount rate of 1.5%	[redacted]	1.11	0.747	[redacted]
Treatment continuation criterion excluded and health effects discount rate of 3.5%	As revised base case but with treatment continuation criterion at 24 weeks excluded	[redacted]	0.77	0.584	[redacted]
Treatment continuation criterion excluded and health effects discount rate of 1.5%	As revised base case but with treatment continuation criterion at 24 weeks excluded	[redacted]	1.26	0.860	[redacted]
Higher drug administration cost	As revised base case but with a drug administration cost of £159 as recommended as a sensitivity analysis by the ERG in the NICE STA for tocilizumab for rheumatoid arthritis	[redacted]	0.81	0.606	[redacted]

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
3 year belimumab treatment duration	Time horizon = lifetime; 3 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; and health effects discount rate of 3.5%	[redacted]	0.61	0.459	[redacted]
3 year belimumab treatment duration and health effects discount rate of 1.5%	Time horizon = lifetime; 3 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; health effects discount rate of 1.5%	[redacted]	0.97	0.67	[redacted]
5 year belimumab treatment duration for the Target subgroup	Time horizon = lifetime; 3 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; and health effects discount rate of 3.5%	[redacted]	0.75	0.560	[redacted]
5 year belimumab treatment duration and health effects discount rate of 1.5%	Time horizon = lifetime; 3 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; health effects discount rate of 1.5%	[redacted]	1.23	0.824	[redacted]
10 year belimumab treatment duration	Time horizon = lifetime; 10 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; and health effects discount rate of 3.5%	[redacted]	0.92	0.698	[redacted]
10 year belimumab treatment duration and health effects discount rate of 1.5%	Time horizon = lifetime; 10 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; health effects discount rate of 1.5%	[redacted]	1.54	1.047	[redacted]

The various alternative scenarios investigated resulted in ICERs ranging from [redacted] to [redacted] per QALY gained compared with the revised base case ICER of [redacted] per QALY gained.

Using a health effects discount rate of 1.5% rather than 3.5% has a significant impact on the ICER, reducing it by over £10,000 per QALY to give an ICER of [redacted] per QALY gained.

When a maximum treatment duration of 3 years for belimumab is considered, the revised base case ICER is reduced by over £9000 per QALY, yielding an ICER of [redacted] per QALY gained when a health effects discount rate of 3.5% was used. When a discount rate of 1.5% was included for health effects the ICER reduced to [redacted] per QALY gained.

In contrast, when a maximum treatment duration of 10 years for belimumab is considered, the revised base case ICER is increased by nearly £6000 per QALY, to give an ICER of [redacted] per QALY gained when a 3.5% health effects discount rate was used. However the ICER was reduced to [redacted] per QALY when a health effects discount rate of 1.5% was incorporated.

When 5 years is considered as a maximum treatment duration for belimumab, the ICER incorporating a health effects discount rate of 3.5% was [redacted] per QALY gained, reducing to [redacted] per QALY for a discount rate of 1.5%.

Excluding the treatment continuation rule from the cost-effectiveness analysis also has a fairly large impact on the ICER, increasing the revised base case ICER to [redacted] per QALY gained, £6779 per QALY higher.

With regards to incorporating the higher administration cost of belimumab of £159 per infusion compared with the value of £126 used in the base case, the ICER was [redacted] per QALY gained, an increase of approximately £2000 per QALY.

Discussion

Incorporating the PAS, which comprised a straight discount on the belimumab list vial prices, resulted in a base case ICER of [redacted] per QALY gained, assuming a maximum of six years of belimumab in the model. Univariate sensitivity analyses ranged from [redacted] to [redacted] per QALY gained. Variables and assumptions which had the greatest impact on the ICER comprised the maximum assumed duration of belimumab treatment, the discount rate incorporated for health effects, the degree of benefit seen on SS score with belimumab, the coefficient for average mean SLEDAI included in the natural history mortality model and the exclusion of a responder rule at after six month of treatment.

Warwick Evidence

ERG commentary on Manufacturer's Response to ACD belimumab

A. Response to Appraisal Consultation Document (ACD) belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (SLE) GlaxoSmithKline 21 October 2011

The GSK response to the ACD consisted of a 16 page "response document" (RD) plus an 18 page appendix (A1) giving details of the economic model adjustments and results.

Below the ERG summarise and comment on these documents.

Manufacturer's executive summary in the RD

The manufacturer's executive summary asserted the following:

- A plausible range for the ICER (belimumab vs. SoC) is [redacted]. This is based on 6 years maximum treatment duration, 1.5 or 3.5% discounting of health benefits and a 24 week discontinuation rule of ≥4 or ≥6 points improvement in SLEDAI score relative to baseline.
- The ICERs would be further reduced if the benefit of belimumab on quality of life (QoL) was more fully captured, particularly with respect to effects on chronic fatigue and the impact on disease flares.
- New evidence for a reduction in steroid use over 6 years supports the model predictions on steroid use and indicates a sustained response so that it is reasonable to expect that near time improvement will translate to long-term improvement with respect to slower development of organ damage. RCT estimates of steroid sparing effects were inaccurate because assessment was limited to a short timeframe and because under double blind conditions clinicians would be cautious and reluctant to remove steroid use from treatment.
- Rituximab is an unlicensed treatment which, in contrast to belimumab is as yet unsupported by RCT evidence of effectiveness in a primary outcome. [redacted]

In the following section the ERG provides a commentary on the manufacturer's supporting text for these main assertions.

1. Maximum duration of belimumab treatment

The manufacturer proposes that the model base case should assume a 6-year maximum treatment duration; the original had some patients receive treatment for 40 years. The original submission stated: *"Stopping belimumab would lead to the benefits of inhibiting the biological activity of BLyS also being curtailed and any beneficial reduction in disease activity. There is no current evidence to demonstrate whether limited durations of treatment, e.g. 5 or 7 years, would still result in clinically important long-term benefits on organ damage and survival."*

The maximum duration of treatment is uncertain and clinical opinion is likely to vary. Given an annual discontinuation of 8% (original submission) or the rates observed in the extension Phase II trial LBL02, it appears probable that if a maximum treatment duration of 6 years is imposed, a substantial proportion of patients will have treatment withdrawn. According to the RD the 6-year extension study of Petri et al (2011) *"demonstrate[s], for the majority of patients in the study, a sustained response to belimumab without compromising safety".* Of 339 patients in treatment at the end of year 2, 167 were still in treatment at the end of year 6. The RD makes no mention of a tapering dose. The ethical considerations of withdrawal may therefore need some consideration. Sudden withdrawal of belimumab may mean that steroid use would need to be increased to cope with a potential recrudescence of symptoms at least for some patients; and this possibility has not been addressed by the manufacturer. Relapse after 6 years might require reintroduction of belimumab, at any stage for a further 6 year duration within the time horizon of the model, but this possibility is assumed never to occur in the new economic modelling.

2. Revised discount rate for health benefits

New NICE DSU advice regarding discount rates for health benefits proposes a 1.5% rate for certain chronic diseases when benefit is substantial and sustained over a long period (e.g. 30 years). The manufacturer suggests that belimumab treatment for SLE fits these criteria. Evidence is presented of a beneficial response to belimumab lasting at least 6 years in an appreciable population of patients. The manufacturer argues that this early effect of belimumab together with the observed 34% reduction in steroid usage would translate into long-term benefit by attenuating the development of organ damage. Clinical opinion should be sought to substantiate this assertion. When a 1.5% discount is applied to the originally submitted model the ICER reduces to [redacted]

3. **Narrow range of SLE manifestations (ACD section 3.5)**

The manufacturer states that patients in the BLISS trials are not appropriately described as representing a narrow range of SLE manifestations. Three manifestations, immunological, musculoskeletal and mucocutaneous, predominated in the trial populations. The manufacturer argues that presence of auto-antibodies to dsDNA and low complement are strongly indicative of wide systemic disease activity and that this concurs with clinical opinion. The ERG reiterates that certain manifestations of SLE were poorly represented amongst the trial populations. For example, major cardiovascular or pulmonary complications.

4. **Under estimation of belimumab's effect on quality of life (disease flares and chronic fatigue: ACD section 4.22)**

The manufacturer's RD states that "*the full benefit of belimumab on disease flares and chronic fatigue are not adequately captured in the quality adjusted life years (QALYs) derived from EQ-5D utility values*". The manufacturer emphasises that chronic fatigue represents a serious impairment of QoL for SLE patients and points out that at 8 and 12 weeks a statistically significant improvement in FACIT fatigue score was observed for the pooled population from the BLISS trials, and further that although statistical significance had faded by week 52 the direction of effect was 'in favour of' belimumab. The ERG note that statistical analyses were not adjusted for repeat measures and comment that: a) these improvements might be expected to be captured with the EQ-5D instrument used in the trials; b) that the benefits seen here were not statistically significant.

The manufacturer argues that the scheduled collection of data using the EQ-5D instrument in the BLISS trials was likely to miss the impact of disease flares resulting in an underestimate in the QOL benefit from belimumab since flares were reduced in the belimumab group relative to the placebo group. This reiterates an argument advanced in the original submission which stated, "*In SLE patients may experience disease flares at any time and not necessarily at the time the EQ-5D was completed for the pre-defined time points in the clinical trials"*. However, the ERG consider that the range of outcomes measured used was considerable and are likely to have captured any substantial differences in populations and response.

5. **Long-term benefit from belimumab and steroid sparing effect (ACD section 4.9)**

The manufacturer argues that a steroid sparing effect was underestimated in the BLISS trials because:

- Under double bind trial conditions clinicians would be cautious in reducing the steroid dose.
- The estimation of steroid sparing was conducted over too narrow a time frame.

The manufacturer points to new evidence from the open label extension of the LB02 study (Petri et al., 2011) in which patients on treatment at 6 years have reduced steroid use by 34% from baseline, representing an absolute reduction of 4.7mg/d. However, the basis of the calculation is not clear and the ERG are unsure from this abstract whether the average baseline steroid use was calculated for the same patients as those used for the estimate at 6 years. The manufacturer proposes that steroid sparing of this magnitude, together with other belimumab benefits such as reduced flare frequency, will reduce the development of organ damage and that therefore this near time effect will translate into long-term benefit; this is a question which could be addressed by clinical opinion, but since data are only available until 6 years there is a substantial degree of uncertainty over whether this 'near-time' effect might translate into a longer time effect. Equally with stopping of belimumab there maybe a recrudescence or rebound of disease symptoms necessitating subsequent increased steroid use. Would a further 6 years of belimumab treatment starting immediately after a previous 6 years be feasible in practice with suggested treatment regimens?

6. Comparison with rituximab (ACD section 4.20)

The manufacturer's RD states, "[redacted]"

In support of this the manufacturer asserts that:

- Rituximab, unlike belimumab, is unlicensed for SLE and it is uncertain how it is used in the UK.
- Rituximab, in contrast to belimumab for SLE, has not been shown to be effective for a primary outcome in an RCT.
- By harnessing acquisition costs of belimumab to rituximab under the Patient Access Scheme (PAS), [redacted].

