

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## SINGLE TECHNOLOGY APPRAISAL

### **Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus [ID416]**

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

1. **Appraisal Consultation Document 2 (ACD2)** as issued to consultees and commentators in July 2013

2. **Consultee and commentator comments on the Appraisal Consultation Document 2 issued in July 2013 from:**

- GlaxoSmithKline
- Lupus UK
- British Society for Rheumatology *endorsed by the Royal College of Physicians*
- Royal College of Nursing

A 'no comments' response was received from the Department of Health and the British Association of Dermatologists.

3. **Response to consultee, commentator and public comments on the Appraisal Consultation Document 2 (ACD2)**

4. **Additional evidence submitted by GlaxoSmithKline**

- Additional evidence submission - research proposal
- BILAG Registry protocol

5. **Clarification letters**

- NICE's request to the company for clarification on their additional evidence submission
- Company's response to NICE's request for clarification

6. **Critique of additional evidence provided by Warwick Evidence**

7. **Report from the Decision Support Unit**

8. **Further supportive evidence from GlaxoSmithKline (not reviewed by the ERG)**

- 5-Year analysis of phase 3 safety and organ damage of belimumab plus standard care in patients with SLE
- Relevance of new organ damage data results to the belimumab appraisal

9. **Managed Access Agreement draft template**

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

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Belimumab for treating active  
autoantibody-positive systemic lupus  
erythematosus**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus in the NHS in England and Wales. The Appraisal Committee has considered the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

**This document has been prepared for consultation with the consultees.**

It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see appendix B) and the public. This document should be read along with the evidence base (the evaluation report), which is available from [www.nice.org.uk](http://www.nice.org.uk)

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using belimumab in the NHS in England and Wales.

For further details, see the 'Guide to the technology appraisal process' (available at [www.nice.org.uk](http://www.nice.org.uk)).

**The key dates for this appraisal are:**

Closing date for comments: 13 August 2013

Second Appraisal Committee meeting: 28 August 2013

Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

## 1 Appraisal Committee's preliminary recommendations

- 1.1 Belimumab is not recommended, within its marketing authorisation, as add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy.
- 1.2 People currently receiving belimumab that is not recommended according to 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

## 2 The technology

- 2.1 Belimumab (Benlysta, GlaxoSmithKline) is a human monoclonal antibody that inhibits the activity of B-lymphocyte stimulator (BLyS). Belimumab has a marketing authorisation 'as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy'.
- 2.2 According to the summary of product characteristics, adverse reactions with belimumab include bronchitis, viral gastroenteritis, cystitis, pharyngitis, nasopharyngitis, leukopenia, hypersensitivity reactions, depression, insomnia, migraine, diarrhoea, nausea, pain in extremity, infusion-related reactions and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Belimumab is available as a 120 mg or 400 mg powder for intravenous infusion in solution. The recommended dose regimen is 10 mg/kg belimumab on days 0, 14 and 28, and at 4-week intervals thereafter. The summary of product characteristics states that discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. The list price of belimumab is £121.50 for a 120 mg vial and £405 for a 400 mg vial (excluding VAT; British National Formulary edition 63). Assuming vial wastage, the drug cost per administration for a patient weighing 65–76 kg is £769.50. Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of belimumab has agreed a patient access scheme with the Department of Health, in which a discount on the list price of belimumab is offered. The size of the discount is commercial-in-confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

### **3 The manufacturer's submission**

- 3.1 The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of belimumab, reviews of the submissions by the Evidence Review Group (ERG; appendix B) and evidence provided in the Decision Support Unit report (DSU; appendix B).
- 3.2 The manufacturer's submission focused on a subgroup of the patients whose disease met the criteria specified in the marketing authorisation. The manufacturer explained that, being aware of NHS resources and to identify patients who are most likely to benefit from belimumab, the submission focused on a high disease activity subgroup (hereafter referred to as the target population). The target population is adults with active autoantibody-positive systemic lupus erythematosus with evidence for serological disease activity (defined as positive anti-double-

stranded DNA and low complement) and a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10.

- 3.3 The manufacturer submitted clinical data for all of the patients enrolled in the clinical trials and for the target populations in the trials. Data were presented for both populations individually for each trial and combined across trials. The patient characteristics and results described in the clinical effectiveness section of this document focus on the manufacturer's target population.

### ***Clinical effectiveness***

- 3.4 The main evidence for the clinical effectiveness of belimumab was from 2 phase III clinical trials. The BLISS-52 (n = 865) and BLISS-76 (n = 819) trials were randomised, double-blind, placebo-controlled, parallel-group studies with follow-up at 52 weeks and 76 weeks respectively. In these trials, belimumab plus standard care (hereafter referred to as belimumab) was compared with placebo plus standard care (hereafter referred to as standard care). Standard care included: non-steroidal anti-inflammatory drugs, antimalarials, corticosteroids or other immunosuppressants (azathioprine, methotrexate and mycophenolate mofetil) either alone or in combination. Although each of the BLISS trials were 3-arm trials (belimumab 10 mg/kg, belimumab 1 mg/kg and placebo), only results for the 10 mg/kg belimumab dose were presented in the manufacturer's submission because this is the dose covered by the marketing authorisation.
- 3.5 Adult patients (aged 18 years or older) who met the American College of Rheumatology criteria for systemic lupus erythematosus and had active autoantibody-positive disease and a SELENA-SLEDAI score of 6 or more at screening were eligible for enrolment in the BLISS trials. Patients with severe active lupus nephritis or central nervous system

lupus were excluded from the trials. Of the patients in the standard care and belimumab 10 mg/kg arms (n = 1125), 52% (n = 585) had disease that met the criteria for the marketing authorisation and 35% (n = 396) had disease that met the criteria for the target population.

- 3.6 The BLISS-52 trial recruited patients from South America, Asia and eastern Europe, whereas the BLISS-76 trial recruited patients from the USA, Canada, Europe (western and eastern) and Israel. In the BLISS-52 trial, approximately 42% of the target population were Asian. In the BLISS-76 trial most of the target population were white (around 65%). Over 90% of the target population included in the trials were women and most (approximately 85%) were aged 45 years or younger. In the target population over 90% of the patients had at least 1A or 1B British Isles Lupus Assessment Group (BILAG) organ involvement and approximately 70% had at least 1A or 2B organ involvement. For the target population, mean SELENA-SLEDAI score was approximately 13 in both trials. About 85% of patients in the target population had a physician's global assessment score of between 1 and 2.5. Most of the patients had a range of manifestations of systemic lupus erythematosus, mainly involving mucocutaneous, immunological and/or musculoskeletal damage.
- 3.7 The manufacturer presented results from the BLISS-52 and BLISS-76 trials separately and pooled. The primary outcome of both studies was the response rate at week 52 compared with baseline, assessed with the Systemic Lupus Erythematosus Responder Index (SRI). With the SRI criteria, a response was defined as: a reduction of at least 4 points in SELENA-SLEDAI score (regarded as clinically meaningful); no new BILAG A organ domain score; no more than 1 new BILAG B organ domain score; and no worsening in physician's global assessment score (increase of less than 0.3).

- 3.8 For the primary outcome of SRI response at 52 weeks, statistically significant differences were observed between belimumab and standard care in both trials. In the BLISS-52 trial, for the target population, 67% of patients on belimumab had disease that responded compared with 41% of patients on standard care (odds ratio [OR] = 3.0, 95% confidence interval [CI] 1.7 to 5.2). In the BLISS-76 study, for the target population the response was 57% for belimumab compared with 34% for standard care (OR = 2.5, 95% CI 1.3 to 4.6). In the pooled analysis for the target population, 63% of the patients on belimumab had disease that responded, compared with 38% of those on standard care (OR = 2.7, 95% CI 1.8 to 4.1). In the BLISS-76 trial, the target population showed a statistically significant difference in response rate between belimumab and standard care at 76 weeks ( $p = 0.02$ ).
- 3.9 For the individual components of the SRI, which were secondary outcomes in the trials, a greater proportion of patients on belimumab in both BLISS trials had a reduction of at least 4 points in SELENA-SLEDAI score compared with standard care. In the pooled analysis for the target population, 65% of patients on belimumab had a reduction of at least 4 points in SELENA-SLEDAI score compared with 41% on standard care (OR = 2.6, 95% CI 1.7 to 3.9), which was statistically significant. For the outcomes of no new BILAG 1A or 2B organ domain involvement and no worsening in physician's global assessment, results from BLISS-52 for the target population showed a statistically significant improvement with belimumab compared with standard care, whereas results from BLISS-76 did not. However, there was a statistically significant improvement for both these outcomes in the pooled analysis for the target population.
- 3.10 For other secondary outcomes, in the pooled analysis of the target population 16% of patients on belimumab compared with 7% of patients on placebo (OR = 2.43, 95% CI 1.05 to 5.65) had an average



prednisone dose reduction of greater than or equal to 25% from baseline, to less than or equal to 7.5 mg per day, during weeks 40 to 52. There were no differences in the Systemic Lupus International Collaborating Clinics (SLICC) index of organ damage in BLISS-52, BLISS-76 or the pooled analyses.

3.11 Quality-of-life measures, the SF-36 and EQ-5D, were also collected as secondary outcomes. At week 24 in the pooled analysis of the target population, there was a statistically significant mean change from baseline EQ-5D index for belimumab compared with standard care, but this was not maintained at week 52. The pooled analysis of the target population showed no statistically significant difference in mean SF-36 physical component summary scores between belimumab and standard care at weeks 24 or 52. In the pooled analysis of the target population for functional assessment of chronic illness therapy (FACIT)-fatigue scores, the difference in FACIT-fatigue scores was statistically significant at weeks 8 and 12 but not thereafter. In the individual trials for the total population, there was a statistically significant difference in FACIT-fatigue scores in favour of belimumab in the BLISS-52 trial at week 52 but not in the BLISS-76 trial.

3.12 In the pooled total trial population, the percentage of people defined as being of African American or African family origin (n = 100) meeting the primary end point was higher in the standard care group (44%) than in the belimumab group (36%). This compared with an overall response rate of 39% in the standard care group and 51% in the belimumab group in the pooled total trial population. For patients of all other family origins, the belimumab group had higher response rates than the standard care group.

3.13 Adverse event data were taken from the total population included in the BLISS trials (that is, not just the target population) and from a phase II extension study (LBSL99). Over 90% of patients in each arm

experienced 1 or more adverse events. The most frequent (occurring in more than 10% of patients) events were headache, upper respiratory tract infection, arthralgia, nausea, urinary tract infection, diarrhoea and fatigue. Of these events, only diarrhoea and nausea occurred slightly more frequently in the belimumab groups than in the standard care groups. Serious adverse events were experienced by 17% in the 10 mg/kg belimumab group, compared with 16% in the standard care group. Across the double-blind treatment periods, 14 people died, including 3 (0.4%) in the standard care group, 5 (0.7%) in the 1 mg/kg group and 6 (0.9%) in the 10 mg/kg belimumab group. Four deaths were infection-related; 1 in the standard care group, 1 in the 1 mg/kg belimumab group and 2 in the 10 mg/kg belimumab group. Infection may have contributed to the deaths of 2 further patients (1 in the 1 mg/kg belimumab group and 1 in the 10 mg/kg belimumab group). There were 2 suicides, both in patients receiving belimumab (1 in the 1 mg/kg group and 1 in the 10 mg/kg group), and 1 cancer-related death in a patient receiving 1 mg/kg belimumab. In the long-term open-label extension phase of the phase II study, the incidence of adverse events and severe adverse events remained stable or declined over time through 5 years of exposure.

- 3.14 The manufacturer explained that some patients with severe, highly active systemic lupus erythematosus routinely receive rituximab. No studies were identified that directly compared belimumab with rituximab. However, in a study that compared rituximab with placebo (the EXPLORER trial) in patients with moderate-to-severe systemic lupus erythematosus disease activity, no statistically significant differences were reported in major or partial clinical responses between the rituximab group and the placebo group. In addition, the rituximab trial demonstrated no difference in secondary end points between the rituximab group and the placebo group over 52 weeks. The manufacturer stated that differences in the end points considered and

the patient populations precluded any meaningful indirect comparison between the belimumab and rituximab studies.

### ***Cost effectiveness***

- 3.15 A de novo decision-analytic model was developed by the manufacturer. The model is a micro-simulation that incorporates the interaction between patient characteristics, disease activity, medication (corticosteroid use), risk of organ damage development (a patient with systemic lupus erythematosus could potentially develop damage in 12 different organ systems) and mortality. The manufacturer presented results on the target population, as well as the proportion of patients in the trial whose disease met the criteria in the marketing authorisation (hereafter referred to as the marketing authorisation population) and total trial populations. The model results presented here focus on the target population.
- 3.16 The health states in the model were informed by data from the BLISS trials, observational cohort data (the Johns Hopkins cohort, see section 3.18), and other data from the literature. A patient's baseline characteristics were simulated based on the pooled target population characteristics in the BLISS trials. The BLISS clinical trials were used to inform the likelihood of response at week 24 (based on a SELENA-SLEDAI score decrease of 4, this being the basis for the manufacturer's proposed continuation rule in which belimumab would be continued for people whose disease had such a response after 24 weeks), the change in SELENA-SLEDAI score up to week 52, the likelihood of discontinuation, and the effect of SELENA-SLEDAI score on utility and treatment costs. Data from the literature were used to inform the standardised mortality rate for a given SELENA-SLEDAI score, and quality-of-life and cost impacts of long-term damage to each organ system.

- 3.17 The patient entered the model in which their lifetime history of systemic lupus erythematosus was simulated, based on the BLISS trial data. A patient's characteristics were 'cloned' so that the same modelled 'patient' entered both standard care plus belimumab 10 mg/kg (hereafter referred to as belimumab) and standard care only (hereafter referred to as standard care) treatment paths and then worked through the model. For a patient entering the model assigned to either belimumab or standard care, it was first determined whether the patient survived for that year. A surviving patient on belimumab could then either continue with belimumab treatment or discontinue treatment. The treatment discontinuation rate was calculated from the BLISS trial data. Patients discontinued treatment after week 24 if they did not have an improvement in SELENA-SLEDAI score of 4 points or more. An annual discontinuation rate in patients whose disease responded to treatment was estimated to be 8% per year.
- 3.18 Prediction models based on data from the Johns Hopkins cohort were used to predict change in adjusted mean SLEDAI score (which is used as a proxy for SELENA-SLEDAI score), average corticosteroid dose per year, risk of organ damage and risk of death. The Johns Hopkins cohort reported data on a large population of patients with systemic lupus erythematosus from Baltimore, Maryland, USA of whom 93% were women, 52% were white and 38% were black. Analyses were conducted on a dataset of 1282 people, with follow-up of greater than 2 years and data after 1992. Mean age at diagnosis was 33 years and mean SLEDAI score at first visit was 3.32. Few people with SLEDAI scores of 10 or more remained at the end of this observational study.
- 3.19 In the first year of the simulation, the effects on disease activity as observed in the BLISS trials were applied, measured by SELENA-SLEDAI score. A linear regression model based on data from the BLISS trials was used to predict the change in SELENA-SLEDAI score at

52 weeks. For subsequent cycles, disease activity was predicted using regression equations based on the natural history data from the Johns Hopkins cohort. Because the baseline characteristics from the Johns Hopkins cohort were different from the patient characteristics in the pooled BLISS trials (patients in the Johns Hopkins cohort had lower disease activity than those in the BLISS trials), the manufacturer adjusted the constant in the regression to obtain a better fit to the data.

3.20 Corticosteroid use was calculated based on a regression equation from the Johns Hopkins cohort, with disease activity as measured by mean SLEDAI score as the sole independent variable. For each organ system contained within the SLICC Damage Index, the probability of damage during that year was calculated based on the patient's characteristics and disease activity at that time. The manufacturer also developed a survival model using the Johns Hopkins cohort, adjusting it by standardised mortality ratios from the literature. Average costs and utilities calculated from regression analyses were assigned to a patient's health state for that particular year. Costs and utilities were recorded together with clinical outcomes for that patient. Time was then increased by 1 year and the process was repeated for the lifetime of the patient. These yearly cycles continued until a patient died. Utilities and costs were discounted at 3.5%. An NHS and personal social services perspective was adopted. Adverse events were not included in the model.

3.21 The baseline quality of life assumed in the cost-effectiveness analysis was determined by a regression equation (which accounted for age, family origin and SELENA-SLEDAI score), which was derived from the BLISS trials. Disutility multiplier values for each type of organ damage were identified from a search of the literature. These disutility multipliers were applied to the utility score if a patient developed organ damage in the model cycle. Costs in the analysis were limited to direct medical

costs and costs associated with disease activity and long-term organ damage. Total resource use varied according to disease severity and was determined using a linear regression analysis. A literature search was conducted to identify the cost of organ damage. All costs were inflated to 2010 values. The base case considered only the additional acquisition costs for belimumab. Because belimumab is given in addition to standard care, it was assumed that the costs for standard care treatments would be the same for people on belimumab as for those not on belimumab and so were not included. The administration cost of £126 for belimumab was calculated based on 2 hours of senior hospital staff nurse time (£63 per hour): 1 hour for the infusion and another 1 hour for patient preparation and monitoring post-infusion. It was assumed that the first year annual cost of treatment and administration of belimumab was £10,918 and, in subsequent years, was £10,138, based on a cost of belimumab of £114.30 for a 120 mg vial and £381 for a 400 mg vial. At the time of submission, the vial price for belimumab had not been finalised, so the expected vial list price was used in the base-case analyses. The effect on cost effectiveness of a maximum expected vial price for both the 120 mg and 400 mg vials was investigated in a scenario analysis. The inclusion of a cost for standard care and different costs of administration were also explored in scenario analyses.

3.22 The model showed lower disease activity for patients on belimumab than in patients on standard care only, which led to decreased corticosteroid dose and decreased risk of organ damage, and contributed to a difference in mortality risk. The model predicted that patients on belimumab live longer than those on standard care. Although a decreased duration of damage was shown for organs on which belimumab has a large effect (cardiovascular, pulmonary and renal), the duration of damage for other organ systems is increased because of the prolonged life expectancy.

3.23 The model predicted that patients treated with belimumab, in the target population, live on average 2.9 years longer (34.9 compared with 31.9 years), have a reduction in average adjusted mean SLEDAI score, have a reduced cumulative monthly corticosteroid dose and similar total SLICC organ damage score compared with those on standard care only. Treatment with belimumab provided an estimated additional 1.1 life years and 0.8 quality-adjusted life years (QALYs) (both discounted values). For both treatment groups, the organ damage costs were the highest expense. In total, the organ damage costs were lower for patients treated with belimumab. The costs related to disease activity were similar in the 2 treatment arms. Because of their increased life expectancy and the cost of belimumab treatment, costs were higher for patients receiving belimumab than for those on standard care.

3.24 For the target population, not including the patient access scheme, total costs were £157,291 for belimumab and £105,366 for standard care. Total QALYs were 10.61 for belimumab compared with 9.81 for standard care. The incremental costs were therefore £51,925, and the incremental QALYs 0.806. This resulted in an incremental cost-effectiveness ratio (ICER) of £64,410 per QALY gained. The probabilistic sensitivity analysis results showed that at a threshold of £30,000 per QALY gained, there is a 0% probability that belimumab is cost effective compared with standard care.

3.25 In comparison, the ICER for the marketing authorisation population was £66,170 per QALY gained (undiscounted life years gained of 2.1 years, reflecting a difference in estimated survival of 35.0 compared with 32.8 years). The ICER for the total trial population (which included a wider population than that specified in the marketing authorisation) was £82,909 per QALY gained.

3.26 In sensitivity analyses conducted in the target population analysis, factors affecting cost effectiveness were: the treatment effect regression

to estimate the effect of belimumab after 52 weeks, the size of the manufacturer's adjustment to the constant of the disease activity prediction equation, the probability of discontinuation, the effect of the adjusted mean SLEDAI score on mortality, and the natural history models for pulmonary and renal involvement. Scenario analyses were conducted, with resulting ICERs ranging from £50,114 to £77,707 per QALY gained. Removing the continuation rule increased the ICER to £72,207 per QALY gained, and increased vial prices of £127.80 for the 120 mg vial and £426 for the 400 mg vial (the maximum expected vial price) resulted in an ICER of £71,297 per QALY gained.

3.27 The patient access scheme comprises a simple discount, which was accepted by the Department of Health and incorporated into the analysis of belimumab compared with standard care. An ICER with the patient access scheme was provided. However, the level of the discount and the results from the economic analysis incorporating the patient access scheme are commercial-in-confidence.

3.28 A comparison of the costs of belimumab and rituximab, taking into account the patient access scheme, was also provided by the manufacturer. The manufacturer calculated the cost of rituximab from the administration schedule used in the EXPLORER trial. A course of rituximab was 1000 mg, provided on days 1, 15, 168 and 182. The total drug cost of rituximab was £6985 per year. The cost of belimumab per year was commercial-in-confidence.

***Further evidence submitted by the manufacturer after the first Appraisal Committee meeting***

3.29 In response to consultation, the manufacturer presented long-term efficacy and safety trial data from the open label, phase II extension study (LBSL99; Petri et al. 2011) for belimumab, which suggested continued efficacy with belimumab and safety over a 6-year follow-up



period. Patients with seropositive disease treated with belimumab showed sustained improvement in disease activity and a decline in BILAG scores and flares over 6 years, accompanied by reductions in corticosteroid use and autoantibody levels. The abstract provided by the manufacturer showed a mean reduction in corticosteroid use of 4.7 mg per day, an average reduction of 34.4% from the baseline dose, by the end of 6 years of follow-up. The manufacturer calculated that based on 6-year follow-up the annual discontinuation rate was approximately 13% in this trial.

3.30 As well as further clinical evidence, in response to consultation the manufacturer submitted additional cost-effectiveness evidence using the same assumptions as in the original base-case model, but incorporating a maximum treatment duration of 6 years and using the confirmed list price for belimumab. The manufacturer's revised base case resulted in an ICER of £47,342 per QALY gained, with an incremental cost of £28,705 and incremental QALYs of 0.61. In a scenario analysis conducted by the manufacturer on the revised base-case analysis, the continuation rule for belimumab was changed from a SELENA-SLEDAI score of greater than or equal to 4 to greater than or equal to 6 and the health effects discount rate lowered from 3.5% to 1.5%. These scenarios had the effect of lowering the ICER to £40,863 and £31,988 per QALY gained respectively. When both scenarios were applied together, they lowered the ICER to £27,807 per QALY gained, with an incremental cost of £20,766 and incremental QALYs gained of 0.747.

3.31 The manufacturer stated that the change from an unlimited treatment duration to a maximum of 6 years was made in response to comments in the appraisal consultation document about the need to align the use of belimumab more closely with how clinicians would consider using belimumab in clinical practice. While recognising the lack of any direct evidence about optimal treatment duration, the manufacturer supported

the use of belimumab for up to 6 years with the newly available long-term data for belimumab from the phase II extension study (see section 3.29). The manufacturer also explained that other treatments for systemic lupus erythematosus, such as immunosuppressants, are prescribed for 2–5 years to maintain suppression of disease activity. The manufacturer stated that it believed that 6 years of treatment with belimumab was long enough for the benefits of belimumab on controlling high disease activity to have an important impact on reducing long-term morbidity.

3.32 According to the manufacturer it was appropriate to use NICE's clarification to section 5.6 of the [Guide to the methods of technology appraisal](#) on the discounting of health benefits in special circumstances for a number of reasons; namely, the nature of systemic lupus erythematosus and the fact that belimumab has been shown to result in 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 corticosteroids, along with their associated risks, and consequently improved survival. Therefore, the manufacturer considered that the discount rate of 1.5% for health effects rather than the 3.5% normally applied in technology appraisals was appropriate. Furthermore, the manufacturer stated that by applying a continuation rule at 24 weeks of a SELENA-SLEDAI score greater than or equal to 6 rather than 4, a more efficient use of NHS resources could be made.

***Further evidence provided by the manufacturer after the appeal***

3.33 After the appeal, the manufacturer submitted a further revised base case using a revised patient access scheme. This used the same assumptions as in the original base-case model (that is, lifetime treatment with a continuation rule of a SELENA-SLEDAI score greater

than or equal to 4), but incorporated an annual discontinuation rate of 13% and an administration cost of belimumab of £154, reflecting the infusion administration cost used in [‘Tocilizumab for the treatment of rheumatoid arthritis’](#) (NICE technology appraisal guidance 247). The total costs were £146,056 for belimumab and £105,366 for standard care. Total QALYs were 10.47 for belimumab compared with 9.81 for standard care. The incremental costs were therefore £40,691, and the incremental QALYs 0.66. This resulted in an ICER of £61,328 per QALY gained. ICERs with the patient access scheme were also provided. These were marked commercial-in-confidence because of the confidential nature of the patient access scheme.

3.34 The manufacturer also presented scenario analyses including a maximum treatment duration of 6 and 10 years, alternative treatment continuation rules and a range of treatment discontinuation rates. The alternative discontinuation rates included the 8% discontinuation rate used in the original base case, and a variable discontinuation rate of 13% up to year 5 and a 30% rate afterwards. The manufacturer stated that the variable discontinuation rate more closely represented the distribution of treatment durations likely to be prescribed in clinical practice for patients in the target population. The manufacturer’s additional evidence also included a cost comparison between rituximab and belimumab.

### ***Evidence Review Group’s critique of the manufacturer’s original submission***

3.35 The ERG stated that the marketing authorisation population and the target population that formed the focus of the submission were subgroups identified from post-hoc analyses aimed at identifying patients with the greatest response to belimumab. The ERG noted that, according to clinical opinion, the SELENA-SLEDAI (a component of the

SRI and one of the measures used to identify people in the target population) is not commonly used to define high disease activity in clinical practice.

3.36 The ERG commented that, although both trials included adults with active autoantibody-positive systemic lupus erythematosus, the population in BLISS-76 is more likely to be similar to that of England and Wales than that of BLISS-52, so the results from BLISS-76 are more likely to be generalisable to the UK. This was because the differences in geography and family origin between the patients in the trials were considered to potentially affect the results of the trials as well as reflecting differences in clinical practice. The ERG stated that, for the target population, the results from the BLISS-52 trial were more favourable for belimumab than those from BLISS-76, and BLISS-52 provided more patients to the pooled target population than BLISS-76 (55% compared with 45%). Therefore, results favourable to belimumab for the pooled target population were more strongly driven by the contribution from the BLISS-52 target population. The ERG, therefore, had concerns about the relevance of the pooled results for patients in England and Wales.

3.37 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 score changes.

3.38 The ERG considered that the manufacturer's model was complex, though generally well constructed. It noted that the model conformed to the NICE reference case and that the longer-term effects of systemic lupus erythematosus had been modelled well, using the Johns Hopkins cohort. An ERG cross-check of the probabilistic modelling for the target population resulted in a central estimate for the ICER of £65,530 per QALY gained.

3.39 The ERG commented that there was a lack of clarity around the reasons for patients' discontinuation of belimumab, the derivation of the 8% annual discontinuation rate among patients showing a response to belimumab at week 24, and whether extrapolation using this value was reasonable. Sensitivity analyses by the manufacturer showed that a low discontinuation rate, such as 2%, increased the ICER for belimumab to £85,893 per QALY gained, whereas a higher discontinuation rate, such as 14%, reduced the ICER to £54,518 per QALY gained.

3.40 The ERG stated that the model assumed that patients whose disease had not responded to belimumab by week 24 (a third of patients) experienced the average SELENA-SLEDAI score seen with standard care. Thus the actual experience of the patients whose disease had not responded to belimumab was not used in the model. There were approximately an equal proportion of patients whose disease had responded to standard care (with an average change in SELENA-SLEDAI score of -6.9) and whose disease had not responded to standard care (with an average change in SELENA-SLEDAI score of -1.1) at week 24 in the pooled target population. The average change in SELENA-SLEDAI score for patients receiving standard care was therefore estimated to be -4.1, while the average change in SELENA-SLEDAI score for the patients whose disease had not responded to belimumab was -0.9 at week 24. The ERG considered that the manufacturer's assumption that patients whose disease does not respond to belimumab have the same change in SELENA-SLEDAI scores as all patients receiving standard care is likely to overestimate the average impact on SELENA-SLEDAI scores in the belimumab arm, both between week 24 and 52 and beyond week 52, leading to an underestimation of the ICER.

3.41 The ERG noted that a higher adjusted mean SLEDAI score was associated with an increased probability of the patient dying and of a

patient developing particular organ involvement. The economic modelling did not take into account a patient's history before entry into the trial and this may also have exaggerated the impact that changes in SELENA-SLEDAI score had on the adjusted mean SLEDAI score for belimumab compared with standard care, with the likely result that the base-case ICER was an underestimate. This is potentially important when comparing the Johns Hopkins cohort, in which most patients had SELENA-SLEDAI scores of less than 10, with the target population, who all had scores of greater than 10 at baseline.

3.42 The ERG stated that the reason for adjusting the Johns Hopkins cohort survival model by standardised mortality ratios from the literature was unclear and may have tended to exaggerate the impact of the individual covariates within the Johns Hopkins cohort survival model. Unpublished data from a UK study obtained by the ERG also suggested that the standardised mortality ratios used by the manufacturer may not accurately represent a UK cohort. An exploratory analysis using the lower standardised mortality ratios derived from the UK study increased the ICER by approximately £6000 to £70,860 per QALY gained.

3.43 The ERG highlighted that the constant in the SELENA-SLEDAI change regression equation from the Johns Hopkins data was originally 2.0577 but was adjusted by the manufacturer to 3.0 to improve the fit to belimumab trial data after week 52. Sensitivity analyses by the manufacturer showed that using the original value of the constant term increased the ICER by approximately £29,000, to £93,654 per QALY gained.

3.44 The ERG considered the impact of using different administration costs than those used in the model (£126). The ERG's exploratory analysis found that, if costs were in line with those from a previous appraisal of another intravenous monoclonal antibody drug ([Tocilizumab for the treatment of rheumatoid arthritis](#)) [NICE technology appraisal guidance

247]), which had a similar duration of administration and an administration cost of £154, then the ICER would increase by approximately £2500 to £66,907 per QALY gained. If the full day-case cost was used (£432), then the ICER would be higher by approximately £27,000, at £91,699 per QALY gained.

3.45 The ERG completed an exploratory analysis that used the estimates from the individual BLISS trials in the disease activity regression equation rather than the pooled estimate. This analysis demonstrated that the economic model was not particularly sensitive to the use of estimates from the individual trials. Using BLISS-76 as the source of the regression increased the ICER by approximately £2000 to £66,318 per QALY gained.

***Critique by the ERG of the manufacturer's new evidence provided after the first Appraisal Committee meeting***

3.46 The ERG commented on the new evidence provided by the manufacturer about the long-term corticosteroid sparing effect of belimumab. The ERG noted that the basis of the calculations was not clear and the ERG questioned whether the average baseline corticosteroid use was calculated for the same patients in whom corticosteroid use was estimated at 6 years. The ERG stated that the manufacturer proposed that the corticosteroid sparing effect, together with other belimumab benefits such as reduced flare frequency, would reduce the development of organ damage and would therefore translate into long-term benefit. However, the ERG stated that data are only available for 6 years, which indicates that there is a substantial degree of uncertainty over whether the effects observed in the data would translate into longer-term effects.

3.47 The ERG reviewed and critiqued the manufacturer's additional economic analysis submitted after consultation. The ERG noted that the

manufacturer's revised base-case model was based on 6 years maximum treatment duration, while the original model had some patients receiving treatment for 40 years. The ERG considered that the maximum duration of belimumab treatment was uncertain because clinical opinion is likely to vary. The ERG stated that the manufacturer's revised base-case model also assumed that while the SELENA-SLEDAI scores for the patients at the end of year 6 revert to scores expected for patients receiving standard care, the adjusted mean SLEDAI score continues to show benefit, which could indicate a sustained reduction in organ damage in the treatment arm. The ERG also noted that, given an annual discontinuation rate of 8% (as in the original submission) or the rate observed in the phase II extension study (13% annual discontinuation rate), if a maximum treatment duration of 6 years was imposed, a considerable number of patients receiving benefit from belimumab would have treatment withdrawn. The ERG calculated that, of 339 patients receiving belimumab at the end of the second year of treatment in the phase II extension study, 167 were still receiving treatment at the end of the sixth year. The ERG commented that the manufacturer did not address tapering-off rules, the issue of potential rebound phenomena, the ethical considerations of withdrawing treatment, or the possibility of reintroducing treatment and the effect of this on cost effectiveness.

3.48 The ERG evaluated the continuation rule used in the analyses. The ERG observed that changing the continuation rule so that a minimum SELENA-SLEDAI improvement of 6 is needed to continue treatment reduces the benefits the patients receive from belimumab, but it accordingly reduces costs and the ICER by a greater proportion than when a continuation rule of a minimum SELENA-SLEDAI improvement of 4 is applied.

3.49 The ERG noted that the manufacturer suggested that belimumab treatment for systemic lupus erythematosus should be appraised using a



1.5% discount rate for health benefits. The ERG noted that the evidence presented showed a beneficial response to belimumab lasting at least 6 years in an appreciable population of patients. The ERG noted that the manufacturer considered that this early effect of belimumab, together with the observed 34% reduction in corticosteroid usage, would translate into long-term benefit by reducing the development of organ damage. The ERG commented that the extent to which short-term benefits translated into longer-term benefits was uncertain and presented data showing that in the economic modelling 63% of the incremental QALY gain (undiscounted) was accrued within 30 years.

3.50 The ERG completed additional analyses, applying a lifetime treatment duration and a maximum 6 year treatment duration. For both of these, separate scenarios were modelled that assumed no continuation rule at 24 weeks, a continuation rule at 24 weeks of SELENA-SLEDAI score greater than or equal to 4 and a continuation rule at 24 weeks of SELENA-SLEDAI score greater than or equal to 6. These analyses also assumed an annual discontinuation rate of 13% after 24 weeks and an administration cost of £154, as had been used in previous appraisals of intravenous monoclonal antibody treatments for rheumatoid arthritis. Benefits and costs were discounted at 3.5%. Analyses were presented both with and without the patient access scheme.

3.51 Assuming a lifetime treatment duration for belimumab, the ICERs without the patient access scheme were £90,002, £61,193 and £53,744 per QALY gained for the scenarios assuming no continuation rule at 24 weeks, a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater than or equal to 4 and a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater than or equal to 6 respectively. The incremental costs in these scenarios were £57,526, £40,499 and £31,878 respectively and incremental QALYs 0.639, 0.662 and 0.593 respectively. ICERs with the patient access scheme were provided.

These were marked commercial-in-confidence because of the confidential nature of the patient access scheme.

3.52 Assuming a maximum 6-year treatment duration for belimumab, the ICERs without the patient access scheme were £70,942, £47,382 and £42,108 per QALY gained for the scenarios assuming no continuation rule at 24 weeks, a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater or equal to 4 and a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater or equal to 6 respectively. The incremental costs in these scenarios were £37,888, £26,300 and £21,104 respectively and incremental QALYs 0.534, 0.555 and 0.501 respectively. ICERs with the patient access scheme were provided. These were marked commercial-in-confidence because of the confidential nature of the patient access scheme.

***Critique by the ERG of the manufacturer's further evidence provided after the appeal***

3.53 The ERG reviewed the manufacturer's revised base case and confirmed that no structural changes were made to the model originally submitted and that only inputs were changed. It noted that, in 1 scenario, an error in the calculations resulted in an incorrect value, which when corrected raised the ICER slightly. The ERG stated that many of its previous concerns about the economic model had not been addressed in the additional evidence and that, if justified, these would increase the estimates of cost effectiveness. The ERG also highlighted the sensitivity of the model to estimates of pulmonary damage and uncertainties in these costs. With respect to the comparison of costs presented by the manufacturer, the ERG noted that there was still no research data that would allow for either a direct or an indirect comparison between belimumab and rituximab. The ERG noted that, in a recent systematic review of rituximab therapy in systemic lupus erythematosus, most

observational studies used less rituximab than used in the rituximab EXPLORER trial.

3.54 The ERG reviewed 7-year data from the belimumab phase II extension study and noted that these new data suggested that there may have been an error in the manufacturer's calculation of the discontinuation rate of 13% from the 6-year data. The ERG stated that, based on the numbers available, and applying a least-squares exponential fit rather than a simple average to the 7-year data, the annual discontinuation rate for the phase II extension study should be 11.7%.

3.55 The ERG presented pairwise ICERs without incorporating the patient access scheme for belimumab compared with standard care for 3 scenarios that assumed:

- an annual discontinuation rate of 11.7%
- lifetime treatment with belimumab
- an administration cost of belimumab of £154, and
- discounting health benefits (that is, QALYs) by 3.5% per annum.

For a scenario assuming no continuation rule, the ERG estimated an ICER of £68,986 per QALY gained. For a scenario assuming a continuation rule of SELENA-SLEDAI score of greater than or equal to 4, the ERG estimated an ICER of £59,946 per QALY gained. For a scenario assuming a continuation rule of SELENA-SLEDAI score greater than or equal to 6, the ERG estimated an ICER of £52,517 per QALY gained. ICERs with the patient access scheme were provided. These are commercial-in-confidence because of the confidential nature of the patient access scheme.

### ***NICE Decision Support Unit work after the appeal***

3.56 NICE commissioned the decision support unit (DSU) to undertake additional work to identify estimates of annual discontinuation rates for people with systemic lupus erythematosus whose disease responds to

belimumab treatment (taking into account its marketing authorisation describing continuous use). A survey questionnaire was developed by the DSU and sent to 41 UK lupus experts who had experience of treating people with systemic lupus erythematosus, but not necessarily with belimumab. The survey questionnaire asked the experts to provide estimates of annual discontinuation rates for people whose disease responded to belimumab treatment at 24 weeks based on a continuation rule of a SELENA-SLEDAI score greater than or equal to 4, or greater than or equal to 6.

3.57 Of the 41 experts invited, 14 (34.1%) responded but only 3 (7.3%) completed the questionnaire (either in part or in full). The most common reason given for non-completion was that clinical experience with belimumab is limited because it is not currently recommended by NICE or the Scottish Medicines Consortium. Therefore, the experts found it difficult to provide reliable estimates of long-term discontinuation rates. All 3 participating experts had experience of treating people with lupus and 2 had experience with belimumab. Two of the 3 experts suggested an initial SELENA-SLEDAI response (that is, a SELENA-SLEDAI score of greater than or equal to 4 or greater than or equal to 6) would lead to different long-term discontinuation rates and all 3 experts believed discontinuation rates would increase over time. The DSU stated that the results of the survey showed variability in the responses provided by the 3 experts on the expected discontinuation rates with belimumab treatment. The DSU concluded that limited confidence could be placed on the estimates provided in the survey questionnaire compared with those already available from the BLISS and phase II extension studies because of the low completion rate.

3.58 Full details of all the evidence are in the manufacturer's submissions, the ERG report, addenda and the DSU report, which are available from [www.nice.org.uk/guidance/TAXXX](http://www.nice.org.uk/guidance/TAXXX)

## 4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of belimumab, having considered evidence on the nature of active autoantibody-positive systemic lupus erythematosus and the value placed on the benefits of belimumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee considered the nature of the condition, and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical signs and symptoms associated with systemic lupus erythematosus. The Committee heard from clinical specialists and patient experts how this disease is a debilitating condition, primarily affecting younger women. It affects daily life, including the ability to work and to have children. The clinical specialists explained that people with systemic lupus erythematosus tend to die younger than the average population. The Committee heard that there are very few licensed treatments for the disease and that patients would welcome an additional treatment option specifically for this disease. Furthermore, it was highlighted that many patients have to take several different drugs daily and that any treatment that might reduce this number would be welcomed. Reduced side effects of other drugs, especially corticosteroids, would also be welcome. The Committee recognised the importance of the availability of treatment options for people with systemic lupus erythematosus and the need to reduce the side effects of immunosuppressants in current use.
- 4.3 The Committee discussed the likely position of belimumab in clinical practice. The Committee noted that standard care is likely to consist of non-steroidal anti-inflammatory drugs, corticosteroids, antimalarials or immunosuppressants. It also noted that the marketing authorisation for

belimumab states that it should be used for patients with high disease activity 'despite standard therapy'. The Committee heard from clinical specialists that 10–15% of patients continue to have high disease activity despite standard therapy and that a proportion of these patients are currently treated with rituximab, but through individual funding requests in exceptional circumstances because the NHS does not routinely fund rituximab for treating severe manifestations of systemic lupus erythematosus. The Committee understood that rituximab is used in people with severe disease to reduce the levels of disease activity (that is, to induce remission) and to reduce the amount of corticosteroids and other immunosuppressants prescribed. The Committee also heard from the clinical specialists that rituximab treatment is repeated in such patients when the disease shows signs of a significant increase in activity and that the re-treatment interval with rituximab varies from patient to patient. The clinical specialists explained that they considered that rituximab would be a relevant comparator for belimumab. However, the Committee considered that, because rituximab is provided through individual funding requests and its use in the NHS is likely to be limited, it should not be considered to be the main comparator in routine practice (although it had been specified in the scope for the appraisal). The Committee therefore concluded that standard care should be the main comparator for belimumab, as included in the final scope and in the manufacturer's decision problem.

- 4.4 The Committee was aware that cyclophosphamide was also included as a comparator in the scope for the appraisal, but noted the manufacturer's justification that it was largely used for lupus nephritis, which was a different population to the one included in the trials of belimumab and covered by the marketing authorisation for belimumab. Furthermore, it heard from clinical specialists that cyclophosphamide is used infrequently because of side effects.

4.5 The Committee discussed how belimumab would be used in clinical practice and heard from the clinical specialists that continuous use of belimumab for a long time would be very unlikely. The clinical specialists explained that, as with other immunosuppressants, one of the aims of treatment with belimumab would be to work towards coming off the treatment. Once a patient was in remission, belimumab treatment would be gradually stopped by reducing its frequency or dose. Serological activity would be monitored and belimumab treatment restarted if a patient became symptomatic or if the serological tests signalled that this was likely. The manufacturer explained that there were no data available that reflected the scenarios described by the clinical specialists, such as treatment holidays or tapering of treatment. However, the Committee noted that the European Medicines Agency has requested that the manufacturer address uncertainties about the effect of stopping treatment with belimumab (treatment holidays) as well as the risk of rebound phenomena, as part of the routine pharmacovigilance programme. The Committee was aware that belimumab is indicated as an add-on treatment in patients with a high degree of disease activity despite standard therapy and it also observed that the European Medicines Agency's European Public Assessment Report for belimumab acknowledged that the BLISS studies were not designed for evaluating whether remission was induced, but rather for evaluating maintenance of remission. In addition the Committee noted that the most recent data supporting longer-term use of belimumab used a continuous schedule of administration over 7 years in patients whose disease responded to treatment. Although the manufacturer had presented data supporting the continuous use of belimumab in patients whose disease responded, the Committee concluded that, in clinical practice, belimumab might be used in the same intermittent way as rituximab, although there are no efficacy data for such an approach and the likely treatment durations and discontinuation rates are not known.

4.6 The Committee discussed the population in the manufacturer's decision problem. It noted that the manufacturer focused on a target population comprising a post hoc subgroup of the population covered by the marketing authorisation and the BLISS clinical trials. The target population was identified by a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10 and evidence of serological disease activity. The Committee noted that although a SELENA-SLEDAI score of greater than or equal to 10 had been a pre-specified stratification factor in the BLISS clinical trials, when combined with the marketing authorisation criterion of a high degree of serological disease activity, this was not a group that had been pre-specified in the BLISS clinical trials. However, the Committee heard from the clinical specialists that, although the SELENA-SLEDAI score was not currently used in clinical practice to measure disease activity, people with a SELENA-SLEDAI score of greater than or equal to 10 would be those with clinically significant disease likely to be considered for treatment with belimumab. The Committee also noted comments from consultation that a more routine use of the SELENA-SLEDAI score in clinical practice could improve the management of systemic lupus erythematosus. The specialists also explained that the biomarkers mentioned in the marketing authorisation (that is, low complement and positive anti-double stranded DNA antibodies), would be used for demonstrating evidence of serological disease activity and would detect changes in disease activity. The Committee concluded that, although specifying a SELENA-SLEDAI score of greater than or equal to 10 may be considered arbitrary, the specified target population is clinically relevant.

### ***Clinical effectiveness***

4.7 The Committee discussed the manufacturer's submission of clinical evidence, noting that most of the evidence in the manufacturer's



submission was from the 2 BLISS trials (BLISS-52 and BLISS-76) that compared belimumab against standard care. The Committee considered the composite end point of the Systemic Lupus Erythematosus Responder Index (SRI) used in the BLISS trials. It noted that this end point was developed in conjunction with the Food and Drug Administration in the USA. The Committee heard from the clinical specialists that the SELENA-SLEDAI score, a component of the SRI, is a relatively crude tool and that the specialists considered the use of the composite tool, which also includes the British Isles Lupus Assessment Group (BILAG) tool (as well as the physician's global assessment), was reasonable. The Committee accepted the evidence from the clinical specialists that the SRI was an appropriate end point in the trials.

- 4.8 The Committee discussed whether the individual BLISS trials were representative of the UK population, in particular, whether data from the BLISS-52 trial were as relevant to UK practice as data from the BLISS-76 trial. The Committee noted that the BLISS-52 trial recruited people from eastern Europe, South America and Asia, and that the BLISS-76 trial recruited people from Europe (western and eastern), the USA, Canada and Israel. The clinical specialists explained that, because the UK is a multi-ethnic country and systemic lupus erythematosus affects many ethnic groups more severely than white populations, data from different populations would still be relevant to the UK. Furthermore, the Committee understood from the clinical specialists that clinical practice varies between countries, for example, in the USA higher doses of corticosteroids are used than in the UK. Therefore, there may also be issues about the relevance of the data from BLISS-76. On balance, the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52. However, data from BLISS-52, and therefore from the pooled analysis would be relevant.

- 4.9 The Committee discussed the characteristics of the patients in the BLISS trials. It noted that the patients in the BLISS trials had mainly immunological, mucocutaneous and musculoskeletal manifestations of systemic lupus erythematosus at baseline. The Committee noted comments from consultation that the range of manifestations in the BLISS clinical trials was similar to those in clinical practice in the UK. Furthermore, it noted comments that serological manifestations are indicative of wider systemic disease activity. The Committee discussed whether, on this basis, belimumab may be expected to also show benefits for other manifestations. The Committee heard from clinical specialists that if the experience of belimumab was like rituximab, then benefits for the range of manifestations may be expected. However, there remained uncertainty, and initially belimumab may be more likely to be used in people with predominantly musculoskeletal and mucocutaneous involvement. The Committee concluded that currently the effect of belimumab on the full range of manifestations of systemic lupus erythematosus was uncertain.
- 4.10 The Committee discussed baseline standard care in the 2 BLISS trials. It noted variations in the treatments people were receiving at baseline and that approximately 50% of people were receiving an immunosuppressant. The Committee understood there was variability in clinical practice in the use of such drugs. However, it heard from the clinical specialists that, in the UK, people for whom treatment with belimumab would be considered would have active disease despite standard therapy, and that standard therapy for most people would include an immunosuppressant. The Committee concluded that there was uncertainty about the extent to which standard care in the belimumab trials represented UK clinical practice, for the target population for whom belimumab is intended.

4.11 The Committee discussed the results of the BLISS trials and noted that, although in the individual trials the difference between the 2 arms for the primary outcome (the SRI) was statistically significant, the difference between the 2 arms for the components of the SRI were not statistically significant in BLISS-76, with the exception of the SELINA-SLEDAI outcome. The Committee also discussed the evidence of corticosteroid sparing, noting that a statistically significant reduction in corticosteroid use was observed in the pooled analysis. The Committee noted the absolute reduction in use was about 1 mg per day in the economic model. The Committee discussed the health-related quality of life outcomes in the clinical trials (EQ-5D and SF-36) and noted that, at week 52, no statistically significant differences between the treatment groups were reported in either trial for the target population. The Committee also noted that the difference between the 2 arms for the functional assessment of chronic illness therapy (FACIT) fatigue scores was not statistically significant at week 52 in the target population. The Committee concluded that, compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the evidence of effect was observed with greater consistency across outcomes in the BLISS-52 trial. Furthermore, the relevance of both the pooled and unpooled data to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, the nature of standard care and the effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus (see sections 4.8, 4.9 and 4.10).