The ERG points out the following issues:

- There is evidence from the EXPLORER trial that rituximab significantly improves levels of biological markers of disease activity (e.g. auto-antibodies to double stranded-DNA, C3 and C4 complement levels).
- The primary outcome in the rituximab RCT was a more stringent criterion for establishing effectiveness than that used in the BLISS trials. In the EXPLORER trial once a patient was classified as a non-responder they remained as such for the duration of the trial, whereas in the BLISS trials a patient could become a responder at week 52 while having been a non-responder at a previous time, even whilst taking belimumab with no beneficial effect for 52 weeks.
- The cost of rituximab was based on the EXPLORER study in which patients received four infusions fixed at 1000mg irrespective of body mass, estimated at an annual cost of £6,985.20. Taking the administrative costs of infusion as either £126 or £159 brings the total to £7,489.20 or £7,621.20, respectively. The annual cost of belimumab is provided in Table A7 of the Appendix to RD as [redacted] (Year 1) and [redacted] (subsequent years) when an administration cost of [redacted] is used. This increases to [redacted](Year 1) and [redacted] (subsequent years) when administration costs is [redacted] per infusion. Based on these numbers [redacted] (using the higher rate of administrative costs). Furthermore, it should be noted that the belimumab estimate includes vial wastage and this is difficult to calculate with any degree of certainty.
- Clinicians at the AC meeting expressed the opinion that rituximab use in clinical practice will be unlikely to reach four doses annually. The manufacturer states that the relevant dosage should be that which would be expected should rituximab be licensed based on the EXPLORER study (i.e. four 1000mg doses per year). However, this is a hypothetical scenario and in the ERG's opinion is less relevant than using current UK clinical practice.

7. Relevance of SELENA-SLEDAI instrument (ACD 4.4-4.5)

The adequacy of the SELENA-SLEDAI (SS) instrument to determine whether a patient qualifies for treatment (≥ 10 points score) and the operation of the 24 week stopping rule (≥ 4 points stopping rule from baseline) was considered by the AC. In the RD the manufacturer presents the same justification for the use of SS as detailed in the original submission, as follows:

- SS correlates reasonably with other independent measures of disease activity (e.g. Bilag).
- There is evidence (e.g. Griffiths et al., 2005) that an SS score of ≥ 10 identifies patients of high disease activity and predicts likely long-term organ damage (Swaak et al., 1999).

- Gladman et al. (2000) indicated that an improvement of ≥ 4 points on SS relates to a clinically meaningful change in disease activity.

Elsewhere in the RD the manufacturer offers help in SS training for staff using SS in the small number of centres anticipated to be responsible for providing belimumab.

8. Survival (ACD section 4.16)

The model predicted longer survival for more severe SLE patients relative to less severe disease. The manufacturer has explained this result on the basis of age distribution of the patients in the BLISS trials which were fed into the model. Data is presented in Table 2 of RD that demonstrates that this is a plausible explanation. However, this does not circumvent the potential problem that the age distribution modelled and which determines the important model output of life years gained is actually non-representative of the UK population which would qualify for belimumab treatment.

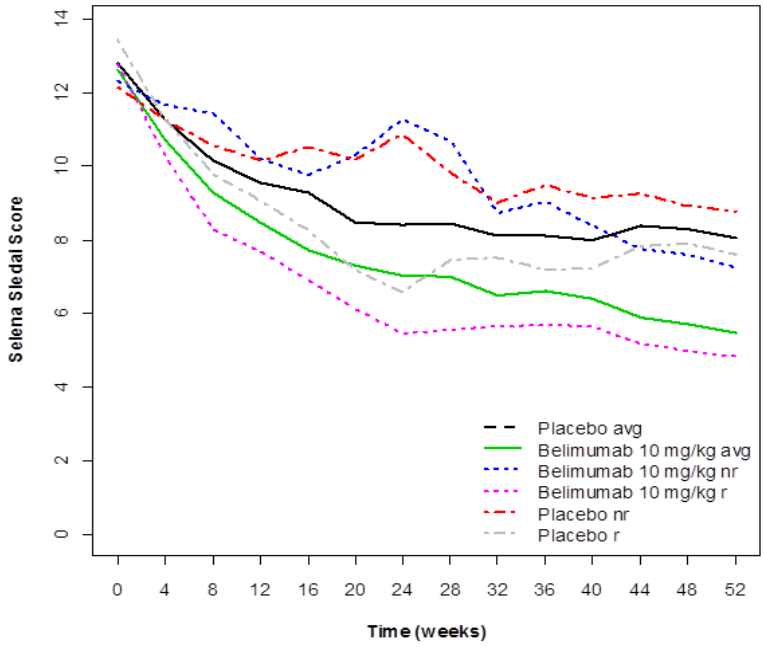
For example, Figure A5 of the Appendix document, showing percentage alive vs. time in years, extends to 70 years from the start of treatment. The mean age for the patients in the BLISS trials was 37.8 year, that for the target population was 34.3 years and mean age at entry into the Johns Hopkins was 38.2 years. In the UK peak incidence of SLE is between age 50-54 years for females and 70-74 years for males, with the mean age at diagnosis for females of 47.3 years (Somers et al., 2007). Therefore the ERG has concerns that Figure A5 in RD Appendix indicates that approximately 20% of patients are still alive at 50 years after start of treatment. If the survival depicted in Figure A5 is interpreted as an average for the BLISS population then a clinically implausible proportion would appear to be reaching their eighth and ninth decade.

B. Commentary on Appendix 1: Additional cost effectiveness analyses relevant to this Single Technology Appraisal

Background

The ERG report highlighted a number of biases in the base case input parameters and model structure in the manufacturer's original submission. These remain unaddressed and are described below.

A key structural issue is whether it is reasonable for the original manufacturer's model to have assumed that when belimumab non-responders at week 24 come off treatment at week 24, they will have the same SS score as the average of the SoC week 24 non-responders and the SoC week 24 responders by week 52. The manufacturer response to the ERG's clarification request included the following graph to explore this.



The manufacturer highlights that belimumab week 24 non-responders who continued with belimumab treatment to week 52 had an average SS score that was superior to the average of the SoC week 24 non-responders and the SoC week 24 responders at week 52. But the crucial point is whether it is reasonable to assume that belimumab week 24 non-responders who discontinue with belimumab treatment at week 24 will follow this curve. At week 24 the belimumab week 24 non-responders actually have a marginally worse SS score than the SoC week 24 non-responders and despite ongoing treatment this continues until week 32. Since within the modelling both groups receive SoC from this week 24 onwards, the ERG is of the opinion that the more natural assumption for the base case of the modelling is that both the belimumab week 24 non-responders and the SoC week 24 non-responders follow the trial based SoC non-responder curve to week 52.

The main additional remaining concerns can be briefly summarised as:

- The risk of organ damage and mortality is a function of the AMS and not the SS score. The manufacturer calculates this from the start of treatment and not from diagnosis of disease

or something approximating entry to the John Hopkins cohort. This exaggerates the impact that belimumab treatment has upon the AMS score compared to SoC.

- The impact of steroid use is also a function of the cumulative average prednisone dose. As for the AMS score the calculation of this average by the manufacturer is from the start of treatment and not from diagnosis of disease or something approximating entry to the John Hopkins cohort. In itself this exaggerates the impact that belimumab treatment has upon the CAPD compared to SoC.
- The requirement to adjust the mortality model with SMRs is not obviously justified for those patients for whom the John Hopkins cohort is reasonably representative, and this may exaggerate the effects identified in the natural history model.
- Treatment costs are based upon a within 6 month period maximum SS score which is then doubled to give an annual cost. This will tend to exaggerate the annual treatment cost associated with an average annual SS score.
- Additional organ involvement costs are added to the above treatment costs. This double counts costs and will further exaggerate the annual treatment cost associated with an average annual SS score.

The manufacturer's revisions to the base case have not addressed any of the above issues, though additional information on steroid use drawn from the open label extension is provided.

Steroid usage

The baseline steroid use assumed for the target patient population is 11.94mg/day, or approximately 363mg/month. This is projected as falling with the SS score over the period of the modelling to give CAPDs of between 200mg per month and 230mg/month; i.e. reductions of around one third. More specifically, the impact of belimumab upon steroid use within the modelling is projected as:

Table 1: Steroid use – lifetime maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
	SoC	Belimumab	net	Belimumab	net
Average monthly steroid	228.1	207.9	-20.2	213.9	-14.2

Table 2: Steroid use – 6 year maximum treatment with belimumab

Belimumab responder	SS change ≥ 4 at week 24	SS change ≥ 6 at week 24

	SoC	Belimumab	net	Belimumab	net
Average monthly steroid	228.1	215.4	-12.7	217.5	-10.5

This can be compared with the average steroid changes over the period of the trials as shown in Table 3.

Table 3: Steroid use – BLISS trials

	BLISS-52		BLISS-76		All BLISS	
	SoC	Belim.	SoC	Belim.	SoC	Belim.
Week 24 responders:	n=63	n=80	n=42	n=50	n=105	n=130
Baseline	12.4 ± 8.6	13.7 ± 10.8	8.9 ± 8.2	10.9 ± 7.6	11.0 ± 8.6	12.6 ± 9.8
Week 24	14.4 ± 11.7	11.5 ± 8.0	9.1 ± 6.7	11.4 ± 8.4	12.3 ± 10.3	11.5 ± 8.1
Week 52	10.5 ± 6.3	8.6 ± 5.9	7.5 ± 6.2	11.9 ± 21.9	9.3 ± 6.4	9.8 ± 14.1
Week 24 non-responders:	n=44	n=32	n=54	n=31	n=98	n=63
Baseline	13.4 ± 8.1	13.6 ± 9.3	11.3 ± 9.2	9.5 ± 8.9	12.2 ± 8.7	11.6 ± 9.3
Week 24	17.8 ± 30.2	14.1 ± 10.1	20.5 ± 54.8	12.5 ± 8.8	19.2 ± 44.8	13.3 ± 9.4
Week 52	13.3 ± 7.0	12.1 ± 9.3	9.9 ± 9.2	9.9 ± 8.3	11.4 ± 8.3	11.0 ± 8.8
Overall:	n=107	n=112	n=96	n=81	n=203	n=193
Baseline	12.8 ± 8.4	13.7 ± 10.4	10.3 ± 8.8	10.4 ± 8.1	11.6 ± 8.6	12.3 ± 9.6
Week 24	15.7 ± 20.6	12.1 ± 8.6	14.9 ± 39.5	11.8 ± 8.5	15.3 ± 30.6	12.0 ± 8.5
Week 52	11.4 ± 6.6	9.4 ± 6.9	8.6 ± 7.8	11.2 ± 18.6	10.2 ± 7.3	10.1 ± 12.9

During the period of the BLISS trials, reductions in steroid use tend to occur for both SoC and belimumab arms. The manufacturer provides additional open label extension data (Petri et al., 2011) which suggests that within 4 to 5 years of ongoing belimumab use the average daily steroid dose has fallen by up to 35%. The modelled steroid use in the belimumab arm appears to broadly follow the reductions in steroid use reported for the open label extension.

Manufacturer's model revisions

The ERG has re-run the manufacturer's model with the revisions outlined in the manufacturer's response to the ACD. The results of this are only presented within the PAS scenario.

The main change to the modelling is the 6-year maximum duration of treatment with belimumab. It should be borne in mind that the reversion to SoC levels of disease activity at year 6 relates to the SS score. But modelled organ damage and mortality both use the AMS. This carries forward the differential SS scores beyond cessation of treatment; i.e. beyond year 6 those patients who have been treated with belimumab but are now on SoC retain a lower risk of organ damage and of

mortality compared to those in the SoC arm. The new modelling implicitly assumes that subsequent to year 6 no patients will relapse and require an additional course of treatment with belimumab.

A further key revision is proposed to the discount rate for benefits since these are considered to extend beyond 30 years. Given the revised guidance on the handling of discount rates:

> *The Institute considers it appropriate to normally discount costs and health effects at the same rate. The annual rate of 3.5%, based on recommendations of the UK Treasury for the discounting of costs, should be applied to both costs and health effects. Where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs.*

The ERG presents the proportion of the undiscounted patient benefits that are modelled as occurring beyond 30 years from baseline[1] in order to help the Appraisal Committee assess whether it is appropriate to undertake the sensitivity analyses around the appropriate discount rate to use for benefits.

Table 4: Proportion of benefits within 30 years undiscounted – lifetime maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
Undiscounted	SoC	Belimumab	net	Belimumab	net
Total life years	31.93	34.87	2.93	34.09	2.16
within 30 years	22.94 72%	24.24 70%	1.30 44%	23.97 70%	1.03 48%
Total QALYs	17.31	19.17	1.86	18.67	1.36
within 30 years	13.12 76%	14.16 74%	1.04 56%	13.93 75%	0.80 59%

Table 5: Proportion of benefits within 30 years undiscounted – 6 year maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
Undiscounted	SoC	Belimumab	net	Belimumab	net

[1] Implemented by summing the columns of the *Results* worksheet over rows 6 to 35 rather than 6 to 105.

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
Undiscounted	SoC	Belimumab	net	Belimumab	net
Total life years	31.93	33.98	2.04	33.62	1.68
within 30 years	22.94	24.03	1.09	23.87	0.93
	72%	71%	53%	71%	55%
Total QALYs	17.31	18.60	1.28	18.37	1.06
within 30 years	13.12	13.93	0.81	13.81	0.68
	76%	75%	63%	75%	65%

As would be anticipated, the proportion of the net benefits from belimumab modelled as occurring beyond 30 years falls if the maximum treatment duration for belimumab is reduced.

These figures are based upon the baseline distribution of patients within the BLISS trials, which for the target population suggests an average age at baseline of 34.3 years. As already noted, the mean age at diagnosis in the UK is 47.3 years for females (Somers et al., 2007). The proportions of benefits simulated as occurring beyond year 30 for a cohort aged 45 is lower (Table 6).

Table 6: Benefits simulated for 45-year-old – lifetime maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
Undiscounted	SoC	Belimumab	net	Belimumab	net
Total life years	20.75	23.73	2.98	22.99	2.24
within 30 years	18.75	20.82	2.07	20.37	1.62
	90%	88%	69%	89%	72%
Total QALYs	10.84	12.61	1.78	12.17	1.33
within 30 years	9.98	11.35	1.36	11.03	1.05
	92%	90%	77%	91%	79%

Table 7: Proportion of benefits within 30 years – 6 year maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
Undiscounted	SoC	Belimumab	net	Belimumab	net
Total life years	20.75	22.99	2.24	22.57	1.82
within 30 years	18.75	20.48	1.73	20.17	1.42
	90%	89%	77%	89%	78%
Total QALYs	10.84	12.15	1.31	11.91	1.07
within 30 years	9.98	11.07	1.09	10.88	0.89
	92%	91%	83%	91%	83%

Retaining the baseline age distribution with the mean age of 34.3 years as within the manufacturer modelling, the discounted costs, benefits and ICERs that result from the alternative discounting regimes are as below for the modelling that assumes that treatment with belimumab can be ongoing.

Table 8: Alternative discounting – lifetime maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
	SoC	Belimumab	net	Belimumab	net
3.5% for benefits					
Belimumab direct drug cost		[redacted]	[redacted]	[redacted]	[redacted]
Total cost	£219,448	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	9.81	10.61	0.81	10.42	0.61
ICER			[redacted]		[redacted]
1.5% for benefits					
Belimumab direct drug cost		[redacted]	[redacted]	[redacted]	[redacted]
Total cost	£219,448	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.17	14.42	1.25	14.10	0.93
ICER			[redacted]		[redacted]

Table 9 shows the parallel results when the maximum duration of treatment with belimumab is assumed to be 6 years.

Table 9: Alternative discounting – 6 year maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
	SoC	Belimumab	net	Belimumab	net
3.5% for benefits					
Belimumab direct drug cost		[redacted]	[redacted]	[redacted]	[redacted]
Total cost	£219,448	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	9.81	10.42	0.61	10.32	0.51
ICER			[redacted]		[redacted]
1.5% for benefits					
Belimumab direct drug cost		[redacted]	[redacted]	[redacted]	[redacted]
Total cost	£219,448	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.17	14.07	0.90	13.92	0.75
ICER			[redacted]		[redacted]

The above results (Table 9) cross check with those presented by the manufacturer.

C. Summary of ERG assessment

1. Our concerns with the original submission have not been addressed (as listed on Page 7-8).

2. We are concerned about the maximum treatment duration of 6 years and how it will be 'policed'. In particular there are issues which need to be considered of:

    a) Effects of summary cessation of treatment for the group of patients who continue to respond to belimumab up to 6 years.

    b) Effects on ICERs of retreatment decisions subsequent to relapse (i.e. whether patients will be given belimumab treatment over one or more subsequent periods of 6 years).

3. The steroid sparing results are from a non-peer reviewed abstract (Petri et al., 2011). Although these results are of interest, the study lacks a control group. In addition the SoC arm from the trials shows a similar trajectory of steroid sparing which suggests that the steroid sparing effect found may not be attributable to belimumab treatment.

4. The manufacturer's case for the use of the 1.5% discount rate for health benefits is not strongly supported and largely rests on the extrapolation of benefits from steroid sparing over a 30 year time horizon. The ERG consider that the 30 year time horizon may be inappropriately long, given the epidemiology of the condition in the UK and mean age at diagnosis (see Somers, 2007).

References

Petri, M., Furie, R. A., Wallace, D. J. et al. Six-year experience with belimumab in patients with SLE. Ann Rheum Dis 70 (Suppl 3)[314]; 2011.

Somers EC, Thomas SL, Smeeth L, Schoonen WM, Hall AJ. Incidence of systemic lupus erythematosus in the United Kingdom, 1990-1999. Arthritis Rheum. 2007 May 15; 57(4):612-8.

ERG errata

The ERG economist reported the undiscounted costs rather than the discounted costs in the previous briefing paper. This does not affect the reported ICERs which were correctly reported. The costs are corrected to be the discounted costs in the tables below.

Retaining the baseline age distribution with the mean age of 34.3 years as within the manufacturer modelling, the discounted costs, benefits and ICERs that result from the alternative discounting regimes are as below for the modelling that assumes that treatment with belimumab can be ongoing.

Table8: Alternative discounting – lifetime maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
	SoC	Belimumab	net	Belimumab	net
3.5% for benefits Belimumab direct drug cost Total cost QALYs ICER	£105,366 9.81	[redacted] 10.61	[redacted] 0.81 [redacted]	[redacted] 10.42	[redacted] 0.61 [redacted]
1.5% for benefits Belimumab direct drug cost Total cost QALYs ICER	£105,366 13.17	[redacted] 14.42	[redacted] 1.25 [redacted]	[redacted] 14.10	[redacted] 0.93 [redacted]

The parallel table that assumes treatment with belimumab is for a maximum 6 years is as below.

Table9: Alternative discounting – 6 year maximum treatment with belimumab

Belimumab responder		SS change ≥ 4 at week 24		SS change ≥ 6 at week 24	
	SoC	Belimumab	net	Belimumab	net
3.5% for benefits Belimumab direct drug cost Total cost QALYs ICER	£105,366 9.81	[redacted] 10.42	[redacted] 0.61 [redacted]	[redacted] 10.32	[redacted] 0.51 [redacted]
1.5% for benefits Belimumab direct drug cost Total cost QALYs ICER	£105,366 13.17	[redacted] 14.07	[redacted] 0.90 [redacted]	[redacted] 13.92	[redacted] 0.75 [redacted]

ERG's additional sensitivity analyses

The manufacturer supplies additional data from the open label study suggesting a treatment discontinuation rate averaging 13% between years 2 and 6. Note that this is not specific to the target group modelled by the manufacturer. The original submission contained a sensitivity analysis which assumed a 13.7% annual discontinuation rate rather than the 8% of the base case. In order to be able to triangulate between results, applying this[1] rate within the current context suggests that for the lifetime modelling the with PAS cost effectiveness falls from [redacted] per QALY to [redacted] per QALY. The effect is more muted among the modelling that assumes a maximum treatment duration of only 6 years, it causing the with PAS cost effectiveness to fall from [redacted] per QALY to [redacted] per QALY.

[1] Implemented by setting cell AR276 of the *BLISS Subgroup Data* worksheet to 0.863.

Additional analyses for belimumab following teleconference before 2nd Committee meeting

These are presented for:

- the with PAS prices for belimumab of [redacted] for 400mg vial and [redacted] for 120mg vial; and
- the prices without the PAS for belimumab of £405 for 400mg vial and £121.50 for 120mg vial.

The revised baseline ICER for belimumab among the target population is based upon:

- A maximum lifetime treatment duration, though the average will be less than this; and,
- A stopping rule of a minimum SS improvement at 24 weeks of 4.

These analyses are presented assuming:

- an administration costs of £154 as applied within the tocilizumab STA;
- an annual discontinuation subsequent to 24 weeks of 13% as drawn from Petri[12]; and
- benefits and costs discounted at 3.5%.

Additional sensitivity analyses of:

- A maximum of six years treatment duration;
- No stopping rule;
- A stopping rule related to an SS improvement at 24 weeks of 6;

are also presented.

Lifetime treatment including PAS:

	No stopping rule			**24 week SS improvement ≥ 4**			24 week SS improvement ≥ 6		
	SoC	Bel.	Net	SoC	Bel.	Net	SoC	Bel.	Net
Life Years	31.93	34.12	2.18	31.93	34.24	2.30	31.93	33.99	2.06
Discounted quantities									
Bel. drug	£0	[redacted]	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]	[redacted]
Bel. admin	£0	£11,196	£11,196	£0	£8,083	£8,083	£0	£6,417	£6,417
Total cost	£105,366	[redacted]	[redacted]	£105,366	[redacted]	[redacted]	£105,366	[redacted]	[redacted]
QALYs	9.809	10.448	0.639	9.809	10.471	0.662	9.809	10.402	0.593
ICER			[redacted]			[redacted]			[redacted]

6 years maximum belimumab treatment including PAS:

	No stopping 24 week rule			24 week SS improvement ≥ 4			24 week SS improvement ≥ 6		
	SoC	Bel.	Net	SoC	Bel.	Net	SoC	Bel.	Net
Life Years	31.93	33.67	1.74	31.93	33.77	1.84	31.93	33.59	1.65
Discounted quantities									
Bel. drug	£0	[redacted]	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]	[redacted]
Bel. admin	£0	£7,610	£7,610	£0	£5,485	£5,485	£0	£4,422	£4,422
Total cost	£105,366	[redacted]	[redacted]	£105,366	[redacted]	[redacted]	£105,366	[redacted]	[redacted]
QALYs	9.809	10.343	0.534	9.809	10.364	0.555	9.809	10.310	0.501
ICER			[redacted]			[redacted]			[redacted]

[1] Implemented in the *Subgroup_BLISS_data* worksheet by setting B276 = 0.870 and C276 = EXP(LN(B276)*(532/(532-168))) = 0.816 rather than the 0.506 of the submitted model, with the parallel changes also being made to I276 & J276, P276 & Q276, AD276 & AE276, AK276 & AL276, AR276 & AS276, BF276 & BG276, BM276 & BN276 and BT276 & BU276. Note that within the model visual basic code it appears the RespAnalysis only has an impact within the UpdSSFirstHalfYear() procedure of clsActivity. The Discontinuation procedure within clsPatient only indexes DiscP(j,k) with k=responder. In the light of this it is not clear to the ERG why altering these antecedents to cells O33:O34, the "no resp" natural discontinuation rates of the Treatment Effects worksheet, has an impact upon the model output. As a consequence, the model outputs for the no responder analysis should be treated with caution. Note that this issue is not necessarily related to the discrepancy in terms of the no responder analysis generating a smaller average patient gain in the belimumab arm than the SS≥4 responder analysis.

[2] Note that within Petri it is unclear what proportion of the 296 entering the continuation trial at week 80 were drawn from the original patient populations randomised to SoC, belimumab 10mg, belimumab 4mg and belimumab 1mg (n=449, of which 296/449=66%). Within the modelling of no discontinuation rule, the annual 13% natural discontinuation rates have been modelled as applying from baseline, though due to the model implementation and the Discontinuation procedure apparently only indexing DiscP(j,k) with k=responder this in effect only applies 7% for the first year.