4.12 The Committee discussed the long-term data provided by the manufacturer from a 6-year follow-up report of the extension of the phase II study. The Committee recognised that this study had been provided by the manufacturer primarily as additional evidence about long-term reduction in corticosteroid dose, but noted that data from the study suggested continued clinical benefit from belimumab treatment

over a 6-year period. The Committee first discussed the data for reduction in corticosteroid dose, noting that these showed an absolute reduction in corticosteroid dose of 5 mg a day at 6 years. The Committee then noted the sustained improvement over 6 years in measures of disease activity (such as the SRI response rate, reduced autoantibody and complement levels) and the reduced frequency of disease flares, as well as the fact that belimumab was generally well tolerated over 6 years. The Committee considered that in the absence of a control group, the phase II data were unable to definitively demonstrate the clinical benefits of continuous belimumab treatment for patients whose disease responded, but the data were suggestive of continuing benefit. The Committee heard from the Evidence Review Group (ERG) that the reduction in corticosteroid use modelled in the economic analyses showed an absolute change in corticosteroid use for belimumab that was similar to the reduction seen in the phase II extension study. The Committee concluded that these data suggested, but were not definitive proof of, a reduction in corticosteroids associated with belimumab treatment. However, the Committee understood the importance of reduction in corticosteroid dose for patients and recognised the positive indications of these findings.

4.13 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. It discussed the available evidence including the uncontrolled observational data and the comparative data for rituximab and placebo from the EXPLORER trial. It considered whether any indirect analysis of the EXPLORER and BLISS data could be conducted. The Committee heard from the clinical specialists that the EXPLORER trial included patients with more severe disease (that is, in terms of corticosteroid use and dose, and existing organ damage) than those in the BLISS studies, so the trial populations were different. The Committee heard from the

ERG that there were 3 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. The Committee concluded that there are no data that would allow a robust calculation of the relative clinical efficacy of belimumab compared with rituximab. The Committee noted that rituximab was used only in exceptional circumstances through individual funding requests (see section 4.3) and therefore concluded that rituximab could not be considered the main comparator for belimumab.

### ***Cost effectiveness***

4.14 The Committee discussed the economic model submitted by the manufacturer that informed both the original and revised analyses. The Committee noted that short-term outcomes from the BLISS studies were linked to long-term outcomes, using data from the Johns Hopkins cohort. The Committee considered the similarity of people in the Johns Hopkins cohort to those in the BLISS trials and noted that the people in the BLISS trials had higher SELENA-SLEDAI scores than the average SLEDAI scores in the Johns Hopkins cohort, indicating that the populations in the trials had more active disease than in the Johns Hopkins cohort. The Committee noted that the SLEDAI scores from the Johns Hopkins cohort were used to inform the equation for disease activity, corticosteroid use, mortality and organ involvement, but that only the equation for disease activity was adjusted so that it more closely matched the BLISS trial populations. The Committee heard from the manufacturer how the model was driven by changes in the SELENA-SLEDAI score based on data from the Johns Hopkins cohort and that cost effectiveness was not particularly driven by other factors, such as by corticosteroid use. The Committee accepted that attempting to link

short-term outcomes to long-term outcomes was appropriate and recognised that there were limited data sources available with which to do this. However, it concluded that there was uncertainty about whether the equations derived from the Johns Hopkins data could be reliably applied to the target population because of differences in study populations.

4.15 The Committee again discussed the expected duration of use of belimumab in clinical practice, noting that the original model predicted continuous treatment with belimumab for some people over the course of 40 years. The Committee had concluded that continuous treatment over many years may not reflect how belimumab would be used in clinical practice (see section 4.5). However, it was aware that the summary of product characteristics for belimumab describes continuous use and noted the manufacturer's statements that there were no data available to model treatment holidays or tapering of treatment. In addition, the Committee noted that the only data for longer-term use of belimumab were for a continuous schedule of administration in patients whose disease responded to treatment. Therefore the Committee was unable to make recommendations taking into account intermittent treatment or alternative administration schedules because there were no efficacy data or any evidence of the cost effectiveness of such an approach, despite suggestions from clinicians that belimumab may be used this way in UK clinical practice.

4.16 The Committee discussed the analyses presented by the manufacturer in its response to consultation, which assumed continuous treatment, but limited to the maximum treatment duration of 6 years. The Committee heard from the manufacturer that, taking into consideration the evidence from clinical specialists at the first Committee meeting and from other consultation with clinicians, it was likely that in clinical practice belimumab would not be used continuously over a lifetime. The

manufacturer stated that belimumab would probably be used in the same way as other immunosuppressants in systemic lupus erythematosus, that is, patients would discontinue belimumab as early as possible once sustained disease control was achieved. The manufacturer explained that the only long-term data available on which to base treatment duration were the 6-year data from the phase II extension study, hence the choice of 6 years. The Committee heard from the clinical specialists that, because of the heterogeneity of systemic lupus erythematosus, some patients may require treatment continuously for longer than 6 years. But for most, it was more probable that belimumab would be used for less than 6 years, once a patient's disease was in remission. The Committee considered the implications of stopping belimumab treatment at 6 years. The Committee noted that the data from the phase II extension study suggested there could be a possibility of continued benefit with continued treatment at 6 years because approximately 50% of patients on treatment with belimumab at the end of the second year were still on it at the end of the sixth year. The results of this study therefore suggested a rationale for continued use of belimumab in a significant proportion of patients beyond 6 years. The Committee was also aware that the ERG had identified 7-year data in relation to the belimumab phase II extension study. The Committee concluded that, although the 6-year maximum treatment duration modelled in the manufacturer's revised analyses improved the cost effectiveness of belimumab, the rationale for the choice of a maximum treatment duration of 6 years could not be considered sufficiently robust for use as the basis of decision-making.

4.17 The Committee discussed the annual discontinuation rates for belimumab after the first 24 weeks assumed in the original and revised economic models. The Committee noted that, in the original model, the manufacturer had based the annual discontinuation rate of 8% on data from the BLISS trials and that, in the manufacturer's additional evidence,

the revised base case used a rate of 13%, based on longer-term 6-year data provided from the phase II extension study. The Committee understood that the 13% rate had been revised by the ERG to 11.7% using the 7-year data. The Committee also noted that the manufacturer had included a scenario analysis that used a variable annual discontinuation rate of 13% for the first 5 years and 30% thereafter. The Committee heard from the manufacturer that it considered the variable annual discontinuation rate better reflected the expected use of belimumab in UK clinical practice, in which clinicians had suggested that belimumab would be used like other immunosuppressants and most patients would not receive belimumab beyond 6 years. The Committee discussed the use of the variable discontinuation rate noting that it was not presented with any evidence supporting an increased rate of discontinuation after 5 years. The Committee heard from the NICE Decision Support Unit that the results of its survey of experts in lupus in the UK did not reduce the uncertainty surrounding the discontinuation rates or have more credibility than the estimates available from the BLISS or phase II extension studies (see sections 3.56–3.57). The Committee also heard from the clinical specialists that, without any long-term evidence on the use of belimumab in clinical practice, it was difficult to provide estimates for the rate of discontinuation with belimumab. The Committee considered that, because the effects of stopping belimumab treatment (rebound phenomena in patients whose disease has responded to belimumab) were not fully understood and because there was no evidence on treatment holidays and the efficacy of re-treatment with belimumab, this could make clinicians less willing to stop. The Committee was therefore not persuaded that the proposed variable discontinuation rate was plausible.

4.18 The Committee then discussed the alternative constant annual discontinuation rates. It questioned whether the discontinuation rate in the phase II extension study may have been higher because of the lower



baseline disease activity observed in the patients in the study compared with the target population from the BLISS trials. Furthermore, the Committee considered that there could be an interaction effect between the annual discontinuation rate and the response criteria for continuing treatment. Therefore, because no response criteria had been applied in the phase II extension study, the appropriateness of using the rates derived from the study were uncertain given the use of response criteria in the manufacturer's model. However, based on the phase II extension study, the Committee accepted that the manufacturer may have underestimated the annual discontinuation rate in the original economic model, and noted that lower rates of discontinuation increased the incremental cost-effectiveness ratio (ICER). The Committee considered it preferable to use an annual discontinuation rate from the available trial data and understood that the phase II extension study was the only available long-term data source. It accepted the error identified by the ERG in the manufacturer's estimated rate of discontinuation. The Committee concluded that the analysis using the ERG's estimated rate of 11.7% annual discontinuation was the most appropriate on which to base its decision.

4.19 The Committee considered the continuation rules applied in the economic model, noting that the summary of product characteristics states that discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. The Committee noted that the original economic model applied a rule that patients would continue treatment after week 24 if there was an improvement in their SELENA-SLEDAI score of 4 points or more and that, after consultation, an additional analysis using a more stringent rule requiring an improvement of 6 points or more on the SELENA-SLEDAI scale had been proposed by the manufacturer. The Committee understood that the SELENA-SLEDAI scale was not widely used in clinical practice, but noted comments that its introduction could

improve patient care. The Committee heard from the clinical specialists that if the patient had not shown any benefit from treatment with belimumab after 6 months of treatment, then they would be likely to discontinue treatment as per the summary of product characteristics. The Committee heard that the clinical specialists indicated that a gain of 4 points on the SELENA-SLEDAI score was generally considered to be a reasonable improvement and that if there was some benefit of treatment at 24 weeks, but less than 4 SELENA-SLEDAI points, the patient may continue treatment with belimumab. The Committee then discussed the difference between the 4 and 6 point continuation rules. It noted that the BLISS trials had included a gain of 4 points on the SELENA-SLEDAI as a secondary outcome and as part of the composite primary outcome (SRI response) as it was regarded as clinically meaningful. It heard from the clinical specialists that they would prefer the lower continuation rule of an improvement of 4 points in the SELENA-SLEDAI score, but would use the higher continuation rule of 6 points if it reduced the base-case ICER to an acceptable level. The Committee agreed that specifying a continuation rule using an improvement in SELENA-SLEDAI score of either 4 or 6 points at 24 weeks could be considered arbitrary, but noted that these could help identify a population for which belimumab was more cost effective. It considered that a clinician's reluctance to discontinue belimumab in a patient whose disease has responded but had not reached a fall in SELENA-SLEDAI score of 4 at 24 weeks would be magnified with a continuation rule of 6 points. On balance, it was persuaded that the application of continuation rules was appropriate, but concluded that, given the uncertainties about the application of SELENA-SLEDAI in clinical practice and the specification of 4 rather than 6 points as part of the primary end point in the clinical trials, it was not appropriate to consider using the more restrictive rule of a SELENA-SLEDAI score improvement of 6 or more as the basis for the most plausible ICER.

However, because the application of the SELENA-SLEDAI score improvement of 6 or more improved the cost effectiveness of belimumab, it agreed that this alternative scenario should still be considered when it examined the range of estimates of the ICER.

4.20 The Committee discussed the assumption in the economic model that the effect of belimumab was maintained over time. The Committee heard from the clinical specialists that there were limited data available about the maintenance of treatment effect in systemic lupus erythematosus. The clinical specialists explained that, in other conditions such as rheumatoid arthritis, patients on biological treatments can experience a reduction in the response to treatment over time. However, the clinical specialists explained that, in their experience with systemic lupus erythematosus, those patients whose disease responded to rituximab and who needed re-treatment with rituximab at a later stage had shown a good response to re-treatment. The Committee was aware that the only longer-term data identified by the manufacturer and the ERG in relation to the benefit of belimumab was the open label phase II extension study that had been reported in conference abstracts and a journal publication (Petri et al. 2011, Merrill et al. 2012a, Merrill et al. 2012b). The Committee concluded that there was still some uncertainty in the evidence about whether it was appropriate to assume that treatment effect was maintained over time. If the treatment effect was not maintained over time, this would lead to an increase in the ICER.

4.21 The Committee discussed the modelling of response in the economic model. The Committee noted the ERG comments that, for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, it was assumed that at week 52 they had the mean benefit observed in the standard care group. The ERG stated that, because the standard care group included both patients whose disease had responded and not responded to standard care, this was likely to

overestimate the benefit of belimumab. The ERG stated that a more appropriate approach would have been to model the changes for the group of patients whose disease did not respond to standard care. The Committee heard from the manufacturer that, rather than reflecting the trial protocol treatment, the economic model was reflecting expected clinical practice with the introduction of a continuation rule, whereby patients whose disease does not respond to belimumab are switched to standard care and therefore receive the benefits associated with standard care. The Committee agreed that, in patients whose disease has not responded to belimumab at 24 weeks, some response was likely when the patient was switched to standard care, but the size of this effect was uncertain. The Committee concluded that the manufacturer's approach may have overestimated the treatment effect of belimumab, and that alternative scenarios exploring the impact on the ICER with respect to the assumed mean benefit experienced by the patients whose disease did not respond to treatment in the belimumab group would help to better reflect the level of uncertainty.

4.22 The Committee noted that the model outputs in the original base-case analysis demonstrated a gain in survival of 2.9 years from treatment with belimumab compared with standard care. The Committee considered the predicted survival from the model, noting that there was no evidence from the trials to support this modelled outcome and that in the trials there was a trend towards higher mortality in the belimumab arms compared with standard care. The manufacturer explained that the modelled benefit was expected as a result of reduced or delayed damage to organ systems, which would in turn have an effect on mortality risk. The Committee heard from the clinical specialists that people with higher disease activity are more likely to have organ damage and die than people with lower disease activity. However, the clinical specialists stated that this was likely to be dependent on the site of organ damage. For example, treatment for people with mainly

musculoskeletal or mucocutaneous damage was unlikely to result in a survival benefit. The Committee was also aware that, because of the prolonged life expectancy of people treated with belimumab, the duration of damage for the other organ systems is increased, affecting cost and health-related quality of life. The Committee also discussed how survival time in the model was predicted to be longer in the 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), even though the target population had more severe disease. The Committee noted comments from consultation that this was because of the different baseline ages of the target and trial populations. The Committee considered that, although the different ages at baseline accounted for the survival difference, it noted that the age of death remained the same for both age groups. This was considered to be an unexpected finding given the longer disease history of the younger age group. The Committee considered that the manufacturer should have explored uncertainty around the estimate of survival in the model and its impact on the ICER by exploring a scenario that assumed no survival gain for treatment with belimumab compared with standard care. The Committee concluded that, although gains in survival from reduced organ damage were plausible, there was considerable uncertainty around the validity of the modelled gains in survival and that alternative scenarios exploring the impact to the ICER around this parameter would better reflect the level of uncertainty.

4.23 The Committee considered the standardised mortality ratios used by the manufacturer and the alternative values identified by the ERG. The Committee heard from the ERG that the values it identified were unpublished data from an English cohort of patients. The Committee heard from the clinical specialists that they considered that the standardised mortality ratios provided by the manufacturer appeared

more appropriate, but highlighted in both sets the very high mortality ratios for the youngest ages (for people aged 24 years or younger). The Committee noted that the model was only modestly sensitive to the use of alternative standardised mortality ratios. The Committee concluded that it was appropriate to use the mortality ratios provided by the manufacturer in its decision-making.

4.24 The Committee discussed the administration costs used in the economic model. It noted that in the original model a cost of £126 had been used, based on 2 hours of specialist nurse time. The Committee noted that that this may be an underestimate of the costs of administration and noted that the ERG had completed a number of scenario analyses using values based on day-case codes and also values used in previous appraisals of intravenous monoclonal antibodies for rheumatoid arthritis (£154). Furthermore, the Committee noted comments from consultation that pharmacy preparation time had not been included in the economic analyses. The Committee noted that the manufacturer included the updated administration cost of £154 in its revised submission. The Committee concluded that the administration cost of £154 was appropriate to use in its consideration of the most plausible ICER.

4.25 The Committee discussed the costs and utilities in the model. The Committee heard from clinical specialists that some of the costs and disutilities may not be accurately captured, specifically the difference in costs associated with renal disease (£1765 in the first year and £2453 in the second year) compared with those associated with pulmonary disease (£9679 and £9603 respectively). The Committee also noted, for example, that the disutility multiplier in the first year of organ involvement for the serious consequence of renal involvement was 0.97, whereas for musculoskeletal organ damage the corresponding figure was 0.67. The Committee expected that the disutility multiplier for renal involvement would be lower than 0.97. The clinical specialists further highlighted that

the assumption that disutilities and costs were the same in second and subsequent years may underestimate the effects of reducing or delaying organ damage because some types of damage, such as renal damage, were associated with increasing costs and reduced health-related quality of life, as damage progresses and people need haemodialysis. The Committee concluded that deriving cost data from different sources may have led to some inconsistencies in the estimates and that the manufacturer may have underestimated some of the benefits associated with delaying certain types of organ damage.

4.26 The Committee noted that the manufacturer had included analyses that assumed a discount rate of 1.5% for health benefits. The Committee discussed whether this appraisal met the criteria for differential discounting of health benefits that can be applied in situations when treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years, as described in the clarification to the NICE [Guide to methods of technology appraisal](#)). The manufacturer provided a sensitivity analysis showing that the ICERs were sensitive to using discount rates of 3.5% for costs and 1.5% for benefits. The Committee considered that the effect of belimumab as it was currently modelled reflected a scenario that assumed continued treatment with continued benefit. This differed from the scenario that had led to the clarification of the methods guide, in which there was limited duration of treatment with curative intent. Therefore the Committee concluded that belimumab did not meet the criteria for differential discounting of health benefits.

4.27 The Committee considered the cost effectiveness of belimumab in comparison with standard care. It discussed the ERG's additional exploratory analyses that included an annual discontinuation rate of 11.7% after week 24, an administration cost of £154, and benefits and costs discounted at 3.5%. It considered scenarios that used a

continuation rule of a fall in SELENA-SLEDAI score of greater than or equal to 4 and also 6 at 24 weeks (see section 4.19). However, it considered that these could overestimate the proportion of patients stopping treatment, and that the overestimate would be greater in the scenario applying a SELENA-SLEDAI score of greater than or equal to 6. The Committee recognised that a scenario reflecting lifetime continuous treatment may not accurately capture how belimumab would be used in clinical practice. However, alternative scenarios including intermittent treatment or maximum treatment durations, and alternative administration schedules, could not be considered in the absence of any clinical- and cost-effectiveness data. On this basis the Committee considered that the most plausible ICER of those it was presented with without the patient access scheme was £59,900 per quality-adjusted life year (QALY) gained provided in the ERG's exploratory analysis, and noted that this reduced to £52,500 per QALY gained with the use of a SELENA-SLEDAI score of greater than or equal to 6. The Committee noted that a patient access scheme that reduced the ICER for belimumab compared with standard care had been agreed with the Department of Health and observed that the ICERs with the revised patient access scheme applied were reduced. The Committee discussed the sensitivity analyses completed by the manufacturer as well as the exploratory analyses from the ERG. The Committee considered that the estimated ICERs with the revised patient access scheme may have been underestimated because of the uncertainties associated with the linking of short-term trial outcomes to long-term data with differing study populations, the annual discontinuation rate, the treatment effect, the mean benefit assumed for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, and validity of the modelled gains in survival that remained in the economic modelling (see sections 4.14, 4.17, 4.18, 4.20, 4.21 and 4.22). The Committee concluded that, because of the considerable uncertainty that remained in the economic



modelling, the revised patient access scheme did not reduce the ICER sufficiently with the application of either SELINA-SLEDAI continuation rule to bring the estimate to within a range in which belimumab could be considered a cost-effective use of NHS resources compared with standard care within its marketing authorisation.

4.28 The Committee heard from the manufacturer that, if belimumab was recommended by the Appraisal Committee, the NHS would be able to recruit people with systemic lupus erythematosus on to the UK BILAG registry and collect real world evidence on the safety and efficacy of belimumab to address the key uncertainties, including rates of discontinuation. The Committee understood that this was proposed by the manufacturer shortly before the meeting but noted that the sufficient details of any such proposal were not provided. In particular, the Committee was unclear about the degree to which the registry would be able to resolve the key uncertainties present in the (economic) evaluation of belimumab, and therefore exactly what data would (need to) be collected, what the exact funding arrangements for the registry would be, when an evaluation of the outcomes of the registry is anticipated, and what would happen with (funding for) patients who are still being treated with belimumab at the end of the evaluation period of the data from the registry if the results are disappointing, to name but a few. Furthermore, the Committee recognised that the [NICE Guide to methods of technology appraisals](#) requires it to accept that 'the intervention should have a reasonable prospect of providing benefits to patients in a cost-effective way'. The Committee considered that, bearing in mind its conclusion in section 4.27, it could not reasonably expect belimumab to provide likely net benefits for all patients in the NHS while the research is carried out, and therefore that it could not accept the company's proposal.

4.29 The Committee considered the comparison of the costs of rituximab and belimumab provided by the manufacturer without any formal economic modelling. The Committee discussed the dosing of rituximab. The Committee noted that the manufacturer relied on the dose and schedule of administration of rituximab used in the EXPLORER trial as the basis for its cost comparison between rituximab and belimumab. The Committee heard from the ERG that, of the available data using rituximab for the treatment systemic lupus erythematosus, EXPLORER used the highest dose regimen, whereas the other trials used doses 25% to 50% less than this. The Committee also heard from the clinical specialists that in clinical practice, the dosing schedule for rituximab would often be lower than that described by the manufacturer. Rituximab would be prescribed as a series of 2 doses followed by a waiting period, rather than 4 doses over the course of a year. If fewer doses were prescribed, the annual cost of rituximab would be reduced below the manufacturer's estimate of £6985. It heard from the manufacturer that it considered it appropriate to compare the drug costs for both treatments because they had been used in clinical trials. Furthermore, the shorter time for infusion of belimumab compared with the longer infusion time for rituximab offset the increased frequency of administration associated with belimumab. However, the Committee concluded that the comparison of costs provided by the manufacturer did not accurately reflect the expected costs of providing rituximab and belimumab in UK clinical practice.

4.30 The Committee considered the cost effectiveness of belimumab compared with rituximab. The Committee had previously discussed the clinical effectiveness of rituximab in comparison with belimumab (see section 4.13) and concluded that no reliable data were available to demonstrate the relative efficacy of belimumab in comparison with rituximab. Furthermore, the Committee noted that standard of care is the main comparator to belimumab because rituximab is only used in some

patients, through individual funding requests and its use in the NHS was likely to be limited. Therefore the Committee concluded that without any comparison of the clinical effectiveness of belimumab with rituximab, it could not reach a conclusion as to the cost effectiveness of belimumab compared with rituximab as an add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double stranded DNA and low complement) despite standard therapy.

4.31 The Committee discussed the innovative nature of belimumab. It specifically noted the comments from clinical specialists and patient experts that few drugs are licensed for treating systemic lupus erythematosus, and the comment from the manufacturer that belimumab was developed to target the underlying pathology of this disease. The Committee also 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 fully included in the economic modelling and that the manufacturer stated that this could underestimate the benefits of treatment. The Committee noted that in the BLISS trials differences in EQ-5D were demonstrated between treatment groups but that this was not statistically significant at 52 weeks, the longest follow-up time for which quality-of-life data are available for the target population. Furthermore, 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.

4.32 The Committee was aware of a potential equalities issue relating to the lower response rates observed in the clinical trials for the subgroup of patients of African American or African origin. The Committee also noted comments received during consultation that systemic lupus erythematosus predominantly affects women of child-bearing age from ethnic minority groups. Given that the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations do not limit access to the technology for any specific group, compared with other groups.

**Summary of Appraisal Committee's key conclusions**

TAXXX	Appraisal title: Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus	Section
<b>Key conclusion</b>		
<p>Belimumab is not recommended, within its licensed indication, as add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded-DNA and low complement) despite standard therapy.</p>		1.1
<p>The Committee concluded that, compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the most plausible incremental cost effectiveness ratio (ICER) without the patient access scheme was £59,900 per quality-adjusted life year (QALY) gained provided by the Evidence Review Group (ERG) The Committee noted that a patient access scheme which reduced the ICER for belimumab compared with standard care had been agreed with the Department of Health. However, the Committee considered that the ICERs with the revised patient access scheme did not bring the estimate to within a range in which belimumab could be considered a cost-effective use of NHS resources compared with standard care.</p>		4.11 4.27
<p>There are no data that would allow a robust calculation of the relative clinical efficacy of belimumab compared with rituximab. For the comparison of belimumab with rituximab the Committee concluded that, without any comparison of the clinical effectiveness of belimumab with rituximab, it could not reach a conclusion as to the cost effectiveness of belimumab compared with rituximab as an add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy.</p>		4.13 4.30
<b>Current practice</b>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>Systemic lupus erythematosus is a debilitating condition, primarily affecting younger women. It affects daily life, including the ability to work and to have children. People with systemic lupus erythematosus tend to die younger than the average population. There are very few licensed treatments for the disease and patients would welcome a new treatment option.</p>	4.2

<b>The technology</b>		
Proposed benefits of the technology	The treatment might be corticosteroid sparing and may reduce the side effects of other drugs, especially corticosteroids.	4.2, 4.12
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Few drugs are licensed for treating systemic lupus erythematosus. Belimumab was developed to target the underlying pathology of this disease. However, 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.	4.31
What is the position of the treatment in the pathway of care for the condition?	Between 10% and 15% of systemic lupus erythematosus patients have high disease activity despite standard therapy. A proportion of these patients are currently treated with rituximab, but through individual funding requests in exceptional circumstances because the NHS does not routinely fund rituximab for treating severe manifestations of systemic lupus erythematosus. Belimumab would be used in a similar way to rituximab.	4.3
Adverse reactions	Adverse reactions were not a key factor in this appraisal.	
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	Most of the evidence in the manufacturer's submission was from the 2 BLISS trials (BLISS-52 and BLISS-76) that compared belimumab against standard care.	4.6
	There are no data that would allow a robust calculation of the relative clinical efficacy of belimumab compared with rituximab.	4.13
Relevance to general clinical practice in the NHS	The Committee concluded that, although BLISS-76 was more representative of the population of England and Wales than BLISS-52, data from BLISS-52, and therefore from the pooled analysis, would be relevant.	4.8
Uncertainties generated by the evidence	The relevance of both the pooled and unpooled data from the BLISS trials to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, nature of standard of care and effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus.	4.8- 4.11

<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The manufacturer focused on a target population comprising a subgroup of the marketing authorisation population and BLISS clinical trials. The target population was identified by a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10 and evidence of serological disease activity. The Committee concluded that, although specifying a SELENA-SLEDAI score of greater than or equal to 10 may be considered arbitrary, the specified target population is clinically relevant.</p>	<p>4.6</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee concluded that, compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the evidence of effect was observed with greater consistency across outcomes in the BLISS-52 trial. Further, the relevance of both the pooled and unpooled data from the 2 BLISS trials 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 systemic lupus erythematosus.</p>	<p>4.11</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The manufacturer submitted an economic model in which short-term outcomes from the BLISS studies were linked to long-term outcomes, using data from the Johns Hopkins cohort.</p>	<p>4.14</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee accepted that attempting to link short-term outcomes to long-term outcomes was appropriate and recognised that there were limited data sources available with which to do this. However, it concluded that there was uncertainty about whether the equations derived from the Johns Hopkins data could be reliably applied to the target population because of differences in study populations.</p> <p>The Committee understood that continuous treatment over many years was unlikely to reflect how belimumab would be used in clinical practice. However, the summary of product characteristics for belimumab describes continuous use as the model for administration. Although the 6-year maximum treatment duration modelled by the manufacturer in their revised analyses improved the cost effectiveness of belimumab, the rationale</p>	<p>4.14  4.15-4.16</p>

	<p>for the choice of 6 years could not be considered sufficiently robust for use as the basis for decision-making.</p> <p>The Committee concluded that the manufacturer may have underestimated the annual discontinuation rate in the original economic model, and therefore overestimated the ICER, and that a higher rate of annual discontinuation as observed in the phase II extension study may be more appropriate. The Committee was not persuaded that the proposed variable discontinuation rate of 13% for the first 5 years and 30% thereafter, as presented by the manufacturer, was plausible. The Committee heard from the NICE Decision Support Unit that the results of its survey of experts in lupus in the UK did not reduce the uncertainty surrounding the discontinuation rates or have more credibility than the estimates available from the BLISS or phase II extension studies. The Committee also heard from the clinical specialists that, without any long-term evidence on the use of belimumab in clinical practice, it was difficult to provide estimates for the rate of discontinuation with belimumab. The Committee considered it preferable to use an annual discontinuation rate from the available trial data and understood that the phase II extension study was the only available long-term data source. The Committee concluded that it was more appropriate to use the ERG's rate of 11.7% annual discontinuation.</p> <p>There was still some uncertainty in the evidence about whether it was appropriate to assume that treatment effect was maintained over time. If treatment effect was not maintained over time, this would lead to an increase in the ICER.</p> <p>The Committee noted the ERG comments that, for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, it was assumed that at week 52 they had the mean benefit observed in the standard care group. The Committee concluded that the manufacturer's approach may have overestimated the treatment effect of belimumab.</p> <p>Although gains in survival from reduced organ damage were plausible, there was considerable uncertainty around the validity of the modelled gains in survival.</p> <p>Deriving cost data from different sources may have led to some inconsistencies in the estimates</p>	<p>4.17 4.18</p> <p>4.20</p> <p>4.21</p> <p>4.22</p> <p>4.25</p>
--	---	--



## CONFIDENTIAL UNTIL PUBLICATION

	and the manufacturer may have underestimated some of the benefits associated with delaying certain types of organ damage.	
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee noted the manufacturer had included analyses that assumed a discount rate of 1.5% for health benefits in its response to consultation. The Committee considered that the effect of belimumab as it was currently modelled reflected a scenario that assumed continued treatment with continued benefit. This differed from the scenario that had led to the clarification of the methods guide, in which there was limited duration of treatment with curative intent. Therefore, the Committee concluded that belimumab did not meet the criteria for differential discounting of health benefits.</p>	4.26
	<p>The Committee also 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 and that the manufacturer stated that this could underestimate the benefits of treatment. However, 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.</p>	4.31
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The manufacturer focused on a target population, comprising a subgroup of the population covered by the marketing authorisation and the BLISS clinical trials. The target population was identified by a SELENA-SLEDAI score of greater than or equal to 10 and evidence of serological disease activity.</p>	4.6
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee considered that the estimated ICERs with the revised patient access scheme may have been underestimated because of the uncertainties associated with the linking of short-term trial outcomes to long-term data with differing study populations, the discontinuation rate, the treatment effect, the mean benefit assumed for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, and validity of the modelled gains in survival that remained in the economic modelling (see sections 4.14, 4.17, 4.18, 4.20, 4.21 and 4.22).</p>	4.27

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee considered that the most plausible ICER without the patient access scheme was £59,900 per QALY gained, provided by the ERG and noted that this reduced to £ 52,500 per QALY gained with the use of a SELENA-SLEDAI score of greater than or equal to 6. The Committee noted that the ICER with the patient access scheme applied remained above the threshold range usually considered as an acceptable use of NHS resources.</p> <p>The Committee concluded that, without any comparison of the clinical effectiveness of belimumab with rituximab, it could not reach a conclusion as to the cost effectiveness of belimumab compared with rituximab as an add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy.</p>	<p>4.27</p> <p>4.29</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>A patient access scheme that reduced the ICER for belimumab compared with standard care has been agreed with the Department of Health. The Committee noted that the most plausible ICER provided by the ERG with the patient access scheme applied remained above the threshold range usually considered as a cost-effective use of NHS resources.</p>	<p>4.27</p>
<p>End-of-life considerations</p>	<p>End-of-life considerations were not discussed.</p>	
<p>Equalities considerations and social value judgements</p>	<p>The Committee was aware of equalities issues relating to the lower response rates observed in the clinical trials for the subgroup of patients of African American or African origin, and that systemic lupus erythematosus predominantly affects women of child-bearing age from ethnic minority groups. Given that the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations do not limit access to the technology for any specific group, compared with any other group.</p>	<p>4.32</p>

Other	The Committee heard from the manufacturer that, if belimumab was recommended, the NHS would be able to recruit people with systemic lupus erythematosus on to the UK BILAG registry and collect real world evidence on the safety and efficacy of belimumab to address the key uncertainties, including rates of discontinuation. The Committee understood that this was proposed by the manufacturer shortly before the meeting but noted that the sufficient details of any such proposal were not provided. The Committee considered that, bearing in mind its conclusion in section 4.27, it could not reasonably expect belimumab to provide likely net benefits for all patients in the NHS while the research is carried out, and therefore that it could not accept the company's proposal.	4.28
-------	---	------

## **5 Implementation**

5.1 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website ([www.nice.org.uk/guidance/TAXXX](http://www.nice.org.uk/guidance/TAXXX)). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

## **6 Proposed recommendations for further research**

6.1 The Committee acknowledged 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 re-treatment, and considered that these studies would be of value.

## **7 Related NICE guidance**

7.1 There is no related NICE guidance for this technology.

## **8 Proposed date for review of guidance**

8.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in July 2016. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh

Chair, Appraisal Committee

July 2013

## **Appendix A: Appraisal Committee members and NICE project team**

### ***A Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Professor Gary McVeigh (Chair)**

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

#### **Professor Jonathan Michaels (Vice Chair)**

Professor of Clinical Decision Science, University of Sheffield

#### **Professor Darren Ashcroft**

Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

#### **Dr Andrew Black**

General Practitioner, Mortimer Medical Practice, Herefordshire

#### **Dr Ian Campbell**

Honorary Consultant Physician, Llandough Hospital, Cardiff

**Professor Usha Chakravarthy**

Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast

**Professor Peter Clark**

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

**Tracey Cole**

Lay member

**Dr Ian Davidson**

Lecturer in Rehabilitation, University of Manchester

**John Dervan**

Lay member

**Professor Simon Dixon**

Professor of Health Economics, University of Sheffield

**Dr Martin Duerden**

Assistant Medical Director, Betsi Cadwaladr University Health Board

**Dr Alexander Dyker**

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

**Christopher Earl**

Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

**Gillian Ells**

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

**Dr Jon Fear**

Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

**Paula Ghaneh**

Senior Lecturer and Honorary Consultant, University of Liverpool

**Niru Goenka**

Consultant Physician, Countess of Chester NHS Foundation Trust

**Dr Susan Griffin**

Research Fellow, Centre for Health Economics, University of York

**Professor Carol Haigh**

Professor in Nursing, Manchester Metropolitan University

**Professor John Henderson**

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

**Dr Paul Hepple**

General Practitioner, Muirhouse Medical Group

**Professor John Hutton**

Professor of Health Economics, University of York

**Professor Peter Jones**

Emeritus Professor of Statistics, Keele University

**Professor Steven Julious**

Professor in Medical Statistics, University of Sheffield

**Dr Tim Kinnaird**

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

**Emily Lam**

Lay Member

**Rachel Lewis**

Advanced Nurse Practitioner, Manchester Business School

**Terrance Lewis**

Lay Member

**Warren Linley BSc**

Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

**Professor Femi Oyebode**

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

National Institute for Health and Care Excellence

Page 62 of 66

Appraisal consultation document – Belimumab for treating active autoantibody-positive systemic lupus erythematosus

Issue date: July 2013

**Dr John Radford**

Director of Public Health, Rotherham Primary Care Trust

**Dr Phillip Rutledge**

GP and Consultant in Medicines Management, NHS Lothian

**Dr Brian Shine**

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

**Cliff Snelling**

Lay member

**Dr Murray D Smith**

Associate Professor in Social Research in Medicines and Health, University of Nottingham

**Paddy Storrie**

Lay member

**Dr Alison Talbot-Smith**

Consultant in Public Health, Herefordshire Clinical Commissioning Group

**Charles Waddicor**

Former Chief Executive, NHS Berkshire

***B NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Richard Diaz and Martyn Burke**

Technical Leads

**Zoe Garrett and Matthew Dyer**

Technical Advisers

**Kate Moore**

Project Managers



## Appendix B: Sources of evidence considered by the Committee

- A The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:
- Connock M, Cummins E, Sutcliffe P et al. Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (June 2011)
- B The NICE Decision Support Unit (DSU) report for this appraisal:
- Tappenden P, Wailoo A, Stevens J et al. Eliciting estimates of long-term treatment discontinuation rates (June 2013)
- C The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.
- I Manufacturer/sponsor:
- GlaxoSmithKline
- II Professional/specialist and patient/carer groups:
- Lupus UK
  - National Kidney Federation
  - 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
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III Other consultees:

- Bolton Primary Care Trust
- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety, Northern Ireland
- Healthcare Improvement Scotland
- Arthritis Research UK
- Cochrane Skin Group
- Kidney Research UK
- National Institute for Health Research Health Technology Assessment Programme
- Warwick Evidence

D The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on belimumab by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Professor David Isenberg, Academic Director of Rheumatology, University College London, nominated by British Society for Rheumatology – clinical specialist
- Dr Liz Lightstone, Consultant Renal Physician, nominated by Renal Association – clinical specialist
- Jane Dunnage, Chair and Trustee of Lupus UK, nominated by Lupus UK – patient expert
- Chris Maker, Director of Lupus UK, nominated by Lupus UK – patient expert

E The following individuals were nominated as NHS Commissioning experts by the selected PCT allocated to this appraisal. They gave their

expert/NHS commissioning personal view on belimumab by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Johanna Taylor, Clinical Effectiveness Pharmacist, Bolton Primary Care Trust, selected by Bolton Primary Care Trust – NHS Commissioning

F Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- GlaxoSmithKline

**Response to Appraisal Consultation Document (ACD)**  
**Belimumab for the treatment of**  
**active autoantibody-positive systemic lupus erythematosus (SLE)**  
**GlaxoSmithKline 13<sup>th</sup> August 2013**

**Introduction**

Thank you for the opportunity to respond to the most recent ACD for the appraisal of belimumab. We are however extremely disappointed by the preliminary recommendation that belimumab should not be a recommended treatment option in the NHS for patients with active systemic lupus erythematosus (SLE). As was highlighted by both clinical and patient expert groups during the appraisal there is considerable unmet medical need in the management of SLE, particularly for patients with serious disease activity, driven by the lack of therapeutic innovation over many years. The situation for patients has actually become more acute since the earlier phase of this appraisal due to NHS England's provisional recommendation to restrict the off label use of rituximab in these patients. In these circumstances SLE patients not controlled on current standard of care may actually have no alternative than other more expensive (and unproven) treatment options, such as admission to hospital for intravenous immunoglobulin therapy, as well as continuing with high levels of oral steroid therapy over many years with the inevitable consequences for their long term health.

The long term, relapsing/remitting nature of lupus inevitably has resulted in challenges in the ability to provide conclusive evidence on long term outcomes, such as mortality, within the clinical development programme. However even in this context we are confident that the clinical data package submitted demonstrates the long term safety and efficacy of belimumab, including the two largest Phase 3 studies ever conducted in SLE as well as the ongoing Phase 2 open-label extension (OLE) study providing evidence of sustained efficacy for seven years to date. In addition, mindful of NHS resources, GSK has provided the benefits of a Patient Access Scheme (PAS) and also made significant attempts to focus the use of belimumab on the patients with the highest disease activity, and to those demonstrating the greatest early response. Whilst we understand this focussed use does provide challenges, we would suggest that for patients even a restricted recommendation of this sort would be considered preferable than the current proposed guidance where belimumab will not be available to any patients on the NHS at all.

As regards cost effectiveness we would highlight that using the most plausible estimates and the proposed PAS, the ICERs demonstrate that belimumab is likely to provide a cost effective use of NHS resources (ICERs with PAS and four-point and six-point stopping rule [REDACTED] respectively) – and we also acknowledge the ERG's recognition that given the complexities of modelling in this disease area the approach that we have taken, particularly with respect to the long-term modelling, is methodologically robust. We do though acknowledge the uncertainty that surrounds this estimate – some of which is inevitable given the long term nature of the disease. However we would challenge the Committee's conclusion that this uncertainty may have necessarily led to an underestimate of the ICER as outlined in 4.27 as some areas would also suggest that an over estimation was also possible. We expand on this further in our response to the detailed questions below. In this context we would ask the Committee to reconsider its decision and recommend the initiation of belimumab in our small target population, and allow this to continue in those patients that have the greatest response to treatment.

## GSK Detailed Response to ACD

### **1. Has all the relevant evidence been taken into account?**

Yes, we believe that all the relevant available evidence has been taken into account.

### **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence**

We do not believe that the summaries of clinical and cost effectiveness are a reasonable interpretation of the evidence in all cases, particularly in reference to the degree of uncertainty that is highlighted. However we are pleased that the ICER, which the ERG believes is the most plausible, is similar to our proposed base case ICER and which we believe represents the best assessment of cost-effectiveness. We will discuss the areas of uncertainty in detail in the following section.

#### **Areas of uncertainty highlighted in the ACD**

##### **1) Uncertainty in the discontinuation rate**

**The Committee acknowledge that using an annual withdrawal rate estimated from the belimumab clinical trials may have underestimated the most plausible ICER. GSK believe strongly that this is the case. Therefore although there is uncertainty in the withdrawal rate likely to be observed in clinical practice, the impact is likely to improve the ICER.**

We believe that the Committee's choice of an annual withdrawal rate of 11.7% for use in the health economic modelling overestimates the most plausible ICER. This value is estimated from the annual withdrawal rate observed over seven years of follow-up in the Phase 2 OLE study. Due to the nature of this study, designed as a ten-year clinical trial to investigate the long-term efficacy and safety of belimumab, clinicians were not actively looking to withdraw patients as soon as they appeared to be well-controlled. This differs from how patients are likely to be managed in UK clinical practice where clinicians are continually interested in reducing their patients' overall drug burden. Hence the withdrawal rate is expected to be much higher in clinical practice than that observed in the belimumab clinical trials, particularly in the longer-term. Assuming an annual withdrawal rate of 11.7% suggests that 31% of patients will still be receiving treatment after 10 years, and 16% and 11% of patients will continue to receive treatment after 15 years and 20 years, respectively. This is very unlikely to be the case and is supported by feedback from lupus experts. Section 4.5 in the ACD states: "The Committee discussed how belimumab would be used in clinical practice and heard from the clinical specialists that continuous use of belimumab for a long time would be very unlikely. The clinical specialists explained that, as with other immunosuppressants, one of the aims of treatment with belimumab would be to work towards coming off the treatment." This is consistent with the discussions we have had with lupus experts when considering the assumptions in our economic modelling.

In addition, of note is that the Decision Support Unit in the discussion section of their report "**Eliciting estimates of long-term treatment discontinuation rates**", dated 6<sup>th</sup> June 2013<sup>1</sup>, state that using a withdrawal rate based on clinical trial data is likely to be an underestimate of the likely true withdrawal rate seen in UK clinical practice.

In conclusion we strongly believe that the Committee's chosen withdrawal rate of 11.7% per annum overestimates the durations patients will be prescribed belimumab and therefore the ICER is higher than would be expected on this account.

### Uncertainty in the modelled gains in survival

**The Committee state that there is uncertainty around the modelled gains in survival with belimumab and that the likely impact is that the most plausible ICER has been underestimated. GSK acknowledge the uncertainty around this estimate however there is no evidence to suggest whether this uncertainty would result in an over or under estimate of the ICER. The observed survival benefits with belimumab are clinically plausible based on the documented evidence of a relationship between disease control and increased survival in SLE and based on the observed benefits belimumab has demonstrated on improving disease control in clinical trials.**

We appreciate that there will be uncertainty in the modelled gains on survival estimated with belimumab due to limited mortality data available from the short BLISS randomised controlled trials to validate the survival assumptions. However the following statement in Section 4.22 in the ACD “The Committee considered the predicted survival from the model, noting that there was no evidence from the trials to support this modelled outcome and that in the trials there was a trend towards higher mortality in the belimumab arms compared with standard care” is an oversimplification of the data. An imbalance in mortality was observed over the randomised controlled period of the belimumab programme (maximum duration 18 months) with too few patients and insufficient duration of follow up to adequately address the question of mortality risk. The deaths observed in studies did not appear to be due a single causative factor and those that occurred on belimumab were considered unlikely to be related to treatment-according to the trial investigators. The mortality rate was consistent with that predicted in a SLE population.



which is less than that reported in the literature for SLE (1.63/100 PY; 95% CI: 1.54,1.72)<sup>2</sup>, although the historical rate may be an overestimate for the current mortality rate given the decreases in SLE mortality rates seen over time. We are evaluating all cause mortality in a large, randomised controlled 1-year safety study (BASE: Protocol HGS1006-C1113) and 5-year safety registry (SABLE: Protocol HGS1006-C1124).

The current data is therefore insufficient to indicate a trend towards higher mortality with belimumab and this statement should be amended.

Whilst the benefits on survival incorporate assumptions this is based on published evidence of a clear link between high disease activity and mortality in SLE:

- Disease activity (i.e. Adjusted Mean SLEDAI (AMS) score) has been shown to be predictive of organ damage and mortality<sup>3</sup>.
- In the Johns Hopkins cohort<sup>4</sup>, a 5 year survival rate of 98% was observed in patients with a baseline SS score <10 points compared with 82% with patients who had a baseline SS score >10
- In the University College Hospital London SLE cohort disease activity as measured by mean total BILAG score was associated with mortality (HR = 1.15, P=0.008)<sup>5</sup>

The notion of the control of disease activity resulting in improved longer term outcomes, including mortality, is well established for SLE and other chronic autoinflammatory diseases (e.g. rheumatoid arthritis). As well as the published evidence, this assumption was endorsed by clinical experts at previous appraisal committee meetings.

The two Phase 3 BLISS trials showed a statistically significant benefit of belimumab over standard of care in SS score and seven years of follow-up data from the Phase 2 OLE trial show that efficacy with belimumab is maintained over this period in a significant percentage of patients.

Therefore both the inclusion of the relationship between AMS and mortality and the assumption that while patients remain on belimumab they continue to benefit from the treatment in terms of reduced disease activity seem clinically justified and hence support a beneficial effect on survival with belimumab.

Exploring the impact of reduced survival benefit with belimumab on the ICER via sensitivity analyses is problematic in a patient simulation model that includes natural history of disease models which link AMS to long-term outcomes. This is because the AMS is also linked to other outcomes in the model (i.e. organ damage and steroid dose) and it is therefore not easy to reduce the benefit with belimumab solely for survival while maintaining the benefit for other outcomes.