Lifetime treatment excluding the PAS:

	No stopping rule			**24 week SS improvement ≥ 4**			24 week SS improvement ≥ 6		
	SoC	Bel.	Net	SoC	Bel.	Net	SoC	Bel.	Net
Life Years	31.93	34.12	2.18	31.93	34.24	2.30	31.93	33.99	2.06
Discounted quantities									
Bel. drug	£0	£50,529	£50,529	£0	£36,480	£36,480	£0	£28,961	£28,961
Bel. admin	£0	£11,196	£11,196	£0	£8,083	£8,083	£0	£6,417	£6,417
Total cost	£105,366	£162,891	£57,526	£105,366	£145,865	£40,499	£105,366	£137,243	£31,878
QALYs	9.809	10.448	0.639	9.809	10.471	0.662	9.809	10.402	0.593
ICER			£90,002			**£61,193**			£53,744

6 years maximum belimumab treatment excluding the PAS:

	No stopping 24 week rule			24 week SS improvement ≥ 4			24 week SS improvement ≥ 6		
	SoC	Bel.	Net	SoC	Bel.	Net	SoC	Bel.	Net
Life Years	31.93	33.67	1.74	31.93	33.77	1.84	31.93	33.59	1.65
Discounted quantities									
Bel. drug	£0	£34,345	£34,345	£0	£24,758	£24,758	£0	£19,960	£19,960
Bel. admin	£0	£7,610	£7,610	£0	£5,485	£5,485	£0	£4,422	£4,422
Total cost	£105,366	£143,253	£37,888	£105,366	£131,666	£26,300	£105,366	£126,470	£21,104
QALYs	9.809	10.343	0.534	9.809	10.364	0.555	9.809	10.310	0.501
ICER			£70,942			£47,382			£42,108

Within the model there are placeholders for "no resp" 18 month discontinuation rates. The current ERG interpretation is that these relate to the no responder analyses. The above has set the value for this equal to 0.816. The submitted model for reasons that are not clear, as per footnote one above, used a value of 0.506. Applying the value of 0.506 results in the following.

No stopping rule, 0.506 18 month continuation rate in placeholders, including PAS

	Lifetime treatment			Maximum 6 years treatment		
	SoC	Bel.	Net	SoC	Bel.	Net
Life Years	31.93	34.12	2.18	31.93	33.65	1.72
Discounted quantities						
Bel. drug	£0	[redacted]	[redacted]	£0	[redacted]	[redacted]
Bel. admin	£0	£9,081	£9,081	£0	£6,439	£6,439
Total cost	£105,366	[redacted]	[redacted]	£105,366	[redacted]	[redacted]
QALYs	9.809	10.449	0.640	9.809	10.342	0.533
ICER			[redacted]			[redacted]

Examination of the model summary outputs suggests that the above more closely corresponds, probably by accident, with a first year discontinuation rate of 13% than the ERG implementation which just causes the model to only apply a 7% discontinuation rate in the first year followed by 13% thereafter. These may be more reasonable implementations of an annual 13% discontinuation rate from baseline.

Inconsistency of results for the no stopping rule

The above raises an additional question around modelling. Tightening the stopping rule to a minimum SS improvement of 6 reduces the benefits from belimumab but reduces costs by a greater proportion. As a consequence, the ICER improves. But while excluding the stopping rule does worsen the ICER as would be anticipated, it is also modelled as reducing both the life expectancy and aggregate QALYs in the belimumab arm.

Note that for the no stopping rule the model adopts the 52 week SS regression based upon SoC, belimumab week 24 non-responders and belimumab week 24 responders as used for the stopping rule of an improvement of SS≥4 points at 24 weeks. This may initially seem peculiar but in essence it is simply retaining the division of the belimumab patient group into those who achieved an SS reduction of at least 4 and those who did not. Those who did not are for the no stopping rule modelling simply assumed not to have the stopping rule applied.

The reason for adopting this approach is not clear to the ERG. A more straightforward approach might have been to classify all belimumab patients as responders and derive the appropriate regression specific to this scenario.

There is the theoretical possibility that the no responder analysis estimates a lower average patient benefit than the SS≥4 responder analysis due to the week 52 SS regression having a marginally lower percentage change of -34.3% for belimumab "non-responder" patients compared to -34.9% for SoC. Revising these to be both -34.9% in the submitted model shows that this is not the source of the discrepancy in that the no discontinuation rule modelling still models a slightly lower average patient gain from belimumab than the SS≥4 responder analysis. The visual basic code adds an additional random element to the annual SS scores within the deterministic patient level modelling for reasons that are not clear to the ERG. This might slow model convergence. But it would be anticipated that the no responder analysis should result in a reasonably higher average patient benefit from belimumab than the SS≥4 responder analysis.

Additional sensitivity analyses to revised baseline

At the 1st AC there was some debate around the appropriate administration cost for belimumab.

The ERG report highlighted a possible double counting of the costs of SLE, due to a cost function based upon the SS score being estimated separately from the costs of individual organ involvement. The possible impact of this can be explored by assuming that costs are flat and do not increase automatically with the SS score, while retaining the costs of individual organ involvement.

The ACD highlighted some concerns around the utility values used. In particular, the possibility of the values for renal disease in the early cycles of the model being over-ridden by a larger utility decrement for musculoskeletal involvement. This importance of this can be explored by first excluding all organ involvement disutility effects, and then individually reapplying the disutility multipliers for renal and pulmonary involvement. These are the two main organ involvements for which belimumab is estimated to have a reasonably large impact upon their incidence.

Possible uncertainty around the rates of organ involvement would affect cost offsets, the disutilities as discussed above and the mortality function. Having explored the disutilities, the mortality impact can be similarly explored by simply excluding organ involvement from the mortality function.

The following sensitivity analyses explore some additional uncertainties within the modelling. These are applied to the revised baseline.

- an administration cost of £216 based upon one half the day case cost HRG HD23C[3];
- Applying a flat cost function per SS point of £1000 per annum, regardless of the SS value
- Applying a flat cost function per SS point of £2000 per annum, regardless of the SS value
- Removing the utility impact of organ involvement by setting all organ utility multipliers to 1.0
- Removing the utility impact of organ involvement by setting all organ utility multipliers to 1.0 except for the 0.69 for pulmonary involvement

[3] Implemented in the *Scenario* worksheet by setting cell E54 = 216

- Removing the utility impact of organ involvement by setting all organ utility multipliers to 1.0 except for the 0.97 to 0.80 for renal involvement
- Setting the organ involvement coefficients of the mortality function to zero
- Applying an adjusted value of 3.5 to the SS evolution regression drawn from the JHU cohort, rather than the base case 3.0

	Costs			QALYs			
	SoC	Bel.	Net	SoC	Bel.	Net	ICER
Revised baseline	£105,366	[redacted]	[redacted]	9.809	10.471	0.662	[redacted]
£216 belimumab administration	£105,366	[redacted]	[redacted]	9.809	10.471	0.662	[redacted]
Flat SS cost £1000	£94,827	[redacted]	[redacted]	9.809	10.471	0.662	[redacted]
Flat SS cost £2000	£112,171	[redacted]	[redacted]	9.809	10.471	0.662	[redacted]
No organ disutility	£105,366	[redacted]	[redacted]	12.113	12.817	0.705	[redacted]
Only pulmonary organ disutility	£105,366	[redacted]	[redacted]	11.178	11.950	0.772	[redacted]
Only renal organ disutility	£105,366	[redacted]	[redacted]	11.919	12.657	0.738	[redacted]
No organ mortality impact	£128,438	[redacted]	[redacted]	10.668	11.256	0.588	[redacted]
3.5 SS regression coefficient	£103,899	[redacted]	[redacted]	9.279	9.960	0.681	[redacted]

CENTRE FOR RHEUMATOLOGY
DIVISION OF MEDICINE
UNIVERSITY COLLEGE LONDON
CENTRE DIRECTOR: PROFESSOR DAVID ISENBERG MD FRCP FAMS
The Rayne Building
[redacted]
5 University Street, London WC1E 6JF
PROFESSOR D ISENBERG: TEL: [redacted]
SECRETARY: Tel: [redacted] **; FAX:** [redacted]
EMAIL: [redacted]

4th November 2011

Robert Fernley
Technology Appraisals Administrator – Committee D
National Institute for Health and Clinical Excellence
Level 1A City Tower
Piccadilly Plaza
Manchester M1 4BD

Dear Robert

Re: Systemic Lupus Erythematosus (autoantibody-positive) - belimumab

Thank you for asking me to comment on Sections 4 and 5 of the report which you kindly sent me yesterday. I would like to make the following comments:-

1. The revised submission from the manufacturers makes much more sense, notably the admission that belimumab is unlikely to be used "for life", though even the proposed six years of use is I think unlikely to be followed in practice. Nevertheless, using belimumab for a shorter period of time clearly reduces its cost. Furthermore, the notion that a decision could be made after a fixed period of time about whether to continue the drug. Using a reduction in the SLEDAI score of 4 points also seems reasonable and, given that some patients will not meet this end point, will keep lower the cost even more.
2. I think it is important to emphasise (certainly before PCTs become too concerned about the costs) that the numbers of patients to whom belimumab is likely to be offered is small. My cohort of lupus patients under active follow up is approximately 450 (and one of the largest in the UK). Of these patients, I estimate that 10-15% do not do well or are unable to tolerate conventional immunosuppressive drugs. In reality for the past 11 years, I have used rituximab in this situation and in total have treated only 100 patients in 11 years. It is this group of patients for whom belimumab could now be considered.
3. The initial NICE report makes several references to rituximab and tries to make comparisons. I find myself in a very odd situation. I was the first person to propose that rituximab be used in the treatment of lupus and my centre probably has the world's largest single centre experience of it. I have seen some remarkable improvements in patients given rituximab and indeed have published that 90% of the patients we have treated here at UCH at six months have shown full or partial remission (in those who failed conventional immunosuppression). Nevertheless the fact is that (much to my chagrin!), rituximab did not meet its endpoints in two major clinical trials. This, in my view, is likely to be due to trial design but let that pass! In contrast, Benlysta, with all the caveats that you and other commentators have made, **did** meet its endpoints in two major international trials, has been approved by the FDA and the European Medicines commission and indeed is the first drug to be approved for the treatment of lupus in over 50 years. These facts should not be ignored.
4. Whilst it is true that Benlysta has only been tried in lupus patients with significant arthritis and skin disease (and immunological parameters) it is I think a reasonable assumption that if it helps these aspsects of lupus, there is an excellent chance that it will be beneficial for other aspects of the disease although this remains to be confirmed.
5. The key issue which I think the NICE committee has to consider is this. A rather small number of lupus patients do not do well with conventional immunosuppressive therapy and require substantial amounts of corticosteroids which leads inevitably to significant damage

(major osteoporosis, cataracts, hypertension etc. with major direct and indirect costs. In the past 10 years many of these patients nationally and internationally have been treated (often with great success) with rituximab. However, given the failure of two international trials of rituximab, PCTs are now becoming much less likely to agree to pay for the drug. For example, I have just had my first outright refusal by Camden to pay for the retreatment of patients with rituximab in whom very clear clinical and serological evidence to show that it worked the first time. The PCT made explicit reference to the failure of the two trials for this refusal. If NICE does not support the use of Benlysta in patients who have done poorly with conventional approaches, the stark reality is that these patients and the physicians treating them have very few places to go. It is increasingly hard to get hold of rituximab and the only options include admitting patients for high dose intravenous steroids (with all the consequent risks) or possibly intravenous immunoglobulin (which is also expensive and increasingly hard to get hold of). These are expensive options.

6. My hope is that the committee will permit the use of Benlysta in particular situations i.e. clinically and serologically active patients (I think use of a SLEDAI score > 10, arbitrary as it is, is reasonable) who have failed or are unable to tolerate conventional immunosuppression. The caveat should be that the treatment must be stopped if there is no improvement. Again I think of SLICC point reduction of 4 is a reasonable minimum after a fixed period of time would be a good way to go. The data would suggest that the time point for making a decision should be one year, but I suspect six months would be reasonable in many cases.

With kind regards,

Yours sincerely

[redacted]

David A Isenberg MD FRCP FAMS
Arthritis Research UK Diamond Jubilee Professor of Rheumatology
at University College London

Appendix 2
Additional cost-effectiveness analyses relevant to this Single Technology Appraisal

Provided below are the results from the health economic analysis for our proposed target (high disease activity) SLE subgroup incorporating our revised base case with a maximum treatment duration of six years and a treatment continuation criterion (SS score decrease of ≥4) after six months of treatment. All data relating to costs and ICERs quoted in this appendix incorporate the list prices for the two vials and do not include our patient access scheme.

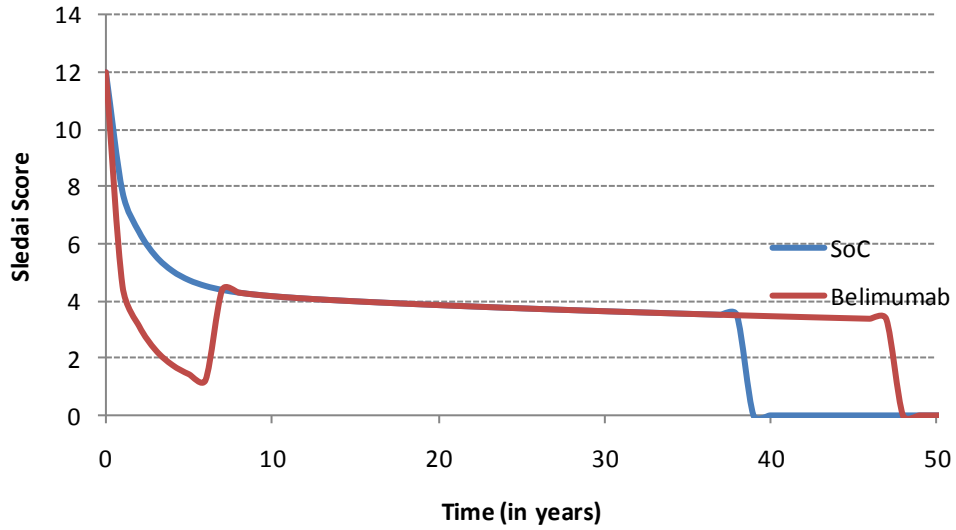
Methodology

All analyses described in this appendix relate to the health economic model supplied to NICE with our original submission in April 2011. The same key assumptions described for our original base case still apply for our revised base case except that a maximum treatment duration of six years for belimumab is now applied; the original base case had allowed up to a lifetime duration. The need to reconsider a treatment duration for belimumab, more in line with how it was likely to be used in clinical practice, was identified after reviewing the comments made in the ACD by the clinical specialists consulted for this appraisal. Our choice for a maximum treatment duration of six years for our revised base case duration was based on a number of considerations. Firstly, there is now long-term efficacy and safety trial data from the Phase II extension study (LBSL99) (Petri et al. 2011) for belimumab which demonstrates continued efficacy with belimumab without compromising safety over a six year follow-up duration. Secondly, other treatments for lupus, such as immunosuppressants, are frequently prescribed for between two and five years to maintain suppression of disease activity. It is through sustained suppression of disease activity that, in addition to improving patients' quality of life, and for some patients enabling steroid dose reductions with a lessening of their associated side effects, there is likely to be a benefit on reducing long term organ damage and on improving survival. Finally, we discussed our proposed treatment duration with a number of lupus specialists to ensure it was considered an acceptable duration for belimumab in the management of their eligible patients.

The methodology for the analysis of the BLISS study SELENA-SLEDAI (SS) scores, and the Johns Hopkins (JH) disease activity, steroid dose and natural history mortality and organ damage models is identical to that presented in our original submission. However detailed below is an explanation of the impact in the model of the incorporation of a maximum treatment duration of six years.

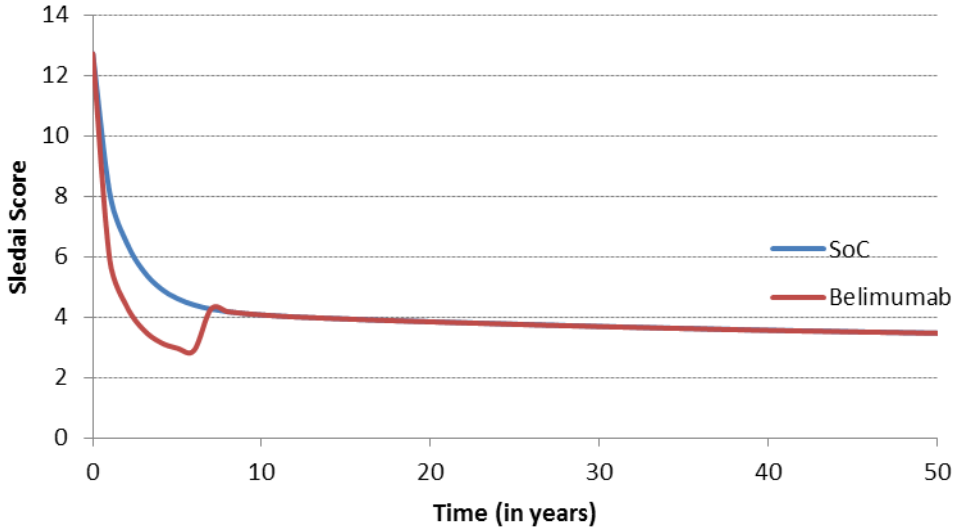
A patient who has not withdrawn early due to reasons related to natural discontinuation, and who successfully completes six years of belimumab treatment, is switched to continue to receive standard of care (SoC) treatments only from the start of the seventh year. This directly affects SLEDAI score in the belimumab arm of the model as it applies a SoC disease activity score for each belimumab patient from the end of Year 6 for the remaining duration of the model horizon, using the same simulation methodology used to generate SLEDAI scores for the patients allocated to the SoC arm in the model. This is graphically illustrated for SLEDAI score in Figure A2.1.

Figure A2.1. Example of SLEDAI score for a SoC patient and for a patient discontinuing belimumab treatment after year 6.



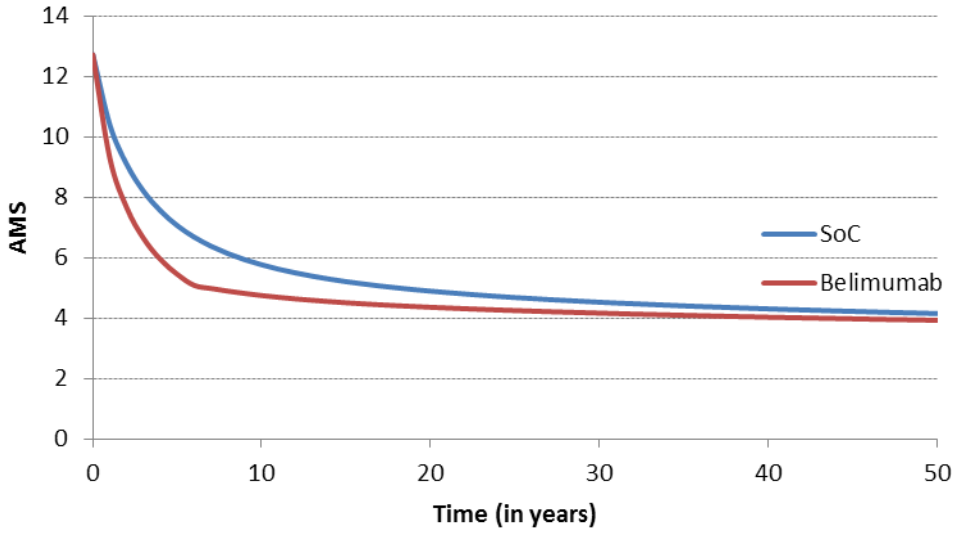
The adjusted (average) SLEDAI score (AMS) over time for 50,000 simulated patients is shown in Figure A2.2 for those patients who remain alive. It is clear from the graph that patients who are treated with belimumab (in addition to SoC) have a larger reduction in SS score than patients who are treated with SoC alone over the first six years.

Figure A2.2. SLEDAI Score over time for 50,000 patients simulated – High disease activity (Target) population.



Although the level of disease activity after discontinuation of belimumab returns to SoC levels, a beneficial effect from belimumab treatment is kept through a decreased average disease activity score over time (Figure A2.3).

Figure A2.3. Adjusted Mean SLEDAI (AMS) over time censored for death - Target population.



The average disease activity score is an important predictor of organ damage in the cardiovascular, renal, pulmonary and peripheral vascular systems (Table A2.1).

The lower disease activity for belimumab patients over six years of treatment will lead to a decreased steroid dose over this time period and a decreased risk for organ damage. The average disease activity (AMS) over lifetime, cumulative average prednisone dose and certain types of organ damage, contribute to the mortality risk (Table A2.2).

Table A2.1. Organ damage time to event models and corresponding covariates from Johns Hopkins cohort analysis

	CV	**Diabetes**	**GI**	**Malignancy**	**MSK**	**NP**	**Ocular**	**PV**	**GF**	**Pulmonary**	**Renal**	**Skin**
Survival model	Loglog	Exp	Exp	Exp	Loglog	Weibull	LogLog	Exp	Exp	Gompertz	Exp	LogLog
Covariates												
Male				0.4981								
Black		0.7805										
Age at diagnosis	-0.054			0.0229	-0.0354							
Past smoker								0.6066				-1.5658
Cholesterol				-0.0088		0.0047			0.005		0.008	
Hypertension	-1.089					0.5167		1.0051				
AAP										1.0132		
LAP								1.3705				
Log of age		2.2481				0.607	-2.97	1.1608		1.2316		
Log of disease duration	-0.741			0.3082	-0.6747							
AMS	-0.209		-0.0606		-0.0407	0.044	-0.045	0.1702		0.1388	0.3234	-0.0466
CAPD	-0.001	0.0019	0.0011		-0.0018		-0.002		0.0022			-0.0025
SLICC/ACR score				0.1467	-0.1448	0.0954				0.1039		
Renal damage	-0.834											
Diabetes at previous visit	-1.067											
Constant	10.123	-14.6564	-4.8419	-4.8106	7.0495	-7.3961	15.993	-11.695	-7.6433	-9.265	-8.293	9.651
Parametric par	1.2164				1.1421	0.8161	1.084			-0.0382		1.5938

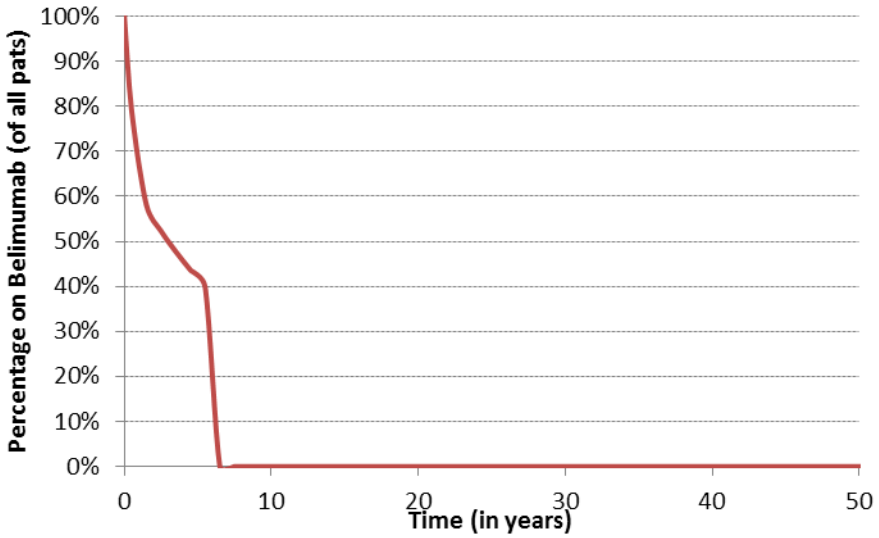
CV = cardiovascular, MSK = musculoskeletal, NP = neuropsychatric, PV = peripheral vascular, GI = gastrointestinal, GF = Gonadal Failure, Loglog = loglogistic, Exp = exponential, AAP = Anticardiolipid antibodies, LAP = Lupus anticoagulant positive, AMS = average mean SLEDAI up to current time, CAPD = cumulative average prednisone dose up to current time, Seros = serositis, Paramteric par = additional parametric distribution parameter for non-exponential survival models.