## **2) Uncertainty around the linking of the high disease activity BLISS sub-population with the John's Hopkins cohort (JHC)**

**In Section 4.14 of the ACD the Committee state that the uncertainty around linking outcomes from two populations which differ in severity is likely to underestimate the most plausible ICER. We would agree that this introduces uncertainty but would challenge whether this would necessarily be an underestimate.**

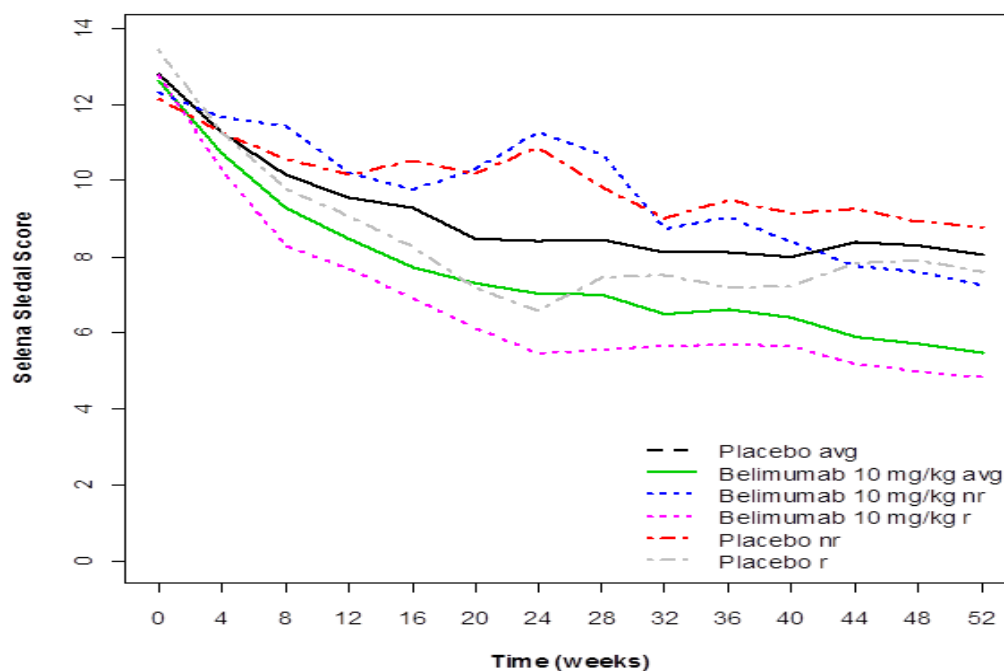
For example, if a cohort of patients experiencing frequent severe flares had been used in place of the JHC, due to the observed benefits belimumab has demonstrated in significantly reducing severe flares in the BLISS studies, greater benefits could have been achieved with belimumab than those estimated from the JHC database and hence the ICER could be lower than currently estimated.

## **3) Uncertainty around the assumption of disease activity level for belimumab non-responders after week 24**

**In Section 4.21 of the ACD it is stated that the ERG believe that assigning the average SELENA-SLEDAI score of the SoC patients to belimumab non-responders, rather than the average score of the SoC non-responders, when they stop belimumab and return to SoC after week 24 in the model may underestimate the most plausible ICER. GSK believe strongly that the assumption used in the model is robust and that the ICER is unlikely to be underestimated.**

The ERG's conclusions suggest that a non-responder to belimumab after week 24 will not respond to treatment in the future. However we see from Figure 1 below, presenting observed SS score data over time from the pooled BLISS trials, that although up to week 32 there is a very similar pattern between the placebo and belimumab non-responders, this is not the case beyond this time-point as by week 52 there is a divergence in the non-responder lines. Table 1 shows that at week 52 the mean change in the belimumab non-responders is -4.1 points and this is closer to the mean change seen for all SoC patients (-4.4 points) than the mean change seen for the SoC non-responders (-2.9 points).

**Figure 1: Summary of observed SELENA-SLEDAI score over time - Pooled BLISS studies for UK Target Population**



**Table 1: Summary of change from baseline to week 52 in observed SELENA-SLEDAI score - Pooled BLISS studies for UK Target Population**

	SoC			Belimumab		
	Responders (N=105)	Non-responders (N=98)	All (N=203)	Responders (N=130)	Non-responders (N=63)	All (N=193)
<b>N</b>	83	53	136	110	39	149
<b>Baseline score</b>	13.0	11.7	12.5	12.6	11.3	12.2
<b>Week 24 score</b>	6.3	10.9	8.0	5.2	11.0	6.7
<b>Week 52 score</b>	7.6	8.8	8.1	4.9	7.2	5.5
<b>Change from baseline to Week 52 score</b>	-5.4	-2.9	-4.4	-7.7	-4.1	-6.8

We validated our assumption with lupus experts, who felt that this approach was a fair reflection of what would be likely to happen in clinical practice i.e. patients who fail on belimumab will be put on higher doses of oral steroids and/or mycophenolate to induce a response.

In summary we believe that the assumption we used in the model is reasonable and provides a fair estimate of cost-effectiveness.



#### **4) Uncertainty around impact on ICER by not accounting for patients' SLEDAI scores prior to start of the BLISS studies.**

**The ERG state that by not taking into consideration patients' SLEDAI scores prior to start of the BLISS studies, the degree of benefit on disease activity assigned to belimumab may have been exaggerated and hence the most plausible ICER has been underestimated. GSK agree that it is possible that the ICER has been underestimated to some degree but due to the complex modelling it is not straightforward to quantify this.**

The ERG suggest that prior to the patients being eligible for recruitment into the BLISS studies their SLEDAI scores may have been lower than those seen at study entry. The impact of these lower scores would be to reduce the AMS score during the years of follow up in the model and hence the degree of benefit seen with belimumab over SoC. The level of AMS over time for both SoC and belimumab is linked to risk of organ damage, estimated steroid dose and mortality risk.

To address the impact of prior SLEDAI scores appropriately in the model would require not only assumptions of prior SLEDAI values for patients recruited into the BLISS studies, but also assumptions on SLEDAI values prior to patient entry into the Johns Hopkins cohort (JHC) database, as neither set of data is readily available. As regards the JHC data it would be necessary to reconstruct all the natural history of disease models (NHDMs) to determine the revised coefficient for AMS and also coefficients for other parameters; this is not an insignificant analysis. It is therefore not possible to conduct a quick sensitivity analysis to determine the likely impact on the ICER. However it is anticipated that the ICER will be increased due to the inclusion of prior SLEDAI data for the BLISS patients but this increase will be reduced due to the expected larger coefficients that would be calculated for AMS in the NHDMs from the inclusion of the prior JHC SLEDAI data. The degree to which the inclusion of JHC SLEDAI data offsets the increase in ICER due to the inclusion of the BLISS patients' prior SLEDAI data is difficult to determine in the absence of a complete re-analysis of the NHDMs.

#### **Assumption that treatment effect is maintained over time is uncertain**

**The Committee state that there is uncertainty around whether the treatment effect seen with belimumab in the clinical trials is likely to be maintained over time. If the benefits of treatment reduce over time then the ICER is likely to have been underestimated. GSK disagree that this should be considered an area of uncertainty which should influence their decision making.**

We are not aware of any data that suggests that the treatment effects observed with belimumab are not maintained over time. Data collected during seven years of follow-up in the Phase 2 open-label extension study<sup>6,7</sup> provide a large body of evidence to support the safety and efficacy of belimumab for the treatment of SLE, and supported the data collected during the BLISS clinical trials. This finding is also consistent with acceptance in Section 4.18 of the ACD that the clinical specialists had referred to experience with SLE where the effects of rituximab did not seem to diminish over time.

The expectation that RCTs should be run for very long durations in order to reduce long term uncertainty in outcomes, prior to obtaining a licence for a medicine, is unrealistic and would be in practice logistically infeasible, particularly in rare diseases.

In summary, based on the available evidence there is no reason to believe that treatment effect will reduce over time therefore we believe this assumption in the model is robust and hence the proposed base case ICER is appropriate in this regard.

#### **5) Uncertainties due to deriving organ damage cost data from different sources**

**In Section 4.25 of the ACD it is stated that the Committee was concerned that deriving cost data for organ damage from different sources may have led to some inconsistencies in the estimates and that some of the benefits associated with delaying certain types of organ damage may have been underestimated.**

Firstly, with regards to the utilities for renal damage, the data from the literature indicates that early stage renal damage does not have a major impact on patients' lives, it is the end stage renal disease requiring dialysis and transplantation that severely affect their quality of life. The utility values for each type and severity of organ damage were extracted from published literature and overall utility values for each organ system were calculated based on the observed events in the JHC database. If these patients generally had less severe disease than our UK target population it does seem reasonable to conclude that as high disease activity is linked to increased organ damage that the disutilities for damage in certain organ systems e.g. renal may have been underestimated and consequently the cost-effectiveness of belimumab may also have been underestimated.

Secondly, in the original NICE model disease activity costs were estimated from a regression analysis of resource use collected in the Phase 2 belimumab study (LBSL99), however it was acknowledged that these costs may also have included costs associated with organ damage. After the original NICE submission results from the LUPus Erythematosus Cost of Care In Europe<sup>8</sup> study data were available for UK patients and these data were used in the model in place of the original Phase 2 study analysis for disease activity. The LUCIE data analysis allowed for costs for organ damage to be excluded from the estimates of disease activity costs i.e. costs for organ damage were no longer double counted in the model. The impact of this was to increase the ICER only very slightly to [REDACTED] per QALY from our estimated base case with PAS of [REDACTED] per QALY using the ERG's preferred assumptions. More details on how the analysis was conducted are presented in Appendix 1.

#### **6) Other areas of uncertainty that may have lead to an underestimate of the level of cost-effectiveness**

Belimumab as an innovative treatment; although the evidence is currently incomplete and therefore introduces uncertainty we strongly believe that belimumab can offer other aspects of value to patients that have not been fully accounted for in the assessment of cost-effectiveness, and these are likely to have a positive effect on the most plausible ICER:

- **Chronic fatigue:** It is well documented that the EQ-5D instrument underestimates certain dimensions of health relevant to SLE, such as fatigue and sensory impairment<sup>9</sup> and this instrument was used in the health economic model. Monitoring fatigue in clinical practice using a more sensitive instrument such as the LupusQoL questionnaire<sup>10</sup>, specifically designed for SLE and which was not available when the BLISS studies were started, may help to demonstrate benefits that belimumab can offer on this debilitating symptom. The FACIT-F questionnaire used in the BLISS studies, but not incorporated into the modelling, went some way in demonstrating this.
- **Steroid sparing potential:** Both the seven year follow-up Phase 2 OLE study<sup>6,7</sup> and the US real-life OBServe study<sup>11</sup> have demonstrated clear reductions in oral steroid doses while patients are prescribed belimumab. Both patients and clinicians stress the importance of this benefit, 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 (with associated increased use of healthcare resources) would also be reduced. Any reduction in the clinical dosage of steroids will therefore be a benefit both to patients and the available healthcare resources.

#### **Summary**

Taking into consideration all the areas of uncertainty discussed above, it is true that some of these may indeed lead to an increase in the most plausible ICER (e.g. a lower survival benefit), but other areas of uncertainty may in fact lead to a decrease (e.g. discontinuation rate and steroid sparing potential), and therefore it seems reasonable to conclude that overall there is no strong evidence that the cost-effectiveness of belimumab has been significantly overestimated.

## **Other areas where the interpretation of the evidence is considered incomplete**

### **The six month stopping rule**

In Section 4.19 of the ACD, the Committee concludes "...that given the uncertainties about the application of the SELENA-SLEDAI in clinical practice and the specification of 4 rather than 6 points as part of the primary end point in the clinical trials, it was not appropriate to consider using the more restrictive rule of a SELENA-SLEDAI score improvement of 6 or more as the basis for the most plausible ICER."

Our comments on this are as follows:

- Lupus experts have informed us that incorporating a treatment continuation rule in clinical practice as part of the management of patients on belimumab would be easily achievable and valuable and would be acceptable if it were a stipulated requirement in NICE guidelines. Patients in our proposed target population will be managed in only a small number of specialist lupus centres and this will help ensure that clinicians adhere to any specific requirements for prescribing belimumab.
- Although using a responder criterion of an improvement of 4-points in SS score at 6 months would be preferable to a 6-point criterion, patients and clinicians would prefer the option of belimumab being made available to a small group of SLE patients who demonstrated a clear improvement in disease activity (using a more stringent 6-point criterion) to the alternative of no patients having the opportunity to benefit from the drug at all.
- The most plausible ICER with the PAS and the 6-point stopping rule does take the estimated level of cost-effectiveness to a level that would be considered an acceptable use of NHS resources [REDACTED]

### **Impact of SLE manifestations on mortality risk**

- In ACD Section 4.22 of the ACD it is stated "...The Committee heard from the clinical specialists that people with higher disease activity are more likely to have organ damage and die than people with lower disease activity. However, the clinical specialists stated that this was likely to be dependent on the site of organ damage. For example, treatment for people 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  $\geq 10$  (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<sup>12, 13</sup> and develop long term organ damage<sup>14</sup> 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.
- 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 space 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.

### Estimated age of death in the total population and UK target population

- Section 4.22 of the ACD discusses 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 standard care arm in the overall pooled BLISS populations), when the opposite would be expected as the target population had the more severe disease.
- As detailed in our response to the first ACD we investigated this further and demonstrated that this was 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. This was accepted by the Committee, however this section of the ACD then states "...The Committee considered that, although the different ages at baseline accounted for the survival difference, it noted that the age of death remained the same for both age groups. This was considered to be an unexpected finding given the longer disease history of the younger age group". However when the same age distribution seen for the total BLISS population is included in the model for the target population, not only is the life expectancy (life years undiscounted) reduced to 28.4 years for the SoC group below that of the total population where the life expectancy was estimated to be 30.5 years, but also the expected age of death was estimated to be 66.2 years in the target population compared with an expected age of death of 68.4 years for the overall trial population which was provided in our original submission in April 2011 (Table 6.30). Tables 2 and 3 below present the summary of the results from the model for each population. These results demonstrate that the long-term modelling is robust and does provide expected results 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 – UK 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

**Table 3: Summary of outcomes from the economic model for the original base case with a lifetime treatment duration for belimumab – Pooled total population**

	SoC	Belimumab	Difference
Age at Death	68.4	69.9	1.45
SLICC at Death	4.0	4.0	-0.03
AMS	4.8	4.35	-0.46
Average Monthly Steroid	214.2	203.6	-10.56
Life Years (undiscounted)	30.47	31.92	1.45
Life Years (discounted)	16.74	17.31	0.57
QALYs (undiscounted)	16.46	17.35	0.89
QALYs (discounted)	9.55	9.97	0.42

Source: Table 6.30 from GSK submission dated 13<sup>th</sup> April 2013.

**3. 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 designed to treat a rare, severely debilitating disease. 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.
- Belimumab addresses an area of significant unmet need in the management of SLE patients who have severe highly active disease, despite being managed on current standard of care. There has been little therapeutic innovation in the treatments for SLE, with no evidence leading to the development of new licensed treatments for several decades.
- There are very few treatment options for our target population. In the absence of rituximab being available on the NHS due to recent draft NHS England policy<sup>15</sup>, SLE patients may be admitted to hospital for alternative more expensive treatments such as intravenous immunoglobulin therapy. The cost of this therapy has not been included in the costs for standard of care.
- Our proposed target population 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. With the level of discount offered to the UK in our patient access scheme and our positioning of belimumab as an alternative to rituximab the prescribing of belimumab will [REDACTED]
- Treatment with belimumab is likely to be more cost-effective in the short-term and so in line with a positive recommendation for belimumab we have proposed supporting a registry in the UK, subject to lupus experts' agreement, where real-life data can be collected on patients prescribed belimumab at specialist centres. This would enable validation of some of the assumptions in the modelling with the aim of reducing some of the uncertainty in the longer-

term estimates of cost-effectiveness and would be available in time for the next NICE guidelines review

**4. Do you think that the preliminary recommendations may need changing in order to better meet the aims of promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others?**

We have not identified any aspects of the recommendations that require changing based on NICE's stated aims.

### References

1. DSU report: Belimumab (Benlysta) for the treatment of systemic lupus erythematosus (SLE): "Eliciting estimates of long-term treatment discontinuation rates", (published online July 2013)
2. Bernatsky S, Boivin, J.-F., Joseph, L., Mortality in Systemic Lupus Erythematosus, Arthritis & Rheumatism; 2006 August 54,(8): 2550–2557
3. Ibanez D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol 2003 Sep;30(9):1977-82.
4. Kasitanon, N., Magder, L. S., & Petri, M. Predictors of survival in systemic lupus erythematosus. Medicine (Baltimore) 85[3], 147-156. 2006.
5. Rekha Lopez, Julie E. Davidson, Matthew D. Beeby, Peter J. Egger and David A. Isenberg. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort Rheumatology 2012;51:491-498
6. Merrill JT et al. Sustained Disease Improvement and Safety Profile Over 1745 Patient-Year Experience (7 years) with Belimumab in Systemic Lupus Erythematosus. ACR 2012 Abstract No 2621, page S1110,
7. JT Merrill, RA. Furie, DJ Wallace, W. Stohl, WW Chatham, A Weinstein, JD McKay, EM Ginzler, ZJ. Zhong, WW Freimuth, MA Petri for teh LBSL02/99 Study Group. Sustained Disease Improvement and Safety Profile Over 1745 Patient-Year Experience (7 years) with Belimumab in Systemic Lupus Erythematosus. Patients; ACR; Washington DC; November 14 2012 No 2621, page S1110,
8. GlaxoSmithKline data on file. 2011.
9. Allan Wailoo, Sarah Davis, Jonathan Tosh. THE INCORPORATION OF HEALTH BENEFITS IN COST UTILITY ANALYSIS USING THE EQ-5D REPORT BY THE DECISION SUPPORT UNIT, 15 November 2010
10. McElhone K, Abbott J, Shelmerdine J, Bruce IN, Ahmad Y, Gordon C, Peers K, Isenberg D, Ferenkeh-Koroma A, Griffiths B, Akil M, Maddison P, Teh LS. Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus. Arthritis Rheum. 2007 Aug 15;57(6):972-9.
11. Collins CE<sup>1</sup>, Narayanan S<sup>2</sup>, Dall'Era M<sup>3</sup>, Dennis G<sup>2</sup>, Oglesby A<sup>4</sup>, Mcguire ME<sup>5</sup>, Pappu R<sup>4</sup>, Molta C<sup>4</sup>, Keenan G<sup>2</sup>. Outcomes Associated with Belimumab in Patients with Systemic Lupus Erythematosus in Clinical Practice Settings: Results from an Observational Cohort Study in the United States, ACR meeting 2012 abstract No.2617

12. Petri M, Singh S, Tesfayone H, Malik A. Prevalence of flare and influence of demographic and serologic factors on flare risk in systemic lupus erythematosus: a prospective study. *J Rheumatol* 2009 Nov;36(11):2476-80
13. Tseng CE, Buyon JP, Kim M, Belmont HM, Mackay M, Diamond B, 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* 2006 Nov;54(11):3623-32
14. Swaak AJ, van den Brink HG, Smeenk RJ, Manger K, Kalden JR, Tosi S, et al. Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. *Rheumatology (Oxford)* 1999 Oct;38(10):953-8.
15. Manual for prescribed specialised services, November 2012. Accessed online at <http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf>, August 13, 2013.

## **Appendix 1**

### **Details of the revised analysis to exclude the double counting for organ damage**

Costs related to disease activity were based on an analysis of the resource utilisation recorded in an European cost of illness retrospective study using patient chart abstraction, The Systemic Lupus Erythematosus Cost of Care In Europe (LUCIE).<sup>8</sup>

#### **Study Objective**

To evaluate direct costs of specialist management for SLE patients with active autoantibody positive disease receiving treatment for SLE. To be eligible for this study patients had to satisfy the following criteria:

- 1) At least one change (increase in dose and/or new treatment) in treatment related to SLE activity, and /or:  
New manifestations and/or worsening of clinical symptoms of SLE.  
OR
- 2) Presence of at least one biomarker of SLE activity, and at the same time, the presence of at least one clinical and/or haematological feature of SLE.

#### **Methods to calculate the disease activity costs:**

- The study recruited a total of 427 SLE patients from 5 European countries (France, Spain, Italy, Germany and the UK) selected from 31 specialty care sites and the study was conducted in 2011.
  - Of 86 UK patients, 38 (44%) were categorised as having severe disease, defined as:
    - at least one of the following major domains actively involved at the start of follow-up period: renal, neurological, cardiovascular or respiratory
- AND
- requiring over 7.5 mg/day of corticosteroids (prednisone equivalent dose) and/or immunosuppressant(s) (including biological drugs).
    - The average duration of follow-up of patients in this UK cohort was 25.1 months (SD 2.6) which enabled approximately two years of cost data to be collected.
    - mean age of the patients was 45.5 years (SD 13.9);
    - mean duration of SLE was 11.9 years (8.3);
    - mean SS score at entry to the study was 7.7 (SD 5.7);
    - mean SLICC/ACR damage index score was 0.8 (1.3).
    - 94% female, and 29.1%, 12.8% and 54.7% were of black, Asian or white ethnicities respectively.
  - These characteristics were not too dissimilar to our UK target population
  - The following cost categories were reported in the LUCIE study: laboratory tests, biopsies and imaging tests, medical treatments, visits to Specialists (secondary and tertiary care), hospitalisation (including emergency rooms and inpatient stays) and rehabilitation stays. Total resource costs for each patient were calculated and annualised.
  - It is likely that resource costs will differ for patients with organ damage and/or high disease activity. In order to derive a statistical model that explains the direct medical costs from disease activity and organ damage, regression modeling was used with the log-transformed



annual direct costs as the dependent variable. All significant demographic and disease characteristics and the presence/absence of damage in different organ systems variables from univariate analyses were included in a multivariate model, and in addition, SLICC/ACR score was forced in the model in order to remove the effect of organ damage from the total costs. A backwards selection process was then applied to identify the final regression model

#### Regression of log transformed annual direct cost – UK patients in the LUCIE study

	Coefficient	Std. Err.	P-value	95% Confidence Interval
Intercept	7.324	0.151	<0.001	7.023, 7.625
SS score	0.068	0.015	<0.001	0.038, 0.098
SLICC score	0.090	0.066	0.177	-0.042, 0.222

This regression equation from the above model ( $\text{Log}_e \text{ cost} = 7.324 + 0.068$ ) was then used to calculate the disease activity costs (costs not associated with organ damage) using a SLICC/ACR score of 0, in order to estimate costs associated with each SS score as shown in the Table below.

#### Non-organ damage related yearly costs for each SS score - UK patients in the LUCIE study

SS score	Direct costs (excl. organ damage)	SS score	Direct costs (excl. organ damage)
0	£1,517	11	£3,211
1	£1,624	12	£3,438
2	£1,738	13	£3,681
3	£1,861	14	£3,940
4	£1,992	15	£4,219
5	£2,133	16	£4,516
6	£2,284	17	£4,835
7	£2,445	18	£5,176
8	£2,617	19	£5,542
9	£2,802	20	£5,933
10	£3,000		

These costs for disease activity were included into the health economic model.

## **Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus [ID416]**

LUPUS UK very much regrets the decision made by NICE not to approve prescribing of the drug Belimumab for those lupus patients who have found other treatments to be ineffective in controlling this serious auto-immune condition. Some patients have seen their lives transformed by other biological treatments and it was our hope that this drug would be approved for funding.

### **Has all the relevant evidence been taken into account?**

Throughout the appraisal process clinicians have reiterated that the target population for this drug was likely to amount to around 10% of all lupus patients. This seems to have been lost sight of in much of the discussion.

We know that a major clinical problem in SLE is accelerated atherosclerosis and premature coronary heart disease (CHD) and that studies have demonstrated that chronic steroid exposure is associated with risk factors for CHD including development of the metabolic syndrome. In addition chronic steroid use is associated with clinical CHD development in SLE patients. Agents that can help control SLE better and reduce steroid requirements are desperately needed and would likely add to our ability to reduce the risk of future morbidity and mortality. Secondary analysis of the Belimumab data supports a role for reducing steroid requirements. (refs 1-3)

Of particular importance is the evidence that the percentage of deaths from lupus is highest in the 16-25 year old group, in other words there is a significant group of patients for whom other treatments are unfortunately ineffectual, and a new drug could have significant impact on their length of life.

As this appraisal has taken such a long time, I am aware that research has been published by M Petri, which has been referred to during later meetings. I would expect that it is likely that other material could also have been published in since the appraisal started, but as I do not have access to scientific journals, I would suggest that you consider any comments made by the clinical experts.

I would however like to draw attention to 2 articles which are reference (4 and 5) on the attachment herewith (I only have access to abstracts for these so am unable to refer to the full article: although these do not contain information on Belimumab I feel that the committee needs to be aware of the bulk of evidence about some of the very serious side effects and the need for new medications which will be more effective:

- the BMJ article(4) highlights problems in pregnancy outcomes for obese patients, particularly in long term health outcomes for their offspring: we have continually highlighted the need to reduce steroid usage in patients with lupus because of the serious side effects, one of which is weight gain.
- the Seminars article reviews data on CVD risk in lupus patients, and draws attention to the particularly high risk to young lupus patients, further emphasising our concerns on the high death rates in this age group.