Table A2.2. Weibull survival model explaining risk of death with AMS included and item involvement effects removed – JH cohort

Covariates	Model coefficient
Constant	-10.366
Black ethnicity	0.7814
Age at diagnosis	0.0321
Cholesterol	0.0044
AMS over lifetime	0.2135
Cumulative Average Prednisone Dose (mg/month)	0.0012
Renal damage	0.652
Musculoskeletal damage at previous visit	0.415
Peripheral vascular damage at previous visit	0.9783
Gastrointestinal damage at previous visit	0.4684
Diabetes at previous visit	0.6764
Malignancy at previous visit	1.1489
Any infection at time of death at current visit	0.7409
Parametric distribution parameter for Weibull	1.6799

The discontinuation of patients on belimumab is shown in Figure A2.4. The steep fall in patients continuing with belimumab in the first year is caused by those patients not satisfying the treatment continuation criterion at 24 weeks and hence moving to SoC in the model. After six years all patients have switched to receiving SoC treatments only.

Figure A2.4. Discontinuation from belimumab (includes death) – Target population.



The survival over time is therefore improved for belimumab patients compared with patients on SoC due to the benefits of belimumab on these components (Figure A2.5). The relatively steep decline in survival in the first year for both arms is caused by the relatively high standardised mortality ratio for patients younger than 24 years (see Table A2.3).

Figure A2.5. Survival of patients over time – Target population

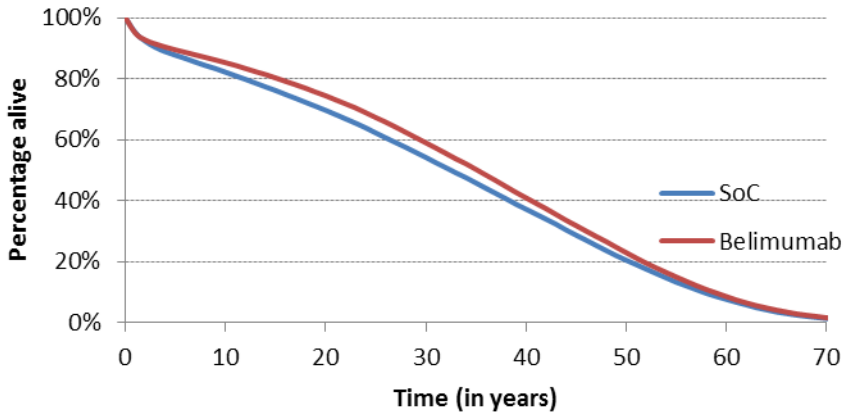


Table A2.3. Standardised Mortality Ratios for SLE patients stratified by age groups according to Bernatsky et al (2006).

Age	Standardized Mortality Ratio	95% CI
16-24	19.2	14.7, 24.7
25-39	8.0	7.0, 9.1
40-59	3.7	3.3, 4
>60	1.4	1.3, 1.5

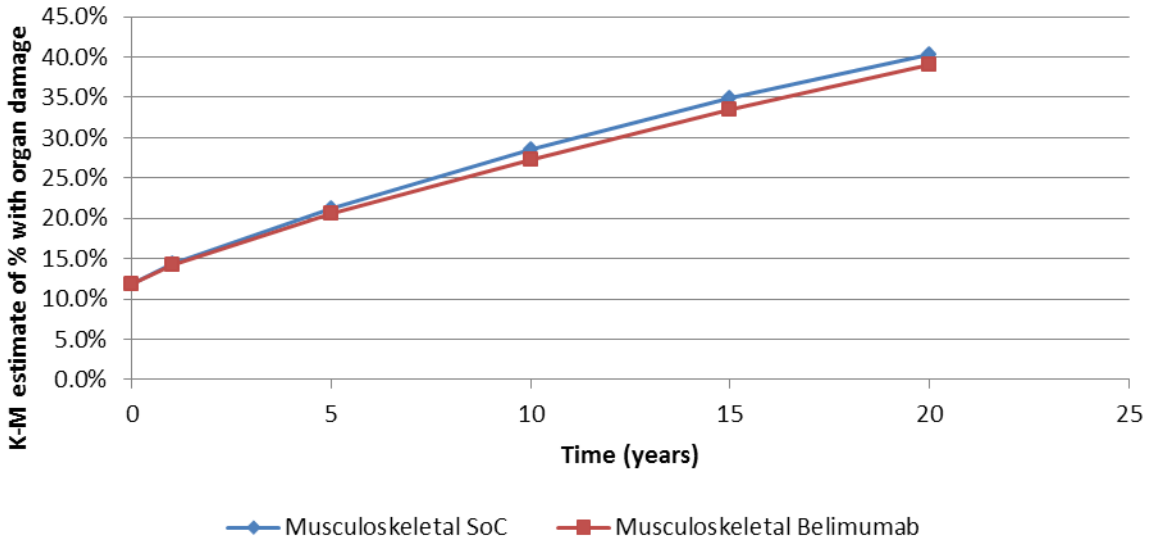
As belimumab patients have an estimated longer life expectancy, the exposure to the risk of organ damage is increased for belimumab patients, hence, for eight of the organs (diabetes, gastrointestinal, malignancy, musculoskeletal, neuropsychiatric, ocular, premature gonadal failure, and skin), the percentage of damage occurrence is similar or higher than for SoC (see Table A2.4). However, for cardiovascular, peripheral vascular, pulmonary and renal systems, fewer patients on belimumab develop damage compared to SoC. This is due to the dependence of damage risk on disease activity and steroid use which is lower for patients receiving belimumab.

Table A2.4. Organ damage occurrence for SLE patients until death - Target population

	SoC	Belimumab	Difference
Cardiovascular	23.9%	21.8%	-2.1%
Diabetes	17.9%	19.0%	1.0%
Gastrointestinal	22.1%	24.2%	2.2%
Malignancy	32.0%	33.4%	1.4%
Musculoskeletal	48.5%	49.0%	0.5%
Neuropsychiatric	44.7%	45.6%	0.9%
Ocular	35.1%	35.7%	0.5%
Peripheral vascular	21.5%	20.8%	-0.7%
Premature gonadal failure	7.2%	7.4%	0.1%
Pulmonary	39.9%	37.5%	-2.4%
Renal	24.3%	19.9%	-4.4%
Skin	7.9%	7.9%	0.0%

As belimumab is estimated to reduce the risk of organ damage for the cardiovascular, peripheral vascular, pulmonary and renal organ systems, this damage will occur later in belimumab patients; organ damage is irreversible and lasts until death. The duration of the organ damage therefore depends on the remaining lifespan of the patient. As discussed above, the occurrence of damage in the remaining organ systems is higher or similar in the belimumab arm compared with the SoC arm, due mainly to the increased life expectancy with belimumab. However, for the patients still alive, the proportion with organ damage is lower with belimumab. This is illustrated in a Kaplan-Meier plot of musculoskeletal damage censoring for death (Figure A2.6).

Figure A2.6. Kaplan-Meier plot of the proportion of patients alive with musculoskeletal damage – Target population



The effect of belimumab on the duration of organ damage is thus a product of the decreased risk, delayed onset of organ damage and the prolonged life expectancy of these patients. Although a decreased duration of damage is shown for the cardiovascular, pulmonary and renal organ system, the duration of damage for most other organ systems is increased due to the prolonged life-expectancy (Table A2.5).

Table A2.5. Average duration (yrs) of organ damage – Target Population

	SoC	Belimumab	Difference
Cardiovascular	5.60	5.24	-0.36
Diabetes	2.64	2.92	0.28
Gastrointestinal	4.62	5.30	0.68
Malignancy	4.39	4.79	0.40
Musculoskeletal	11.24	11.90	0.66
Neuropsychiatric	11.17	11.76	0.60
Ocular	7.88	8.18	0.30
Peripheral vascular	3.66	3.65	-0.02
Premature gonadal failure	1.77	1.85	0.07
Pulmonary	9.87	9.44	-0.43
Renal	5.38	4.49	-0.89
Skin	2.47	2.62	0.15

Table A2.6 summarises the main outcome results for the revised base case including a maximum treatment duration of six years. As demonstrated previously in Figure A2.5, belimumab patients have an estimated increased life-expectancy. The model predicts that belimumab-treated patients, in the subgroup with high disease activity, live on average 2.0 years longer, have a reduction in average mean SLEDAI score of -0.6, and a similar total SLICC organ damage score at death compared with SoC patients (Table A2.6). Treatment with belimumab in this Target population provides an estimated additional 0.8 life years and 0.6 QALYs (discounted at 3.5%).

Table A2.6. Summary of health economic outcomes – Target population

	SoC	Belimumab	Difference
Age at Death	66.19	68.23	2.04
SLICC at Death	4.12	4.05	-0.08
AMS	5.5	4.89	-0.57
Average monthly steroid cumulative dose	228.08	215.36	-12.72
Life Years (undiscounted)	31.93	33.98	2.04
Life Years (discounted at 3.5%)	17.05	17.87	0.81
QALYs (undiscounted)	17.31	18.60	1.28
QALYs (discounted at 3.5%)	9.81	10.42	0.61

Yearly drug acquisition costs for belimumab are presented in Table A2.7 below.

Table A2.7. Unit costs associated with the new technology in the economic model

Unit Costs	Belimumab 10mg/kg	Description
Mean cost of technology treatment based on an average weight of 65.4 kg as seen in the pooled BLISS study Target population	Year 1 annual cost = £9,731 Year 2 annual cost = £9,036	The list price vial costs are £121.50 and £405.00 for the 120 mcg and 400 mcg vials respectively. For each weight, the optimal vial combination is chosen and costs for waste are added. Weight distribution according to the trials is used to determine average yearly belimumab costs.
Administration cost per infusion	£1,764 (Year 1) £1,638 (Year 2+)	£126 per infusion (14 in Year 1 and 13 in Year 2 onwards)
Monitoring and test costs	£0	No additional monitoring or tests are required for implementation of this technology
Total Year 1 costs	£11,495	
Total Subsequent Year costs	£10,674	

Table A2.8 below summarises disaggregated costs from the model. The total costs for patients consist of resource costs related to disease activity, belimumab acquisition and administration costs, and longer-term costs incurred by organ damage. For both treatment groups, the organ damage costs are the highest component of the total costs. These costs are influenced by the duration of the organ damage shown in Table A2.5, the onset of organ damage through the discount rate, and the

increase of costs over time. For the cardiovascular, pulmonary and renal organs, the costs are lower as the estimated duration was shorter. In total, the organ damage costs are slightly lower for belimumab-treated patients due to the benefits on the pulmonary and renal systems. The costs related to disease activity are slightly higher in the belimumab arms. Although belimumab patients have less disease activity and consequently lower direct resource costs per year on average, the costs increase due to the estimated increased life expectancy. Overall, the main difference in costs is caused by belimumab acquisition and administration, amounting to £32,521 (83.0%) of the total absolute cost difference of £39,178.

Table A2.8. Summary of (discounted) costs over a lifetime model horizon - Target population

Discounted	SoC	Belimumab	Difference	Absolute difference	% absolute difference
Disease activity related costs	£27,882	£28,537	£655	£655	1.7%
Belimumab drug acquisition	£0	£27,530	£27,530	£27,530	70.3%
Belimumab administration	£0	£4,991	£4,991	£4,991	12.7%
Organ damage costs					
Cardiovascular	£1,838	£1,660	-£179	£179	0.5%
Diabetes	£2,493	£2,693	£201	£201	0.5%
Gastrointestinal	£359	£391	£32	£32	0.1%
Malignancy	£998	£1,019	£21	£21	0.1%
Musculoskeletal	£9,758	£10,060	£302	£302	0.8%
Neuropsychiatric	£6,434	£6,644	£211	£211	0.5%
Ocular	£392	£390	-£2	£2	0.0%
Peripheral vascular	£1,380	£1,327	-£53	£53	0.1%
Premature gonadal failure	£0	£0	£0	£0	0.0%
Pulmonary	£42,692	£39,727	-£2,966	£2,966	7.6%
Renal	£11,139	£9,102	-£2,037	£2,037	5.2%
Skin	£0	£0	£0	£0	0.0%
Sum of organ damage costs	£77,483	£73,013	-£4,470	-	
Total direct costs	£105,366	£134,071	£28,705	£39,178	100.0%

Table A2.9 summarises the results for the revised base case analysis. Belimumab-treated patients are estimated to live longer, however, due to their increased life expectancy and due to belimumab acquisition and administration costs, the total costs of managing SLE patients with high disease activity are higher than for SoC patients. The incremental costs are £28,705, with 0.8 added life years, or 0.6 added QALYs, discounted at 3.5%, resulting in an ICER of £47,342 per QALY gained.

Table A2.9. Discounted revised base case results – Target population

	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
SoC	£105,366	17.05	9.81	-			
Belimumab	£134,071	17.87	10.42	£28,705	0.81	0.61	£47,342
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity Analyses

Identical deterministic sensitivity analyses and PSA were conducted for this revised base case as documented in our original submission with our base case which included a lifetime duration of belimumab treatment.

Results of the Univariate Sensitivity Analyses

Tornado diagrams for the ICERs, QALYs and Costs resulting from the univariate sensitivity analyses are presented in Figures A2.7, A2.8, A2.9 and Tables A2.10, A2.11, and A2.12 respectively.

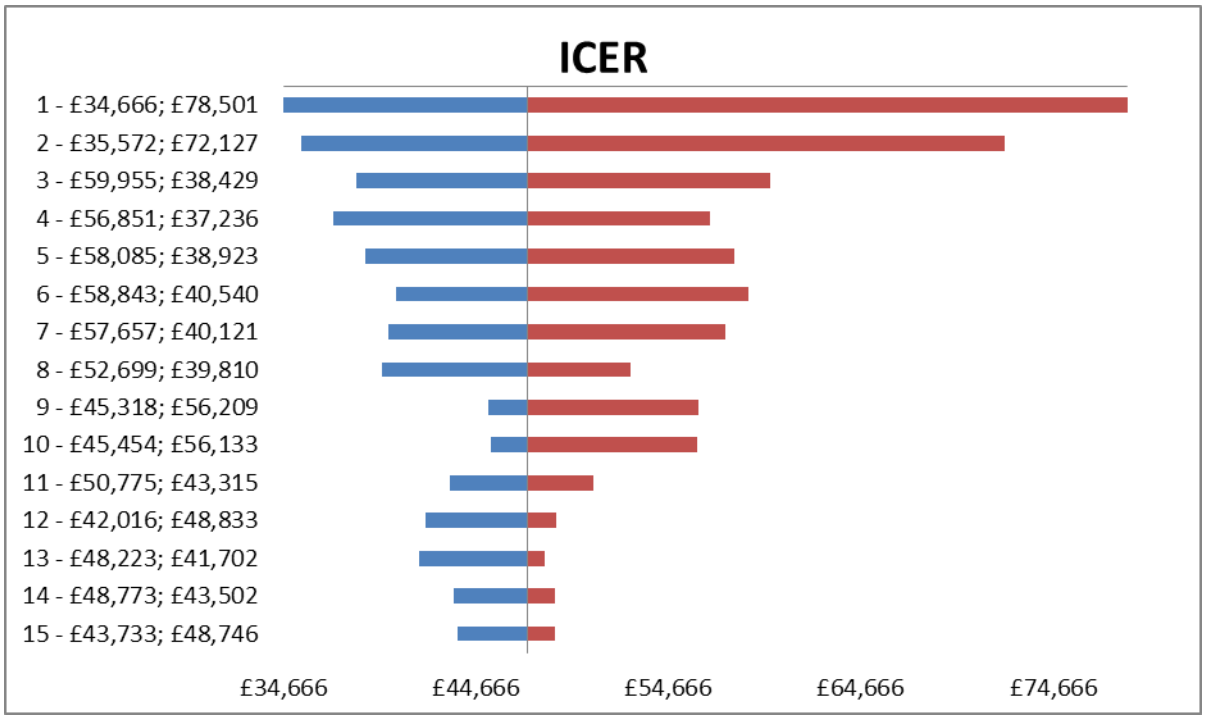
The main drivers of cost-effectiveness in our revised base case modelling, are similar to those specified in our original submission. The most important model driver is the treatment effect regression to estimate the effect on SS score of belimumab after 52 weeks; the smaller the benefit seen with belimumab compared to SoC, the lower the incremental QALY and hence the higher the ICER.

The effect of the AMS on mortality is also an important driver of the model results. The greater the reduction in AMS with belimumab, the greater the increase in life expectancy with belimumab compared with SoC and consequently the higher the QALY gain leading to more favourable ICERs.

The constant and effect of log age in the utility regression also have an important effect on the incremental effects and the ICER. However for these particular parameters, a univariate analysis is conditional on keeping the other parameters fixed, which in this case is not very likely due to the dependence between both coefficients. As discussed in our original submission there is substantial negative correlation between the constant and the effect of log age in the utility regression). As such, changing one parameter to the upper limit implies that the other parameter would likely be lower and hence they will (partly) cancel each other out.

The ICERs yielded from the univariate sensitivity analyses ranged from £34,666 to £78,501 per QALY gained.

Figure A2.7. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on ICERs – Target population



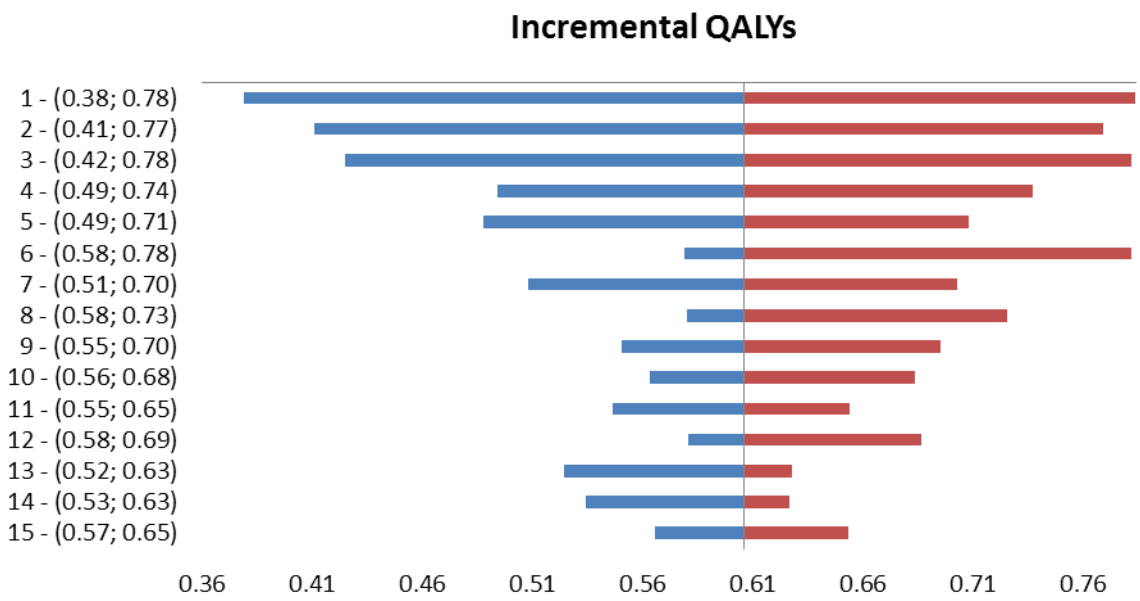
Note: Table A2.10 below details the variables identified as numbers in this tournado plot.

Table A2.10. Description of key variables with the largest impact on the ICER

Variable ID	Variable Name	Base Value	Lower bound	Upper bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
4	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
5	Coefficient of Log of age from the "clean utility" regression	0.15	-0.18	-0.10
6	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
7	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
8	Adjusted Mean SLEDAI coefficient at current visit from the natural history renal model	0.31	0.23	0.39
9	Constant coefficient from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
10	Log of age at current visit coefficient from the natural history neuropsychiatric model	0.61	0.03	1.23
11	Constant coefficient from the natural history renal model	-8.29	-9.01	-7.56
12	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history cardiovascular model	-0.21	-0.34	-0.07
13	Constant coefficient from the natural history pulmonary model	-9.17	-11.41	-6.54
14	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31

15	Coefficient of log of disease duration at current visit from the natural history cardiovascular model	-0.74	-1.31	-0.15

Figure A2.8 Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental QALYs – Target population



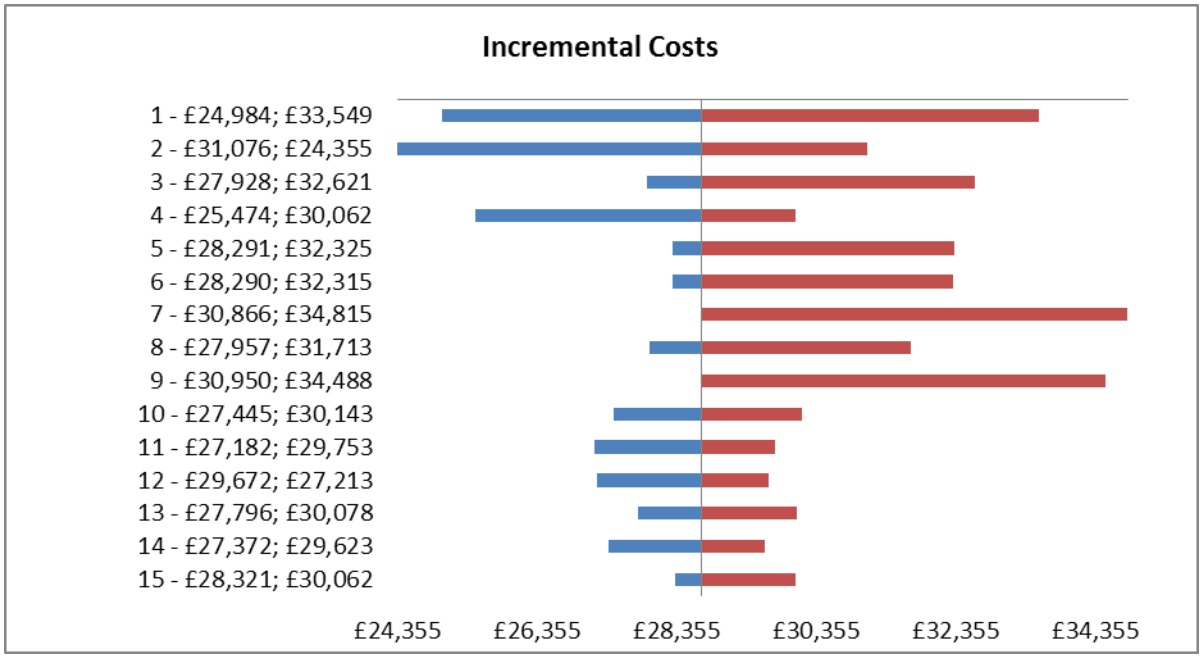
Note: Table A2.11 below details the variables identified as numbers in this tournado plot.