I would reiterate details of our suggestion to the Appeal committee that this drug is used in specified clinics on patients who have not responded successfully to any treatment and data collected in the BSR Biologics Registry: this would then provide evidence to NICE (see below).

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

We are extremely disappointed that, despite consistent reiteration from all of the clinical experts called and from our patient 'expert' about the complex nature of this condition, the Appraisal Panel seem to have based their decision solely on the cost effectiveness of the drug. Discussion during meetings seems to have centred on requiring treatment of the illness to be predictable enough to 'fit' into a model or algorithm for costs. Information about the unpredictable nature of this condition especially in relation to the timeliness of response to medication, has been repeatedly presented at every meeting of the panel, but seems to have been ignored.

NICE asked their Design Support Unit to carry out an exercise to contact a number of lupus experts to ask about the treatment of lupus patients; the response reiterated that the course of this illness is extremely difficult to predict and also pointed out that as the drug has not been authorised by NICE, most clinicians are unable to prescribe it. We would contend that NICE has not considered this evidence, which was presumably intended to help them reach a decision.

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

Belimumab has been approved by the European Medicines Agency and by the FDA: we are very concerned as to where this refusal by NICE leaves British patients.

We do not feel that these recommendations provide sound or suitable guidance for the NHS. The only drugs which are approved for use in lupus are hydroxychloroquine and steroids: we rehearsed the problems of steroids and their serious, long term side effects at every meeting. Steroid-sparing drugs are now used in treating many lupus patients, as are other biologics, but these remain 'off label' and funding approval for these drugs is a constant problem in most parts of the country. Again, there are patients for whom these drugs are ineffectual and NICE is leaving clinicians and their patients with no other option available in this life-threatening situation.

### **QUALITY OF LIFE ISSUES**

We would point out that Quality of life issues do not seem to have been adequately considered.

We consistently detailed the problems which lupus patients experience, especially the serious, long term side effects of existing treatments, but also other difficulties, particularly with pregnancy. Lupus patients will continue to struggle day to day to live with this unpredictable illness: the small group for whom no other drug is effective will continue to face an extremely limited, uncertain life, dominated by frequent hospital visits and an inability to function properly, never mind experience any 'quality of life' such as normal relationships, bringing up children or being able to have a career. They will be unable to work and will need to draw on a variety of benefits in order to support themselves.

Other biological drugs have enabled lupus patients to lead full lives with careers, families and other meaningful activities: as these treatments have been ineffectual for some patients, our hope was that NICE would approve use of Belimumab (even if only on a limited basis, see below) and broaden this benefit to those for whom no other treatment has proved effective.

### **COSTS TO NHS**

The costs to the NHS of not funding this drug are that consultant clinicians will continue to devote a large proportion of time and attention to these unfortunate patients resulting in more costs to the NHS because of increased number of appointments and fuller clinics which delay access to all patients.

Patients will also need to access other NHS services as lupus makes them, alongside other health problems, particularly susceptible to cardiovascular problems. Thus more time is taken up with appointments, investigations and treatment for co-morbidities, many of which are could be reduced or prevented if clinicians were able to offer a more effective treatment.

Lupus causes the immune system to be dysfunctional, and many drugs used on patients dampen down their immune system in order to reduce damage to other systems: this leads to increased risk of infection resulting in frequent visits to medical professionals and increased cost of drugs to fight these infections.

There may well be costs to the NHS in the long term for the worsened health outcomes of children whose mothers gained weight before pregnancy due to heavy steroid medication (BMJ article).

Consultants will be exercised by the inability to prescribe a drug which, they believe, could have been effective in controlling the illness for the worst affected patients.


Other costs to government will be payment of benefits because patients are unable to work, care costs for those unable to carry out normal tasks at home, and adapted housing for those who have mobility/access difficulties.

### **SUGGESTED LIMITED ACCESS TO TREATMENT**

During the Appeal Process LUPUS UK, supported by medical experts, put forward the suggestion that this drug should be allowed to be used by a small number of highly experienced lupus consultants in

cases where no other treatment was found to be effective: detailed data would be collected on the Biologics Registry already in operation at Manchester University. This would have provided accurate information of the drug's appropriateness in a UK population (which was mentioned as a drawback with existing research), as well as giving patients reassurance about the treatment and its effects.

This would seem to be a way forward to making an evidence-based decision about whether to fund the drug or not. There has been no attempt by NICE to take this idea forward, despite support from the clinical experts. We find this surprising if not mystifying, given NICE's role to 'help medical professionals deliver the best possible care based on the best possible evidence'.

 LUPUS UK  
August 2013

## References

- 1: Parker B et al Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort.  
*Ann Rheum Dis.* 2013 72:1308-14.
- 2: Haque S et al Risk factors for clinical coronary heart disease in systemic lupus erythematosus: the lupus and atherosclerosis evaluation of risk (LASER) study.  
*J Rheumatol.* 2010 37:322-9.
- 3: Bruce IN. 'Not only...but also': factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus.  
*Rheumatology* 2005 44:1492-502.
- 4: Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years  
*BMJ* 2013; 347: f4539
- 5: The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: A systematic review  
Seminars in Arthritis and Rheumatism, 2013 [43:1](#) 77-95,

## **Response to NICE Single Technology Appraisal (STA) Consultation Document**

*Submitted by Dr David Isenberg (BSR's nominated expert) and approved by the Chair of the Clinical Affairs Committee*

### **Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus [ID416]**

#### **General Observations**

1. The final sentence of 4.27 (See page 48) states that the “Revised patient access scheme did not reduce the ICER sufficiently .....” to bring the estimate within a range which belimumab could be considered a cost effective use of NHS resources compared with standard care within its marketing authorisation. This observation ignores the “off-stated” point that the manufacturers (GSK) and the scientific advisers are asking that belimumab be considered specifically for those patients in whom standard of care has failed.
2. It is worth noting that NICE has never approved the use of rituximab for lupus and that there is a lack of evidence available, particularly in terms of the company's suggestion that the drug could be used for up to six years in appropriate patients.
3. While NICE exists to determine, not so much whether a drug is clinically effective, but rather if it is cost-effective, there is “a greater good” argument that the NICE committee should not ignore. In particular, the numbers of patients with lupus in the UK is perhaps in the region of 25,000. The numbers of patients who fail to respond to conventional therapy i.e. steroids and immunosuppressives, is perhaps 10-15% of this total. We are thus dealing with a rather small number of patients, but it is vitally important that the following key facts should not be forgotten:
  - i) Lupus retains the power to kill patients.
  - ii) Lupus in the main affects a young to early middle-aged population.
  - iii) Very few drugs have ever been approved formally for the treatment of lupus.
  - iv) The Rheumatology Community has matured in terms of developing biologic registers to capture real life experience of the use of biologic drugs. This experience has been gathered principally through the British Society for Rheumatology's Biologics Register, established in 2000, which now records information on 20,000 patients with rheumatoid arthritis and currently over a 100 with lupus.

## Comments on the particular points that the Appraisal Committee is interested in receiving

### **1. Has all the relevant evidence been taken into account?**

The Appraisal Committee might be interested to read a paper by Condon et al<sup>1</sup> which describes the use of rituximab and mycophenolate given to patients with lupus nephritis at the time of diagnosis with a stated aim to try and to control the severe aspect of lupus and avoid the use of oral steroids. By a median time of 37 weeks, 90% of patients achieve complete or partial remission and of those who did respond, only two required more than two weeks of oral steroids. Thus biologics can be used to try and treat lupus and avoid the use of steroids. Benlysta can have a role to play here.

### **2. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?**

The BSR may not be best placed to argue about the nuances of the various formulae and theoretical assumptions used to determine the question of the cost effectiveness of Benlysta. However, in light of the Appraisal Committee's support for the view that the patients included in the BLISS 76 trial, as opposed to the BLISS 52 trial, were more typical of UK lupus populations, it is worth noting that 40% of the patients in Dr Isenberg's current lupus cohort (n=650) are non-Caucasians and that BLISS 52 patient cohort should therefore not be so lightly dismissed. While accepting the fact that some aspects of the outcome in the BLISS trials e.g. patient perception and fatigue scores showed no or little benefit for Benlysta, the fact is that in two major clinical trials, Benlysta did meet its endpoints (using the SRI endpoint formulation).

### **3. Are the provisional recommendations sound and a suitable base for guidance to the NHS?**

BSR's nominated expert considers that the proposal put to the NICE committee and strongly supported by himself, Professor Bruce and Dr Lanyon at the meeting last July offers the best solution, i.e., that NICE should accept that at the moment there are insufficient data to be sure about the value (clinical and health economic) of the use of Benlysta in patients with lupus long term. The proposal made to NICE is relatively straightforward and would proceed as follows:-

- i) The use of Benlysta in patients with lupus will be restricted to those patients who have failed to respond adequately to prednisolone and or one or two immunosuppressive drugs, and who have skin and joint disease as their principal manifestation.
- ii) Patients will be treated at a restricted number of lupus centres with considerable expertise in seeing these patients (approximately 15 in the UK).
- iii) Patients entering the study would have a SLEDAI score of 10 or more
- iv) Patients would be asked to agree that their data be sent in an anonymised fashion to the BSR's Biologics Lupus Register currently housed in the

---

<sup>1</sup> (Annals of Rheumatic Diseases 2013; 72: 1280)

Epidemiology Unit at the University of Manchester and currently directly by Professor Ian Bruce.

- v) Treatment would be given for six months at which point a decision would be made about whether an improvement in the SLEDAI of at least four points had taken place, in which case, the drug could be continued or that it had not, in which the drug would be stopped.
- vi) Those physicians entering patients into the study would give as undertaking that SLEDAI (or BILAG) forms would be completed at the time that Benlysta is given and ideally, every time the patient is seen during the initial six-month period or at least as a minimum at the time of entering the study and at six months, followed by six-monthly updates. These data would be supplied to the biologics lupus register for subsequent analysis.
- (vii) It seems to me that this would provide a perfect platform to gather vital, detailed, real life experience of the use of Benlysta and would help to determine whether it really does have a place in the management of 'hard to treat' lupus.

**4. Are there any major aspect of the recommendations that need further particular consideration....?**

Our nominated expert, Dr Isenberg, believes that a drug which has met its endpoints in two international clinical trials, is approved by the FDA and is approved by the European Medicines Agency (EMA) should be available in the UK.



---

National Institute for Health and Care Excellence

**Single Technology Appraisal (STA)**

**Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus [ID416]**

---

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 systemic lupus erythematosus reviewed the documents on behalf of the RCN.

**Appraisal Consultation Document – RCN Response**

The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below:

i) **Has the relevant evidence been taken into account?**

The Appraisal Committee has considered the findings from the 2 phase III clinical trials, BLISS-52 and BLISS-76 where Belimumab was compared against standard care, the submitted data for the licensing of Belimumab in the treatment of autoantibody positive SLE. This data has been further supported by long term efficacy and safety data from the phase II extension study over a six year period where sustained improvement in disease activity was reported with a decline in BILAG

scores and flares, accompanied by reductions in steroid usage and autoantibody levels. A revised patient access scheme has been agreed.

It seems that all the available evidence has been considered.

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

It was considered that the UK population is most closely represented by the BLISS-76 data in the study although pooled analysis was also reviewed in the appraisal document. It reports that a number of uncertainties remain unanswered although it concludes that there is some evidence of the clinical effectiveness of Belimumab. The cost effectiveness is considered to be above the threshold considered as an acceptable use of NHS resources despite the patient access scheme.

However, we do not believe that due consideration has been demonstrated of the significant impact on quality of life for somebody with severe systemic lupus erythematosus (SLE) which can be fatal. For instance, the uncertainty of living with this condition, reduced life expectancy, the flares, the fatigue, multi-organ involvement, admission to hospital, frequent hospital appointments (often to different hospitals and departments), difficulty walking due to a multi-organ involvement (musculoskeletal, pulmonary, cardiac) and therefore difficulty attending appointments, body image issues (due to skin involvement, hair loss, being cushingoid from corticosteroid use) an inability to work, being an active member of the family all impact on the patient's quality of life. As a condition that primarily affects females of child bearing age, it can be devastating, making having a family impossible or very difficult and for those who already have young children caring for the family because of the impact of SLE can be an enormous struggle often impacting on other family members. This means the condition often prevents not only the sufferer from SLE being unable to work but also the partner due to having to look after young children. These clinical and quality of life issues often also have a significant psychological impact on the person

with SLE. The lives of people with severe SLE are often ruled by hospital appointments. Some patients with severe SLE are on many medications to control their disease including corticosteroids, anti-malarials, immunosuppressants and other medications to directly target the organs effected for example anti-hypertensive. Therefore anything that would reduce the need to take so many medications would greatly improve the person's quality of life. Further, anything that would improve such a seriously debilitating quality of life even for a few years would make a major difference and these patients should not be denied a treatment that would do this. SLE can be more difficult to treat and more debilitating than rheumatoid arthritis (RA), yet there is no third line / biologic options available as there are for RA or other patient groups with long term conditions.

We also do not believe it has been demonstrated when considering cost-effectiveness that the cost of social factors such as not working has been fully taken into account. If a person were to be in remission, even if drug induced remission via Belimumab and were able to return to work they would be able to contribute to society in many ways including financially. While there are numerous mentions of the use of corticosteroids in the treatment of SLE and brief mention of side-effects, this does not seem to have been considered in the cost effectiveness review, steroid induced osteoporosis and fracture risk and the cost of screening for and treating this, steroid induced diabetes and the cost of treating this, potential ophthalmology problems, etc should be considered.

If in the small number of patients, 10-15% as stated of those with severe SLE, who would potentially be treated with Belimumab has their quality of life improved as a result, it would offer more than any other option currently available to these patients. Although Rituximab is used in some patients by completing Exceptional Circumstances Funding forms it is not a targeted therapy in the same way as Belimumab is. Rituximab may be given to these patients as per the RA protocol but it is difficult to compare costs as it may be given by various other protocols also. For

example, we have seen it given as 375mg/m also, making cost comparison very difficult.

Treating SLE patients with Rituximab is not as straight forward as treating RA patients with Rituximab, therefore it would be inappropriate to use the RA regime as a comparison.

The BILAG registry if approved would be used presumably in the same way the biologics registry was and is used for RA patients and should not necessarily be viewed as research per se. The biologics registry for RA has provided very useful information and as far as we are aware did not prevent biologic drugs for RA being approved by NICE.

iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

Whilst the appraisal consultation document has detailed the trials associated with Belimumab and its evidence base, with its clinical and cost effectiveness, there seems little awareness of the impact to the patient that a drug like this could make. The only licensed drugs for lupus are Prednisolone and Hydroxychloroquine, despite the fact that numerous different types of disease modifying agents are used in clinical practice off licence. Within its licence, the prescribing of Belimumab offers a real possibility to some patients who have failed conventional treatments and remain on higher doses of steroids than is preferred.

We therefore do not consider that the provisional recommendation is a sound and suitable basis for guidance to the NHS.

iv) **Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology or have any adverse impact on people with a particular disability or disabilities?**

There is no doubt that there is an equal opportunities impact for people with musculoskeletal and mucocutaneous complications of lupus who **will be disadvantaged** if they are not able to access Belimumab. Whilst the Committee have to make a decision on evidence based data, there is no doubt that we are sadly lacking options for treatments for this patient group. In clinical practice, we know that trying to get funding for drugs such as Rituximab for lupus through IFRs using applications to the CCGs/NHS England, are getting increasingly difficult and many hours of clinicians' time is taken up in fighting the patients' corner in order to access these high cost drugs. Sometimes these applications are turned down only on grounds of lack of available evidence.

It is our considered opinion that the Appraisal Committee **strongly reconsiders their decision about Belimumab for sero-positive lupus patients** as there is an important place for this treatment to enable clinicians to improve quality of life these patients and reduce risks associated with long term steroid treatments.

Confidential until publication

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SingleTechnology Appraisal**

**Belimumab for treating active autoantibody-positive systemic lupus erythematosus**

**Response to consultee, commentator and public comments on the 2<sup>nd</sup> Appraisal Consultation Document (ACD2)**

**Definitions:**

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

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

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

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

Confidential until publication

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

### Comments received from consultees

Consultee	Comment [sic]	Response
British Association of Dermatologists	Our T&G committee had no comments on the belimumab ACD.	Comment noted.
British Society for Rheumatology (endorsed by the Royal College of Physicians)	<b>General Observations</b>  1. The final sentence of 4.27 (See page 48) states that the “Revised patient access scheme did not reduce the ICER sufficiently .....” to bring the estimate within a range which belimumab could be considered a cost effective use of NHS resources compared with standard care within its marketing authorisation. This observation ignores the “oft-stated” point that the manufacturers (GSK) and the scientific advisers are asking that belimumab be considered specifically for those patients in whom <u>standard of care has failed</u> .	Comment noted. It was established during the scoping process that standard care should be considered a comparator in this patient population.
British Society for Rheumatology (endorsed by the Royal College of Physicians)	2. It is worth noting that NICE has never approved the use of rituximab for lupus and that there is a lack of evidence available, particularly in terms of the company’s suggestion that the drug could be used for up to six years in appropriate patients.	Comment noted.



Consultee	Comment [sic]	Response
<p>British Society for Rheumatology (endorsed by the Royal College of Physicians)</p>	<p>3. While NICE exists to determine, not so much whether a drug is clinically effective, but rather if it is cost-effective, there is “a greater good” argument that the NICE committee should not ignore. In particular, the numbers of patients with lupus in the UK is perhaps in the region of 25,000. The numbers of patients who fail to respond to conventional therapy i.e. steroids and immunosuppressives, is perhaps 10-15% of this total. We are thus dealing with a rather small number of patients, but it is vitally important that the following key facts should not be forgotten:</p> <ul style="list-style-type: none"> <li>i) Lupus retains the power to kill patients.</li> <li>ii) Lupus in the main affects a young to early middle-aged population.</li> <li>iii) Very few drugs have ever been approved formally for the treatment of lupus.</li> <li>iv) The Rheumatology Community has matured in terms of developing biologic registers to capture real life experience of the use of biologic drugs. This experience has been gathered principally through the British Society for Rheumatology’s Biologics Register, established in 2000, which now records information on 20,000 patients with rheumatoid arthritis and currently over a 100 with lupus.</li> </ul>	<p>Comment noted. NICE technology appraisals guidance assesses the clinical and cost effectiveness of health technologies to ensure that all NHS patients have equitable access to the most clinically- and cost-effective treatments that are available. The Appraisal Committee considered advice from NICE on the appropriate approach to making scientific and social value judgements as described in <a href="#">Social value judgements: principles for the development of NICE guidance</a>.</p>

Consultee	Comment [sic]	Response
<p>British Society for Rheumatology (endorsed by the Royal College of Physicians)</p>	<p><u>Comments on the particular points that the Appraisal Committee is interested in receiving</u></p> <p><b>1. Has all the relevant evidence been taken into account?</b></p> <p>The Appraisal Committee might be interested to read a paper by Condon et al<sup>1</sup> which describes the use of rituximab and mycophenolate given to patients with lupus nephritis at the time of diagnosis with a stated aim to try and to control the severe aspect of lupus and avoid the use of oral steroids. By a median time of 37 weeks, 90% of patients achieve complete or partial remission and of those who did respond, only two required more than two weeks of oral steroids. Thus biologics can be used to try and treat lupus and avoid the use of steroids. Benlysta can have a role to play here.</p>	<p>Comment noted.</p>
<p>British Society for Rheumatology (endorsed by the Royal College of Physicians)</p>	<p><b>2. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?</b></p> <p>The BSR may not be best placed to argue about the nuances of the various formulae and theoretical assumptions used to determine the question of the cost effectiveness of Benlysta. However, in light of the Appraisal Committee's support for the view that the patients included in the BLISS 76 trial, as opposed to the BLISS 52 trial, were more typical of UK lupus populations, it is worth noting that 40% of the patients in Dr Isenberg's current lupus cohort (n=650) are non-Caucasians and that BLISS 52 patient cohort should therefore not be so lightly dismissed. While accepting the fact that some aspects of the outcome in the BLISS trials e.g. patient perception and fatigue scores showed no or little benefit for Benlysta, the fact is that in two major clinical trials, Benlysta did meet its endpoints (using the SRI endpoint formulation).</p>	<p>Comment noted. The Committee concluded that although BLISS-76 was more representative of the population of England and Wales than BLISS-52, data from BLISS-52, and therefore from the pooled analysis, were relevant (see section 4.8 of the FAD).</p>

<sup>1</sup> (Annals of Rheumatic Diseases 2013; 72: 1280)

Consultee	Comment [sic]	Response
<p>British Society for Rheumatology (endorsed by the Royal College of Physicians)</p>	<p><b>3. Are the provisional recommendations sound and a suitable base for guidance to the NHS?</b></p> <p>BSR's nominated expert considers that the proposal put to the NICE committee and strongly supported by himself, Professor Bruce and Dr Lanyon at the meeting last July offers the best solution, i.e., that NICE should accept that at the moment there are insufficient data to be sure about the value (clinical and health economic) of the use of Benlysta in patients with lupus long term. The proposal made to NICE is relatively straightforward and would proceed as follows:-</p> <ul style="list-style-type: none"> <li>i) The use of Benlysta in patients with lupus will be restricted to those patients who have failed to respond adequately to prednisolone and or one or two immunosuppressive drugs, and who have skin and joint disease as their principal manifestation.</li> <li>ii) Patients will be treated at a restricted number of lupus centres with considerable expertise in seeing these patients (approximately 15 in the UK).</li> <li>iii) Patients entering the study would have a SLEDAI score of 10 or more</li> <li>iv) Patients would be asked to agree that their data be sent in an anonymised fashion to the BSR's Biologics Lupus Register currently housed in the Edpidemiology Unit at the University of Manchester and currently directly by Professor Ian Bruce.</li> <li>v) Treatment would be given for six months at which point a decision would be made about whether an improvement in the SLEDAI of at least four points had taken place, in which case, the drug could be continued or that it had not, in which the drug would be stopped.</li> <li>vi) Those physicians entering patients into the study would give as undertaking that SLEDAI (or BILAG) forms would be completed at the time that</li> </ul>	<p>Comment noted. Following discussions at the 6<sup>th</sup> Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details).</p>

Consultee	Comment [sic]	Response
	<p>Benlysta is given and ideally, every time the patient is seen during the initial six-month period or at least as a minimum at the time of entering the study and at six months, followed by six-monthly updates. These data would be supplied to the biologics lupus register for subsequent analysis.</p> <p>(vii) It seems to me that this would provide a perfect platform to gather vital, detailed, real life experience of the use of Benlysta and would help to determine whether it really does have a place in the management of 'hard to treat' lupus.</p>	
<p>British Society for Rheumatology (endorsed by the Royal College of Physicians)</p>	<p><b>4. Are there any major aspect of the recommendations that need further particular consideration....?</b></p> <p>Our nominated expert, Dr Isenberg, believes that a drug which has met its endpoints in two international clinical trials, is approved by the FDA and is approved by the European Medicines Agency (EMA) should be available in the UK.</p>	<p>Comment noted. Following discussions at the 6<sup>th</sup> Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details).</p>
<p>Department of Health</p>	<p>Thank you for the opportunity to comment on the appraisal consultation document (ACD) for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.</p>	<p>Comment noted.</p>
<p>Lupus UK</p>	<p>LUPUS UK very much regrets the decision made by NICE not to approve prescribing of the drug Belimumab for those lupus patients who have found other treatments to be ineffective in controlling this serious auto-immune condition. Some patients have seen their lives transformed by other biological treatments and it was our hope that this drug would be approved for funding.</p>	<p>Comment noted. Following discussions at the 6<sup>th</sup> Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details).</p>
<p>Lupus UK</p>	<p><b>Has all the relevant evidence been taken into account?</b></p> <p>Throughout the appraisal process clinicians have reiterated that the target population for this drug was likely to amount to around 10% of all lupus patients. This seems to have been lost sight of in much of the discussion.</p> <p>1 We know that a major clinical problem in SLE is accelerated</p>	<p>Comments noted.</p>

Consultee	Comment [sic]	Response
	<p>atherosclerosis and premature coronary heart disease (CHD) and that studies have demonstrated that chronic steroid exposure is associated with risk factors for CHD including development of the metabolic syndrome. In addition chronic steroid use is associated with clinical CHD development in SLE patients. Agents that can help control SLE better and reduce steroid requirements are desperately needed and would likely add to our ability to reduce the risk of future morbidity and mortality. Secondary analysis of the Belimumab data supports a role for reducing steroid requirements. (refs 1-3)</p> <p>2</p> <p>Of particular importance is the evidence that the percentage of deaths from lupus is highest in the 16-25 year old group, in other words there is a significant group of patients for whom other treatments are unfortunately ineffectual, and a new drug could have significant impact on their length of life.</p> <p>As this appraisal has taken such a long time, I am aware that research has been published by M Petri, which has been referred to during later meetings. I would expect that it is likely that other material could also have been published in since the appraisal started, but as I do not have access to scientific journals, I would suggest that you consider any comments made by the clinical experts.</p> <p>I would however like to draw attention to 2 articles which are reference (4 and 5) on the attachment herewith (I only have access to abstracts for these so am unable to refer to the full article: although these do not contain information on Belimumab I feel that the committee needs to be aware of the bulk of evidence about some of the very serious side effects and the need for new medications which will be more effective:</p> <ul style="list-style-type: none"> <li>• the BMJ article(4) highlights problems in pregnancy outcomes for obese patients, particularly in long term health outcomes for their offspring: we have continually highlighted the need to reduce steroid usage in patients with lupus because of the serious side effects, one of which is weight gain.</li> <li>• the Seminars article reviews data on CVD risk in lupus patients, and draws attention to the particularly high risk to young lupus patients, further emphasising our concerns on the high death rates in this age group.</li> </ul> <p>I would reiterate details of our suggestion to the Appeal committee that this drug is used in specified clinics on patients who have not responded successfully to any</p>	

Consultee	Comment [sic]	Response
	treatment and data collected in the BSR Biologics Registry: this would then provide evidence to NICE (see below).	
Lupus UK	<p><b>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</b></p> <p>We are extremely disappointed that, despite consistent reiteration from all of the clinical experts called and from our patient ‘expert’ about the complex nature of this condition, the Appraisal Panel seem to have based their decision solely on the cost effectiveness of the drug. Discussion during meetings seems to have centred on requiring treatment of the illness to be predictable enough to ‘fit’ into a model or algorithm for costs. Information about the unpredictable nature of this condition especially in relation to the timeliness of response to medication, has been repeatedly presented at every meeting of the panel, but seems to have been ignored.</p> <p>NICE asked their Design Support Unit to carry out an exercise to contact a number of lupus experts to ask about the treatment of lupus patients; the response reiterated that the course of this illness is extremely difficult to predict and also pointed out that as the drug has not been authorised by NICE, most clinicians are unable to prescribe it. We would contend that NICE has not considered this evidence, which was presumably intended to help them reach a decision.</p>	<p>Comment noted. The Decision Support Unit’s findings are described in sections 3.64 and 3.65 of the FAD.</p>
Lupus UK	<p><b>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</b></p> <p>Belimumab has been approved by the European Medicines Agency and by the FDA: we are very concerned as to where this refusal by NICE leaves British patients.</p> <p>We do not feel that these recommendations provide sound or suitable guidance for the NHS. The only drugs which are approved for use in lupus are hydroxychloroquine and steroids: we rehearsed the problems of steroids and their serious, long term side effects at every meeting. Steroid-sparing drugs are now used in treating many lupus patients, as are other biologics, but these remain ‘off label’ and funding approval for these drugs is a constant problem in most parts of the country. Again, there are patients for whom these drugs are ineffectual and NICE is leaving clinicians and their patients with no other option available in this life-threatening situation.</p>	<p>Comment noted. Following discussions at the 6<sup>th</sup> Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details).</p>

Consultee	Comment [sic]	Response
Lupus UK	<p><b>QUALITY OF LIFE ISSUES</b></p> <p>We would point out that Quality of life issues do not seem to have been adequately considered.</p> <p>We consistently detailed the problems which lupus patients experience, especially the serious, long term side effects of existing treatments, but also other difficulties, particularly with pregnancy. Lupus patients will continue to struggle day to day to live with this unpredictable illness: the small group for whom no other drug is effective will continue to face an extremely limited, uncertain life, dominated by frequent hospital visits and an inability to function properly, never mind experience any 'quality of life' such as normal relationships, bringing up children or being able to have a career. They will be unable to work and will need to draw on a variety of benefits in order to support themselves.</p> <p>Other biological drugs have enabled lupus patients to lead full lives with careers, families and other meaningful activities: as these treatments have been ineffectual for some patients, our hope was that NICE would approve use of Belimumab (even if only on a limited basis, see below) and broaden this benefit to those for whom no other treatment has proved effective.</p>	<p>Comment noted. The Committee's consideration of the nature, signs and symptoms of the condition is described in section 4.2 of the FAD.</p> <p>Following discussions at the 6<sup>th</sup> Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details).</p>

Consultee	Comment [sic]	Response
Lupus UK	<p><b>COSTS TO NHS</b></p> <p>The costs to the NHS of not funding this drug are that consultant clinicians will continue to devote a large proportion of time and attention to these unfortunate patients resulting in more costs to the NHS because of increased number of appointments and fuller clinics which delay access to all patients.</p> <p>Patients will also need to access other NHS services as lupus makes them, alongside other health problems, particularly susceptible to cardiovascular problems. Thus more time is taken up with appointments, investigations and treatment for co-morbidities, many of which are could be reduced or prevented if clinicians were able to offer a more effective treatment.</p> <p>Lupus causes the immune system to be dysfunctional, and many drugs used on patients dampen down their immune system in order to reduce damage to other systems: this leads to increased risk of infection resulting in frequent visits to medical professionals and increased cost of drugs to fight these infections.</p> <p>There may well be costs to the NHS in the long term for the worsened health outcomes of children whose mothers gained weight before pregnancy due to heavy steroid medication (BMJ article).</p> <p>Consultants will be exercised by the inability to prescribe a drug which, they believe, could have been effective in controlling the illness for the worst affected patients.</p> <p>Other costs to government will be payment of benefits because patients are unable to work, care costs for those unable to carry out normal tasks at home, and adapted housing for those who have mobility/access difficulties.</p>	<p>Comment noted. The Committee recognised the importance of the availability of treatment options for people with systemic lupus erythematosus and the need to reduce the side effects of immunosuppressants in current use (see section 4.2 of the FAD). It also concluded that deriving cost data from different sources may have led to some inconsistencies in the estimates and that the company may have underestimated some of the benefits associated with delaying certain types of organ damage (see section 4.25 of the FAD).</p> <p>The NICE reference case in the <a href="#">‘Guide to methods of technology appraisal’ (2013)</a> states that costs and benefits should be calculated from an NHS and PSS perspective in the base case of the economic model (that is, excluding non-health costs such as benefits payments). This is because the appropriate objective of the NICE technology appraisal programme is to offer guidance that represents efficient use of available NHS and PSS resources.</p>
Lupus UK	<p><b>SUGGESTED LIMITED ACCESS TO TREATMENT</b></p> <p>During the Appeal Process LUPUS UK, supported by medical experts, put forward the suggestion that this drug should be allowed to be used by a small number of highly experienced lupus consultants in cases where no other treatment was found to be effective: detailed data would be collected on the Biologics Registry already in operation at Manchester University. This would have provided accurate information of the drug’s appropriateness in a UK population (which was mentioned as a drawback with existing research), as well as giving patients reassurance about the treatment and its effects.</p> <p>This would seem to be a way forward to making an evidence-based decision about whether to fund the drug or not. There has been no attempt by NICE to take this idea forward, despite support from the clinical experts. We find this surprising if not mystifying, given NICE’s role to ‘help medical professionals deliver the best possible care based on the best possible evidence’.</p>	<p>Comment noted. Following discussions at the 6<sup>th</sup> Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details).</p>



Consultee	Comment [sic]	Response
Royal College of Nursing	<p>The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below:</p> <p>i) <b>Has the relevant evidence been taken into account?</b></p> <ul style="list-style-type: none"> <li>• The Appraisal Committee has considered the findings from the 2 phase III clinical trials, BLISS-52 and BLISS-76 where Belimumab was compared against standard care, the submitted data for the licensing of Belimumab in the treatment of autoantibody positive SLE. This data has been further supported by long term efficacy and safety data from the phase II extension study over a six year period where sustained improvement in disease activity was reported with a decline in BILAG scores and flares, accompanied by reductions in steroid usage and autoantibody levels. A revised patient access scheme has been agreed.</li> <li>• It seems that all the available evidence has been considered.</li> </ul>	Comment noted.
Royal College of Nursing	<p>) <b>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</b></p> <ul style="list-style-type: none"> <li>• It was considered that the UK population is most closely represented by the BLISS-76 data in the study although pooled analysis was also reviewed in the appraisal document. It reports that a number of uncertainties remain unanswered although it concludes that there is some evidence of the clinical effectiveness of Belimumab. The cost effectiveness is considered to be above the threshold considered as an acceptable use of NHS resources despite the patient access scheme.</li> <li>• However, we do not believe that due consideration has been demonstrated of the significant impact on quality of life for somebody with severe systemic lupus erythematosus (SLE) which can be fatal. For instance, the uncertainty of living with this condition, reduced life expectancy, the flares, the fatigue, multi-organ involvement, admission to hospital, frequent hospital appointments (often to different hospitals and departments), difficulty walking due to a multi-organ involvement (musculoskeletal, pulmonary, cardiac) and therefore difficulty attending appointments, body image issues (due to skin involvement, hair loss, being cushingoid from corticosteroid use) an inability to work, being an active member of the family all impact on the patient's quality of life. As a condition that primarily affects females of</li> </ul>	<p>Comments noted.</p> <ul style="list-style-type: none"> <li>• The Committee recognised the importance of the availability of treatment options for people with systemic lupus erythematosus and the need to reduce the side effects of immunosuppressants in current use (see section 4.2 of the FAD). It also concluded that deriving cost data from different sources may have led to some inconsistencies in the estimates and that the company may have underestimated some of the benefits associated with delaying certain types of organ damage (see section 4.25 of the FAD).</li> <li>• The NICE reference case in the <a href="#">'Guide to methods of technology appraisal' (2013)</a> states that costs and benefits should be calculated from an NHS and PSS perspective in the base case of the economic model (that is, excluding non-health costs such as benefits payments). This is because the appropriate objective of the NICE technology appraisal programme is to</li> </ul>

Consultee	Comment [sic]	Response
	<p>child bearing age, it can be devastating, making having a family impossible or very difficult and for those who already have young children caring for the family because of the impact of SLE can be an enormous struggle often impacting on other family members. This means the condition often prevents not only the sufferer from SLE being unable to work but also the partner due to having to look after young children. These clinical and quality of life issues often also have a significant psychological impact on the person with SLE. The lives of people with severe SLE are often ruled by hospital appointments. Some patients with severe SLE are on many medications to control their disease including corticosteroids, anti-malarials, immunosuppressants and other medications to directly target the organs effected for example anti-hypertensive. Therefore anything that would reduce the need to take so many medications would greatly improve the person's quality of life. Further, anything that would improve such a seriously debilitating quality of life even for a few years would make a major difference and these patients should not be denied a treatment that would do this. SLE can be more difficult to treat and more debilitating than rheumatoid arthritis (RA), yet there is no third line / biologic options available as there are for RA or other patient groups with long term conditions.</p> <ul style="list-style-type: none"> <li>• We also do not believe it has been demonstrated when considering cost-effectiveness that the cost of social factors such as not working has been fully taken into account. If a person were to be in remission, even if drug induced remission via Belimumab and were able to return to work they would be able to contribute to society in many ways including financially. While there are numerous mentions of the use of corticosteroids in the treatment of SLE and brief mention of side-effects, this does not seem to have been considered in the cost effectiveness review, steroid induced osteoporosis and fracture risk and the cost of screening for and treating this, steroid induced diabetes and the cost of treating this, potential ophthalmology problems, etc should be considered.</li> <li>• If in the small number of patients, 10-15% as stated of those with severe SLE, who would potentially be treated with Belimumab has their quality of life improved as a result, it would offer more than any other option currently available to these patients. Although Rituximab is used in some patients by completing Exceptional Circumstances Funding forms it is not a targeted therapy in the same way as Belimumab is. Rituximab may be given to these patients as per the RA protocol but it is difficult to compare costs as it may be given by various other protocols also. For example, we have seen it</li> </ul>	<p>offer guidance that represents efficient use of available NHS and PSS resources.</p> <ul style="list-style-type: none"> <li>• NICE technology appraisals guidance assesses the clinical and cost effectiveness of health technologies to ensure that all NHS patients have equitable access to the most clinically- and cost-effective treatments that are available. The Appraisal Committee considered advice from NICE on the appropriate approach to making scientific and social value judgements as described in <a href="#">Social value judgements: principles for the development of NICE guidance</a>.</li> </ul>

Consultee	Comment [sic]	Response
	<p>given as 375mg/m also, making cost comparison very difficult.</p> <p>Treating SLE patients with Rituximab is not as straight forward as treating RA patients with Rituximab, therefore it would be inappropriate to use the RA regime as a comparison.</p> <p>The BILAG registry if approved would be used presumably in the same way the biologics registry was and is used for RA patients and should not necessarily be viewed as research per se. The biologics registry for RA has provided very useful information and as far as we are aware did not prevent biologic drugs for RA being approved by NICE.</p>	
<p>Royal College of Nursing</p>	<p><b>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</b></p> <p>Whilst the appraisal consultation document has detailed the trials associated with Belimumab and its evidence base, with its clinical and cost effectiveness, there seems little awareness of the impact to the patient that a drug like this could make. The only licensed drugs for lupus are Prednisolone and Hydroxychloroquine, despite the fact that numerous different types of disease modifying agents are used in clinical practice off licence. Within its licence, the prescribing of Belimumab offers a real possibility to some patients who have failed conventional treatments and remain on higher doses of steroids than is preferred.</p> <p>We therefore do not consider that the provisional recommendation is a sound and suitable basis for guidance to the NHS.</p>	<p>Comment noted. Following discussions at the 6<sup>th</sup> Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details).</p>

Consultee	Comment [sic]	Response
Royal College of Nursing	<ul style="list-style-type: none"> <li>• <b>Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology or have any adverse impact on people with a particular disability or disabilities?</b></li> </ul> <p>There is no doubt that there is an equal opportunities impact for people with musculoskeletal and mucocutaneous complications of lupus who <b>will be disadvantaged</b> if they are not able to access Belimumab. Whilst the Committee have to make a decision on evidence based data, there is no doubt that we are sadly lacking options for treatments for this patient group. In clinical practice, we know that trying to get funding for drugs such as Rituximab for lupus through IFRs using applications to the CCGs/NHS England, are getting increasingly difficult and many hours of clinicians' time is taken up in fighting the patients' corner in order to access these high cost drugs. Sometimes these applications are turned down only on grounds of lack of available evidence.</p>	<p>Comment noted. Following discussions at the 6th Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details). The Committee's consideration of potential equality issues is described in section 4.29 of the FAD.</p>
Royal College of Nursing	<p>It is our considered opinion that the Appraisal Committee <b>strongly reconsiders their decision about Belimumab for sero-positive lupus patients</b> as there is an important place for this treatment to enable clinicians to improve quality of life these patients and reduce risks associated with long term steroid treatments.</p>	<p>Comment noted. Following discussions at the 6<sup>th</sup> Appraisal Committee meeting, belimumab is recommended, with further evidence collection, as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus (see section 1 of the FAD for further details).</p>

**Comments received from clinical experts and patient experts**

None

**Comments received from commentators**

None

**Comments received from members of the public**

None

**GlaxoSmithKline's (GSK) Additional Submission for the Single Technology  
Appraisal (STA) of Belimumab in the Treatment of Active Autoantibody-  
Positive Systemic Lupus Erythematosus (SLE)  
9<sup>th</sup> May 2014**

**Background**

The second draft Appraisal Consultation Document (ACD) (1) for belimumab in the treatment of SLE published in July 2013 states that belimumab is not recommended for use in England and Wales. As detailed in our response to this ACD (2), GSK is disappointed that the Appraisal Committee are unable to recommend belimumab for the treatment of SLE to the NHS. This recommendation is a stark contrast to the Interim Clinical Commissioning Policy Statement for Rituximab published by NHS England in September 2013 (3) where rituximab received positive guidance despite being unlicensed for use in SLE and having limited efficacy and safety data and no cost-effectiveness data to support its use in patients with refractory, highly active SLE disease. As discussed in the ACD, there is currently insufficient evidence to enable a robust comparison of clinical effectiveness between belimumab and rituximab.

We appreciate that much of the concerns raised by the Appraisal Committee in reaching its recommendations resulted from uncertainty arising from the evidence base for belimumab and the assumptions used in the health economic modelling. To address this we are proposing that some of this uncertainty could be addressed by further real world data collection and would inform a future review of the guidance. We propose to utilise an established UK biologics registry for SLE (4) and collect real-life efficacy, safety and quality of life (QoL) data on all patients prescribed belimumab as per UK clinical practice over at least three years. In addition, as the NHS England interim policy for rituximab also stipulates data collection via this registry this would enable a future review of NICE guidance to be able to further consider the relative effectiveness of the two therapeutic approaches.

Detailed in this document are the specific data relevant to the prescribing of belimumab which are already captured in the lupus registry. We would like to work with NICE to ensure that additional data that are informative to the decision making of the Committee are captured. This proposal is supported by leading UK SLE experts whom recognise the clinical value that belimumab offers and would like the opportunity to explore it as a treatment for those patients for whom current therapies are ineffective. Generation of this real world data for belimumab may also be very informative to the wider SLE community i.e. beyond the UK.

In order to ensure adequate numbers of patients are prescribed belimumab and thus provide sufficient real world data to inform future NICE guidance a positive "Access with further evidence generation" recommendation would be required, without this, recruitment of patients would be very slow and problematic. In consideration of the opportunity costs and net benefit to all NHS patients for this recommendation over the short-term (three to five years is proposed) additional cost-effectiveness analyses have been provided which include the latest Patient Access Scheme (PAS), accepted by the Department of Health in October 2012. These analyses demonstrate that allowing access to belimumab while real-life data are being collected would be an efficient use of NHS resources.

In this submission GSK has provided additional information which we believe will support this recommendation for belimumab and we would therefore ask the Committee to

reconsider the draft outcome for belimumab, the first licensed product for SLE for many decades, and allow a small subset of patients, with highly active SLE disease and a significant clinical unmet need, access to this innovative medicine whilst this further data collection is ongoing. To retain a negative recommendation would leave patients with no alternative but to receive treatment with off-label rituximab rather than licensed belimumab, a situation which is inconsistent with the purposes underpinning the EU medicines regulatory regime.

### **1. Collection of real-life efficacy, safety, quality of life (QoL) and cost-effectiveness data**

In the event of a NICE positive recommendation for belimumab with further evidence generation, GSK proposes to utilise the UK British Isles Lupus Assessment Group (BILAG) Registry (4) over a minimum of three years to generate real-life data for belimumab as prescribed in UK clinical practice for the treatment of our proposed subgroup of SLE patients with highly active disease despite current standard of care. BILAG represents a consortium of 10 rheumatology centres across Great Britain who share a specific commitment to the study of SLE. Collaborative work involving this group has led to the development and validation of the original BILAG disease activity instrument (Hay et al.1993 (5)) and the development of the LupusQoL (McElhone et al. 2007 (6)), as well as work with the British Society for Rheumatology (BSR) – Lupus Special Interest Group (BSR-LSIG), the UK Juvenile SLE Group and the Renal Association.

Collection of real-life data will help to confirm some of the assumptions used in the health economic model and address some of the concerns the Committee has raised in the uncertainty in the evidence. It may also identify whether some health benefits have been underestimated in the randomised controlled trials (RCTs) and/or as part of the current assessment of cost-effectiveness. Firstly, in terms of chronic fatigue, it is well documented that the EQ-5D instrument underestimates certain dimensions of health relevant to SLE, such as fatigue and sensory impairment (7) and this instrument was used in the health economic model consistent with the NICE reference case. Monitoring fatigue in clinical practice using a more sensitive instrument specifically designed for SLE, the LupusQoL questionnaire (6), and already included in the UK BILAG registry, may help to demonstrate more accurately the benefits that belimumab can offer on this debilitating symptom. Secondly, based on long-term clinical trial evidence (Phase 2 Open Label Extension (OLE) study (8)) and clinical practice experience with the US real-life OBServe study (9) it has been observed that belimumab allows for the reduction in the use of corticosteroids. More recently, these findings have been replicated in the German OBServe study (10) also. This reduction in steroid dose is expected to be greater than that observed in the RCTs as clinicians would apply their own judgement as to when these dose reductions should occur and are free to see their patients when appropriate for follow-up. In the belimumab RCTs there was more caution in reducing steroid dose in order to protect patients from experiencing disease flares as due to the blinded nature of the trials it was not known if they were in the SoC treatment arm. Both patients and clinicians stress the importance of this steroid sparing benefit, 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 (with associated increased use of healthcare resources) would also be reduced. Any reduction in the clinical dosage of steroids will therefore be a benefit both to patients and the available healthcare resources. If greater benefits with belimumab in

reducing fatigue and steroid use are observed in clinical practice compared with the clinical trials, this will improve the estimate of cost-effectiveness.

The BILAG Registry was setup in 2011 to study the safety and 'real-world' efficacy of novel biological therapies in the treatment of SLE in the UK and there is an approved study protocol to support collection of these data (4) which is ongoing. This is a national registry involving the main lupus specialist centres. Twenty-nine specialist centres around the UK, including renal, rheumatology and paediatric centres, have been approved to participate, and of these 19 centres are actively recruiting patients. To date more than 200 SLE patients have been recruited and have provided data into the registry (11).

The cohort followed comprises SLE patients aged 5 yrs or older who are newly prescribed either:

- Biologics: (including patients treated in the last 12 months) or
- Standard therapies for SLE: e.g. azathioprine, mycophenolate mofetil (MMF) or cyclophosphamide

The study is led by Professor Ian Bruce, Arthritis Research UK Epidemiology Unit and The Kellgren Centre for Rheumatology, University of Manchester. The University of Manchester is the sponsor and the BILAG steering committee has ownership of the data. A steering group and a data monitoring and ethics committee (DMEC) under the auspices of the BILAG oversee the project. The DMEC are independent of the principal investigators and also of any of the pharmaceutical industries involved, and have the power to request interim analyses and advise on the timing and nature of any publications. The DMEC comprises an epidemiologist, a rheumatologist and a statistician.

Funding for the project is from the National Institute for Health Research Greater Manchester Comprehensive Local Research Network (NIHR CLRN) and from the pharmaceutical industry including GSK. GSK will ensure sufficient funding is available to the BILAG registry to collect the required quality assured data to successfully deliver the proposal in time for the NICE review of the guidance. Agreement has been obtained from the BILAG group that they support the use of the BILAG Registry for this purpose?

### **Registry data relevant to belimumab**

#### **Sample Size**

It is anticipated, based on the current recruitment observed for rituximab, that with a NICE 'Access with further evidence generation' recommendation the number of patients prescribed belimumab and included in the registry will be between 9 to 11 per month, amounting to approximately 360 patients after three years. This number of patients should be sufficient to provide useful estimates of relevant parameters of interest; with a longer period of follow-up i.e. 4 or 5 years the patient numbers would be higher thus increasing the precision of the estimates. Given the registry is already including a number of patients being treated with rituximab this would also allow a comparison of outcomes between the two treatments assuming a comparable cohort can be identified.