Table A2.11. Description of key variables with the largest Impact on Incremental QALYs

Variable ID	Variable	Base Value	Lower Bound	Upper Bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
4	Coefficient of Log of age from the "clean utility" regression	-0.15	-0.18	-0.10
5	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
6	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
7	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
8	Coefficient Log of age at current visit in natural history peripheral vascular model	1.16	0.43	1.89
9	Annual Discontinuation rate year 2 onwards for belimumab patients who were defined as “responders”	0.92	0.86	0.98
10	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history renal model	0.32	0.23	0.41
11	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history pulmonary model	0.14	0.06	0.22
12	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
13	Coefficient constant from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
14	Coefficient for log of age at current visit in natural history neuropsychiatric model	1.16	0.03	1.23

15	Coefficient for renal damage at previous visit in the natural history mortality model	0.65	0.16	1.19

Figure A2.9. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental costs– Target population



Note: Table A2.12 below details the variables identified as numbers in this tournado plot.

Table A2.12. Description of key variables with the largest impact on Incremental costs

Variable ID	Variable	Base value	Lower Bound	Upper Bound
1	Annual Discontinuation rate year 2 onwards for belimumab patients who were defined as "responders"	0.92	0.86	0.98
2	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
3	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
4	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
5	Constant coefficient in the natural history diabetes model	-14.66	-19.14	-10.29
6	Log of age coefficient at current visit in natural history diabetes model	2.25	1.16	3.35
7	Log of age at current visit coefficient in natural history pulmonary model	1.23	0.59	1.92
8	Log of age at current visit coefficient in natural history peripheral vascular model	31.23	0.43	1.89
9	Constant coefficient from the natural history pulmonary model	-9.27	-11.78	-6.86
10	Coefficient for renal damage at previous visit from the mortality model	0.65	0.16	1.19
11	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
12	Adjusted Mean SLEDAI at current visit coefficient from the renal model	0.32	0.23	0.41
13	Adjusted Constant coefficient in the natural history Disease Activity Model	3.0	2.20	3.93
14	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
15	Constant coefficient from the natural history malignancy model	-4.81	-6.05	-3.53

Probabilistic Sensitivity Analyses (PSA)

The results for the probabilistic sensitivity analyses are presented in the form of a scatter plot (Figure A2.10) and a cost-effectiveness acceptability curve (Figure A2.11) below.

Figure A2.10. Scatter plot of the PSA - Target population

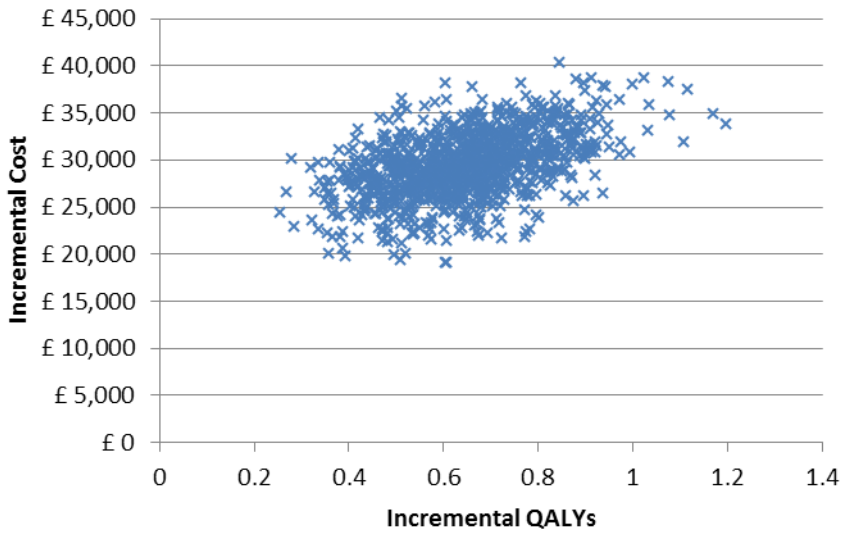
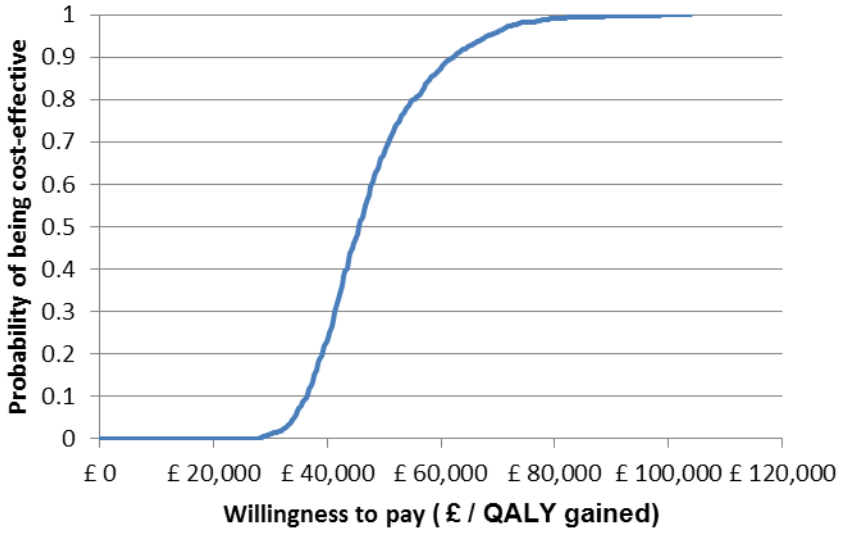


Figure A2.11. Acceptability curve of PSA - Target population



The PSA results show that at a willingness to pay of £30,000 per QALY gained, there is a 1.1% probability that belimumab is cost-effective compared to SoC. With a willingness to pay of £40,000 and £60,000 per QALY gained, there is a 23.2% and 87.3% probability, respectively, that belimumab is cost-effective compared to SoC.

Scenario Analyses

The following two key scenario analyses have been considered for this revised base case:

1. AS detailed in our main response section we believe a discount rate for health effects of 1.5% is justified for this technology appraisal and therefore consider this a key alternative scenario for consideration by the Appraisal Committee.

2. Being mindful of the annual cost to the NHS of treating patients with belimumab and of limited NHS resources, introducing a more stringent treatment continuation criterion after six months treatment would help to target belimumab to those patients believed to gain the greatest continued benefit with this treatment. In order to continue treatment with belimumab after six months patients would need to show a reduction in SELENA-SLEDAI (SS) score of at least 6 points.

Other scenario analyses considered are detailed below:

- Alternative maximum treatment durations for belimumab of 3, 5 and 10 years have also been examined to demonstrate the effect on the assessment of cost-effectiveness of shorter and longer maximum treatment durations compared with the base case. A maximum of 5 years is consistent with the maximum treatment duration used by clinicians for immunosuppressants currently used to treat SLE.

- The effect of excluding the treatment continuation criterion in the model has been examined to demonstrate the impact on estimated cost-effectiveness of not reviewing patient response in terms of reduced SS score after six months of treatment with belimumab.

- A different administration cost of £159 has been used in a scenario analysis, as this was suggested by the ERG who reviewed the STA appraisal for tocilizumab, a human monoclonal antibody for the treatment of rheumatoid arthritis, which also requires administration over one hour.

The results of the scenario analyses are presented in Table A2.13 below.

Table A2.13. Summary of Scenario Results - Target population

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised Base Case: 6 year maximum belimumab treatment duration	Time horizon = lifetime; 6 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; and health effects discount rate of 3.5%	£28,705	0.81	0.606	£47,342
Health effects discount rate of 1.5%	As revised base case but with discounting for benefits set to 1.5%.	£28,705	1.33	0.897	£31,988
More stringent treatment continuation criterion	As revised base case but with treatment continuation criterion at 24 weeks of SS score of ≥6 and health effects discount rate of 3.5%	£20,766	0.68	0.508	£40,863
More stringent treatment continuation criterion and health effects discount rate of 1.5%	As revised base case but with treatment continuation criterion at 24 weeks of SS score of ≥6 and health effects discount rate of 1.5%	£20,766	1.11	0.747	£27,807
Treatment continuation criterion excluded and health effects discount rate of 3.5%	As revised base case but with treatment continuation criterion at 24 weeks excluded	£33,384	0.77	0.584	£57,152
Treatment continuation criterion excluded and health effects discount rate of 1.5%	As revised base case but with treatment continuation criterion at 24 weeks excluded	£33,384	1.26	0.860	£38,808

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Higher drug administration cost	As revised base case but with a drug administration cost of £159 as recommended as a sensitivity analysis by the ERG in the NICE STA for tocilizumab for rheumatoid arthritis	£30,012	0.81	0.606	£49,498
3 year belimumab treatment duration	Time horizon = lifetime; 3 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; and health effects discount rate of 3.5%	£16,304	0.61	0.459	£35,497
3 year belimumab treatment duration and health effects discount rate of 1.5%	Time horizon = lifetime; 3 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; health effects discount rate of 1.5%	£16,304	0.97	0.67	£24,491
5 year belimumab treatment duration for the Target subgroup	Time horizon = lifetime; 3 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; and health effects discount rate of 3.5%	£25,047	0.75	0.560	£44,696
5 year belimumab treatment duration and health effects discount rate of 1.5%	Time horizon = lifetime; 3 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; health effects discount rate of 1.5%	£25,047	1.23	0.824	£30,391

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
10 year belimumab treatment duration	Time horizon = lifetime; 10 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; and health effects discount rate of 3.5%	£38,823	0.92	0.698	£55,607
10 year belimumab treatment duration and health effects discount rate of 1.5%	Time horizon = lifetime; 10 year maximum belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; health effects discount rate of 1.5%	£38,823	1.54	1.047	£37,066

The various alternative scenarios investigated resulted in ICERs ranging from £24,491 to £57,152 per QALY gained compared with the revised base case ICER of £47,342 per QALY gained.

Using a health effects discount rate of 1.5% rather than 3.5% has a significant impact on the ICER, reducing it by over £15,000 per QALY to give an ICER of £31,988 per QALY gained.

When a maximum treatment duration of 3 years for belimumab is considered, the revised base case ICER is reduced by just under £12,000 per QALY, yielding an ICER of £35,497 per QALY gained when a health effects discount rate of 3.5% was used. When a discount rate of 1.5% was included for health effects the ICER reduced to £24,491 per QALY gained.

In contrast, when a maximum treatment duration of 10 years for belimumab is considered, the revised base case ICER is increased by just over £8,250 per QALY, to give an ICER of £55,607 per QALY gained when a 3.5% health effects discount rate was used. However the ICER was reduced to £37,066 per QALY when a health effects discount rate of 1.5% was incorporated.

When 5 years is considered as a maximum treatment duration for belimumab, the ICER incorporating a health effects discount rate of 3.5% was £44,696 per QALY gained, a little less than £3000 below the base case ICER, reducing to £30,391 per QALY for a discount rate of 1.5%.

Excluding the treatment continuation rule from the cost-effectiveness analysis also has a fairly large impact on the ICER, increasing the revised base case ICER to £57,152 per QALY gained, just under £10,000 per QALY higher.

With regards to incorporating the higher administration cost of belimumab of £159 per infusion compared with the value of £126 used in the base case, the ICER was £49,498 per QALY gained, an increase of just over £2000 per QALY compared with the base case ICER.

Discussion

Assuming a maximum of six years of belimumab in the model yielded a base case ICER of £47,342 per QALY gained. Univariate sensitivity analyses and scenarios ranged from £24,491 to £78,501 per QALY gained. Variables and assumptions which had the greatest impact on the ICER comprised the treatment effect regression to estimate the effect on SS score of belimumab after 52 weeks, the coefficient for average mean SLEDAI included in the natural history mortality model, the coefficients in the utility regression, the maximum assumed duration of belimumab treatment, the discount rate incorporated for health effects, and the exclusion of a responder rule at six months of treatment.