#### **Data Collection**

Consistent with the data currently collected in the registry for all biologics, the following data, as a minimum, would be collected for belimumab:

### **Efficacy data**

- Clinical response measured by BILAG Index 2004 and SLEDAI – 2K
- Organ damage accrual using the SLICC Damage Index and BILAG Index 2004

### **Safety data**

- Incidence of serious adverse events (SAEs): hospitalisation for infection, malignancy and death, other SAEs

### **Patient Reported Outcomes (PROs)**

- EQ-5D (12)
- SF-36
- LupusQoL (6)

### **Other Data**

- Lifestyle questionnaire (e.g. drinking, smoking, employment status)
- Patient diary (recording hospital admissions, visits to outpatients and medications)
- Clinical serology – autoantibody profiles
- Prior therapy
- Concomitant medications (including steroid use and dose over time)
- Comorbidities
- Laboratory parameters

The protocol and the case record forms for the current biologics study are provided with this submission.

### **Time of Assessments**

#### **Pre-assessment:**

- Prior to new biologic added or re-treatment

#### **Follow-up:**

- Clinical assessment at 3, 6, 12 months; annual assessment thereafter
- Six-monthly questionnaires to patients for 2 years; annual assessment thereafter

### **Auditing the conduct of the study and research governance**

The registry has a number of formal quality control and assurance steps in place to ensure the integrity of the data such as centre staff training and data quality checks.

### **Key outcomes that can address some of the Appraisal Committee's concerns regarding uncertainty in the evidence for belimumab.**

Table 1 below summarises areas of uncertainty highlighted during the belimumab appraisal process that could be addressed from data collected on the registry over the short-term. Analysis of the data is proposed to take place in time for the scheduled review of the NICE guidance for belimumab. Manchester University is currently supporting the analyses of the registry data. Any requested analyses required by NICE would be funded by GSK.



**Table 1: Summary of data collected in the UK BILAG Registry relevant for the assessment of real-life use of belimumab**

<b>Area of uncertainty with belimumab to be addressed</b>	<b>BILAG Registry Data Record</b>	<b>Data available after 3 to 5 Years</b>
Treatment duration/annual withdrawal rate (ACD Sections 4.17 and 4.18)	<ul style="list-style-type: none"> <li>▪ Date belimumab started/ stopped and restarted</li> <li>▪ Reason for discontinuation</li> <li>▪ Dose and IV frequency</li> </ul>	<ul style="list-style-type: none"> <li>▪ Distribution of cumulative treatment duration over 3 to 5 years</li> <li>▪ % patients with each discontinuation reason</li> <li>▪ % patients re-starting belimumab</li> </ul> <p>More comprehensive data on treatment duration would be available for longer follow-up periods</p>
Type of standard of care in England and Wales. Is it representative of SoC seen in the BLISS trials (ACD Section 4.10).	<ul style="list-style-type: none"> <li>▪ All SoC treatments are recorded in the registry.</li> </ul>	<ul style="list-style-type: none"> <li>▪ % Patients receiving the various SoC options.</li> </ul>
Likely benefits of belimumab on the full range of possible manifestations of SLE (ACD Section 4.9).	<ul style="list-style-type: none"> <li>▪ Disease characteristics for each patient will be captured in the registry</li> </ul>	<ul style="list-style-type: none"> <li>▪ Distribution of the % patients with the different SLE manifestations.</li> <li>▪ Investigate improvements in subgroups of patients with different manifestations if sufficient patients allow.</li> </ul>
Steroid sparing benefit (ACD Section 4.11).	<ul style="list-style-type: none"> <li>▪ Date started/stopped for each steroid dose change</li> </ul>	<ul style="list-style-type: none"> <li>▪ Mean dose and mean change in dose over time on belimumab over 3 to 5 years</li> <li>▪ % patients stopping steroids</li> </ul>
Benefits on fatigue/QoL (ACD Section 4.31).	<ul style="list-style-type: none"> <li>• SF-36 (SF-36 vitality score is relevant to fatigue)</li> <li>• LupusQoL score</li> <li>• EQ-5D</li> </ul>	<ul style="list-style-type: none"> <li>▪ Mean score and mean change in score over time for each instrument/domain</li> </ul>
Stopping rule adherence (ACD Section 4.19)	<ul style="list-style-type: none"> <li>▪ SLEDAI score at start and after 6 months</li> </ul>	<ul style="list-style-type: none"> <li>▪ Change in SLEDAI score at 6 months from start of treatment</li> <li>▪ % patients defined as responders (<math>\geq 4</math> point change in SLEDAI) and non-responders after 6 months of treatment</li> <li>▪ For patients not satisfying responder criterion map to date of discontinuation of belimumab to check adherence rate to stopping rule.</li> </ul>
Benefit on disease activity maintained over time (ACD Section 4.20)	<ul style="list-style-type: none"> <li>▪ SLEDAI score</li> </ul>	<ul style="list-style-type: none"> <li>▪ Mean SLEDAI score and mean change in SLEDAI score over 3 to 5 years of follow-up would allow validation of the assumption that the results seen in the RCTs can be extrapolated beyond one year and to the prescribing of belimumab</li> </ul>

Area of uncertainty with belimumab to be addressed	BILAG Registry Data Record	Data available after 3 to 5 Years
		<p>in clinical practice.</p> <ul style="list-style-type: none"> <li>▪ The impact on SLEDAI score after discontinuation of belimumab can also be observed.</li> <li>▪ Compare with scores recorded for an appropriate comparator cohort.</li> </ul>
Development of organ damage accrual over time	<ul style="list-style-type: none"> <li>▪ SLICC score</li> <li>▪ BILAG score</li> </ul>	<ul style="list-style-type: none"> <li>▪ Prevalence and incidence of each type of organ damage over 3 to 5 years.</li> <li>▪ Mean score and mean change in score over time on belimumab.</li> <li>▪ Compare with damage recorded for appropriate comparator cohort and published data.</li> </ul> <p>A longer follow-up period (5+ years) would provide more informative data.</p>
Safety profile and possibility of rebound phenomenon	<ul style="list-style-type: none"> <li>▪ Serious adverse events (death, hospitalisation for infection, malignancy, other SAEs)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Incidence of SAEs while on belimumab</li> <li>▪ Incidence of SAEs experienced on stopping belimumab</li> <li>▪ Compare with rate recorded for comparator cohort and published data</li> </ul>

**Further considerations for a positive recommendation supported by further evidence generation**

**Likelihood that the research will report successfully**

Given that the UK BILAG Registry is already successfully recruiting patients on biologics, the data currently being collected are relevant to belimumab, and that the drug is likely to be prescribed in a limited number of specialist centres rather than primary care, NICE should have confidence that this particular research to support belimumab will be conducted to an appropriate standard and will report successfully at the required time. As detailed in the table above, after three to five years of follow-up, information on patient numbers, duration of treatment, SLEDAI disease activity score, adherence to the proposed stopping rule, development of organ damage, the requirement and doses of steroid and patient QoL can be obtained. Outcomes such as long-term survival could not be addressed over the proposed initial follow-up period, however there is respected published evidence to show that maintained control of disease activity in SLE is related to improved survival (13;14). This relationship was also endorsed by the lupus experts present at the previous appraisal committee meetings. There is also considerable long-term evidence from the phase 2 open-label uncontrolled extension (OLE) study (over at least seven years) demonstrating that control of disease activity is maintained with belimumab in SLE patients with high disease activity (8;15). Therefore it does not seem unreasonable to believe that belimumab should improve survival in SLE patients with highly active disease.

**Future evidence likely to be available.**

In addition to the real-life observational data collected via the UK registry, further data to support belimumab will be available at the time NICE decide to review the guidance. The

Phase 3 RCT for the subcutaneous formulation will have reported (expected 2015) and there will be available interim data from the long-term real-life multinational GSK SLE registry study (SABLE study). Although the UK is not participating in the SABLE study, many other European countries with similar standard of care (SoC) are taking part. Although it is primarily a safety study, data on efficacy, QoL, and steroid use will also be collected. In addition, the ten-year Phase 2 OLE study and the Phase 3 OLE studies will have completed in 2016-7 which will provide further data to support long-term efficacy and safety of this biologic. One of the Phase 3 OLE studies will also include an analysis of organ damage accrual (SLICC Damage Index (SDI)) over five to six years of belimumab exposure. There will also be longer term follow-up data from observational studies of belimumab effectiveness in clinical practice currently ongoing in the US, Germany and Spain. A full list of ongoing belimumab clinical trials is provided in Appendix 1, along with their expected year of reporting where available.

### **Irrecoverable costs**

There should not be any significant irrecoverable costs from providing provisional access to belimumab during the real world data collection period. No new service infrastructure needs to be put in place to support belimumab as the same service that is already available to manage these patients with rituximab and other immunosuppressants in specialist centres will be used. The administration cost of treating patients with belimumab has been included in the cost-effectiveness estimates. In addition, there will be no cost to the NHS to support the evidence generation as this will be funded by GSK and other organisations.

### **Implications of any future change in the NICE guidance**

At the time of the future review of the guidance, should as a worse case, the decision be taken to reverse the recommendation or introduce further restrictions on the population for whom belimumab would be recommended, an appropriate strategy between NICE and clinicians regarding the management of current or future patients would be agreed. GSK confirms that it would continue to offer belimumab at the discounted PAS price for those patients remaining on belimumab until their respective clinicians consider it an appropriate time for discontinuation. The opinion of a number of lupus experts we consulted during this appraisal is that most of their patients would only require treatment with belimumab for a maximum of five to six years and only a very small percentage would require the medicine for significantly longer periods. In addition, those patients that do need to stay on belimumab for long periods of time are likely to be those with very severe disease who are demonstrating significant benefits with belimumab, and hence are likely to be more cost-effective to treat. The stipulation of a stopping rule in the final guidance would help to ensure that only patients who demonstrate a clinically important benefit from belimumab will continue on the medicine beyond six months.

## **2. Comparison with Rituximab**

On 10 September 2013, NHS England published an Interim Clinical Commissioning Policy Statement for Rituximab (3), which although recognises the limitations in the available evidence for rituximab in the treatment of SLE, recommends use of the product, off-label, for the following defined patients:

1. Diagnosis of SLE (fulfilling either ACR or SLICC criteria)  
AND;

2. Active disease (defined as at least one BILAG A score and/or 2B scores, or a SLEDAI-2K score >6) AND;
3. Failure to respond or having adverse events to, two or more standard immunosuppressive therapies (one of which must be either mycophenolate mofetil or cyclophosphamide, unless contraindicated) in combination with corticosteroids. A failed response is defined as being unable to achieve sustained disease control and still having evidence of at least one BILAG A or at least 2 BILAG B scores (or requiring unacceptably high levels of long term oral corticosteroids to maintain a lower disease activity state).

All patients who meet the above criteria of refractory disease activity sufficient to justify the use of rituximab must be managed at, or in collaboration with, a centre commissioned to provide specialised services that has expertise in the assessment and management of SLE. The policy also stipulates that all patients prescribed rituximab should be included on the UK BILAG Registry. Since publication of this interim policy the average monthly recruitment of patients prescribed rituximab into the registry over the last 8 months (since July 2013) has been 9 patients per month (11). Prior to this publication, recruitment to the registry was considerably lower with 1 to 2 patients recruited per month as prescriptions of rituximab for SLE had to be agreed through individual funding requests (IFRs).

As stated previously, GSK finds it an inappropriate situation that rituximab, unlicensed for SLE and with unproven efficacy and effectiveness in this indication, is funded by the NHS, while belimumab, which does have a substantial evidence base to support its use in SLE, a defined risk management plan agreed with the MHRA, and which has been offered with a significant PAS, currently is not recommended for use in a similar patient population.

In our previous submissions for this appraisal standard of care (SoC) has always been considered the most relevant comparator for belimumab, as prior to the NHS England guidance, rituximab was only prescribed in a small number of patients. NHS England's support for the prescribing of rituximab in the above patient population (which is consistent with our proposed UK target population for belimumab) elevates rituximab as a key comparator in this appraisal. However there is currently no direct or indirect RCT comparative efficacy data for belimumab and rituximab in SLE due to significant trial design differences, different outcomes measured and the fact that rituximab failed to reach its primary end point in both its Phase 3 trials; this means that a robust comparison of clinical and cost effectiveness is not feasible, as outlined in the ACD.

In order to identify whether there was any additional relevant published data from observational studies to support rituximab's use in SLE patients since our previous submission a new literature review was conducted. A key paper identified was a recent systematic review and meta-analysis assessing the efficacy of rituximab in SLE reported by Duxbury *et. al.* (16). This robust systematic review summarises all the key studies they found, which comprise mainly small numbers of patients (most ranging from 10 to 49) receiving rituximab. The largest study the authors identified is the French AutoImmunity and Rituximab (AIR) Registry (17) which reported 136 patients on rituximab, 40 of whom had lupus nephritis. The majority of studies had a follow-up duration of a year or less and so there is no long term efficacy or safety data to support the use of rituximab in SLE (unlike belimumab which has published efficacy and safety data at seven years (8;15)). In addition, the cohorts studied were very heterogeneous between studies and had a broad mix of

patients including those with lupus nephritis and CNS lupus, which are outside of our current licence for belimumab (16). The authors of this systematic review state that the data generated from the observational studies, although possibly overestimating rituximab efficacy because of publication bias, indicate that rituximab may exhibit a degree of efficacy in a subset of patients (16). The pooled global response rates in the open trials were similar whether BILAG or SLEDAI were used with 95% CI's ranging from 38.8% to 56.8% in BILAG and 32.4% to 78.1% in SLEDAI. It is of note that the 29.6% (complete response 12.4% + partial response 17.2%) response rate observed with BILAG in the EXPLORER RCT(18) falls below the lower range of uncontrolled studies which is also true for the control arms at 28.4% (complete response 15.9% + partial response 12.5%) (16). Hence, treatment of a very selective cohort of patients in these small observational studies is likely to show greater efficacy than a broader population recruited in RCTs. There is no reason to suggest similar results would not also be seen with belimumab. One further study on rituximab use in SLE (Witt *et al*, 2013 (19)) has been published since the Duxbury *et. al.* review was conducted in 2012. This study is based on the German Registry of Autoimmune Diseases (GRAID) which included patients with off-label treatment of rituximab (19). The SLE cohort comprised 85 patients with a mean follow-up of 9.6 months and 37% had lupus nephritis. Data were collected retrospectively. Complete, partial or no response was based on the investigators' clinical judgement and was reported in 47%, 34%, and 19% of patients, respectively. Efficacy was further evaluated by comparison of mean SELENA-SLEDAI (SS) scores at baseline (12.2) and after last infusion (3.3). The authors conclude that the study demonstrates rituximab is efficacious in SLE but also acknowledge the inherent biases in this type of study.

Therefore after consideration of the currently published observational data for rituximab it is still not possible to draw any conclusions as to its true level of effectiveness in SLE and to the relative efficacy or cost effectiveness compared with belimumab. It still remains that the evidence base for belimumab is significantly stronger than that of rituximab. Belimumab has demonstrated clinically relevant benefits for patients in its two Phase 3 RCTs and this is supported by seven years of efficacy data from the Phase 2 OLE study, whereas there is a lack of robust evidence to support the efficacy of rituximab in SLE. Therefore GSK believe that we are taking a conservative approach in assuming belimumab is at least as effective as rituximab in SLE. More importantly, there does not seem to be any evidence to suggest that patients will be at a disadvantage with respect to the management of their condition by being prescribed belimumab rather than rituximab.

### **3. Revised Health Economic Analysis**

Detailed below in Table 2 are the summary results from the additional cost-effectiveness analyses considered most relevant to support a provisional positive recommendation for belimumab in the context of 'Access with further evidence generation'. The detailed methodology and complete results are presented in Appendices 2 and 3. Analyses including a maximum belimumab treatment period of three and five years were considered to provide a base case range to enable a comparison of results depending on the treatment duration assumed. Cost-effectiveness for four years of belimumab treatment was summarised as a scenario analysis only as it sits within this base case range.

Except for the restriction placed on the belimumab treatment duration, all other assumptions used in the model are consistent with those detailed in the most recent ACD and which the Appraisal Committee considered the most plausible based on current available evidence.

## Base Case

The base case for these analyses comprised:

- A subgroup of the licensed population (UK Target Population) of SLE patients with high disease activity (low complement and anti-dsDNA and a SELENA-SLEDAI (SS) score of  $\geq 10$ ).
- The comparator was standard of care treatments.
- A treatment continuation rule at week 24 based on demonstrating an improvement in disease activity, defined as a  $\geq 4$  point reduction in SELENA-SLEDAI (SS).
- A maximum treatment duration with belimumab ranging between 3 and 5 years
- A lifetime model horizon.
- A natural discontinuation rate of 8% during Year 1 and 11.7% for year 2 onwards.
- The assumption that once patients stop treatment with belimumab their SS score reverts to the average score seen with SoC. A belimumab responder patient who has not withdrawn early due to reasons related to natural discontinuation, and who successfully completes three years (or five years) of belimumab treatment, is switched to continue to receive standard of care (SoC) treatments only from the start of the fourth year (or sixth year as appropriate). This directly affects SLEDAI score in the belimumab arm of the model as it applies an average SoC disease activity score for each belimumab patient from the end of Year 3 (or Year 5) 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. However it is important to note that as the Adjusted Mean SLEDAI (AMS) is calculated and included in the natural history of disease and mortality models, there will be some carry-over benefit on organ damage and survival of these higher SS scores during belimumab treatment, but this beneficial effect diminishes over time as demonstrated in Figure 2.2, Appendix 2 and Figure 3.2, Appendix 3 for the three year and five year analyses, respectively.

## Scenario Analyses:

An alternative maximum belimumab treatment duration of four years assumption and the impact of excluding the treatment continuation rule from the base case analyses of maximum of three and five years belimumab treatment were considered the key scenario analyses to support this additional submission. However, other scenarios investigated were the incorporation of the more stringent stopping rule at 24 weeks ( $\geq 6$  point reduction in SS score), and, due to the concerns the Appraisal Committee have raised related to the SoC SLEDAI score that belimumab non-responders assume once they discontinue belimumab at 24 weeks, an alternative assumption on SLEDAI score for non-responders have also been explored.

## Summary of Cost-Effectiveness Results

All ICERs presented in this additional submission incorporate the revised PAS.

### Base case Analyses

From the maximum three year belimumab treatment duration analysis the incremental costs for belimumab treated patients compared to SoC alone are **XXXXXX** with 0.59 added life years, or 0.45 added QALYs, all discounted at 3.5%, resulting in an ICER of **XXXXXX** per QALY gained (Table A2.9, Appendix 2). Similarly, when the maximum five year belimumab treatment duration was assumed, the incremental costs are **XXXXXX** with 0.73 added life

years, or 0.54 added QALYs, discounted at 3.5%, yielding an ICER of ██████████ per QALY gained (Table A3.5, Appendix 3).

These base case ICERs are lower than those previously submitted to NICE. The reason for this is that these ICERs are mainly driven by the lower total belimumab acquisition costs over the limited treatment duration and because, even over the relatively short period of treatment, there is still an important benefit on long-term outcomes (organ damage and mortality) by reducing cumulative disease activity and the cumulative dose of steroids in the shorter-term.

### Scenario Analyses

Only the key scenario analyses are considered here, all other scenario results are presented in Table A2.13 in Appendix 2 and Table A3.9 in Appendix 3. From the analysis assuming a maximum belimumab treatment duration of four years, an ICER of ██████████ per QALY gained was obtained. When the treatment continuation rule was excluded from the health economic modelling the ICERs for three and five year maximum belimumab treatment durations were ██████████ and ██████████ per QALY respectively.

**Table 2. Summary of scenario results including the PAS - Target population**

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Base Case lower range: 3 year belimumab treatment duration	Time horizon = lifetime; 3 year belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model; annual withdrawal rate of 8% Year 1 and 11.7% for Year 2 onwards; health effects discount rate of 3.5%	██████	0.59	0.45	██████
Base case upper range: 5 year belimumab treatment duration	Time horizon = lifetime; 5 year belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model;	██████	0.73	0.54	██████
4 year belimumab treatment duration	Time horizon = lifetime; 4 year belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; adjusted natural history model;	██████	0.69	0.52	██████
Treatment continuation criterion excluded with maximum of 3 years of belimumab	As base case lower range but with treatment continuation criterion at 24 weeks excluded	██████	0.58	0.44	██████
Treatment continuation criterion excluded with maximum of 5 years of belimumab	As base case upper range but with the treatment continuation criterion at 24 weeks excluded	██████	0.62	0.52	██████

These cost-effectiveness analyses demonstrate that over the duration of time that real-life data could be collected via the UK BILAG registry the prescribing of belimumab would be an efficient use of NHS resources. It is also important to note that these estimates will underestimate the true level of cost-effectiveness as inherent in the modelling is that patients who discontinue belimumab due to lack of efficacy return to standard of care and the associated costs with these cheaper treatments. In reality these patients would be given rituximab or may be hospitalised for intravenous immunoglobulin (IVIG) therapy as they will require treatment additional to standard of care in order to manage their highly active disease. These additional treatment costs have not been accounted for in the modelling.

Furthermore, even with the exclusion of a stopping rule at 6 months the prescribing of belimumab over three or five years can still be considered to demonstrate an acceptable level of cost-effectiveness. This should provide some reassurance to the Committee that if this rule were not rigidly adhered to it would not have a significant negative impact on the estimated cost-effectiveness. In addition, the data collected in the registry would allow the monitoring of adherence to this stopping rule.

All these analyses have taken an NHS perspective consistent with the NICE reference case at the start of the appraisal. Were we to be submitting in the future and include a societal perspective, these ICERs would likely be even lower, as indirect societal costs in SLE are high (20;21) and analyses including a societal perspective in other countries such as Italy and Portugal (22;23) have shown this to be the case. The ongoing consultation around the incorporation of value based assessment in to the current NICE methodology makes proposals for recommendations of medicines up to thresholds of £50K/QALY for medicines that either treat a more severe condition (burden of disease) or disease which is associated with wider societal impacts. While we appreciate the details still need to be finalised, we believe that belimumab has demonstrated value in both the management of a severe disease and to the wider societal impact of SLE.

### **Budget Impact**

With an approximate 360 SLE patients expected to have been prescribed belimumab by three years and approximately 480 by five years (assuming a slower rate of prescribing after three years (5 patients per month) due to the availability of other treatment options, such as newer biologics), most of whom would, in the absence of belimumab, likely to be prescribed rituximab or be hospitalised for intravenous immunoglobulin therapy, the budget impact of a provisional positive recommendation is limited. For example, after three years the total estimated prescribing cost to the NHS for belimumab with the PAS is **XXXXXXXXXX**. For simplicity this calculation does not account for patient withdrawal or for inclusion of a stopping rule after six months, so will over estimate the costs. For rituximab the comparative cost has been estimated as £3,013,632 (assuming only two doses per patient over three years @ £4,185.60 per dose including administration costs (see Table 3)). This is significantly more conservative than assuming the annual dosing schedule of four doses per year used in the EXPLORER trial (18). These estimated drug acquisition costs show an incremental cost for the prescribing of belimumab of **XXXXXXXXXX** over three years. Similarly, after five years the estimated cost for 480 patients treated with belimumab is **XXXXXXXXXX** and for rituximab, assuming all patients require three doses within this period, which does not seem an unreasonable assumption given these patients have severe disease and are likely to experience repeat flares, is £6,027,264. This gives an estimated incremental cost of prescribing belimumab over five years as **XXXXXXXXXX**, which translates into an annual



incremental cost of [REDACTED] per patient. However these fairly simplistic budget impact analyses will over inflate the incremental costs of prescribing belimumab if it is not infused every month or if rituximab is dosed more frequently than has been assumed here (based on very short-term observational studies and clinician anecdotal reporting and what is stated in the NHS England guidance).

**Table 3. Summary of Estimated Budget Impact.**

	<b>Belimumab</b>	<b>Rituximab</b>	<b>Cost Difference (belimumab – rituximab)</b>
<b>Dose</b>	10 mg/kg infusion (given over 1 hour) on days 0, 14 and 28, and at 4-week intervals thereafter	1,000mg as an infusion (given over 4-5 hours) on days 1 and 15	-
<b>Price</b>	120mg vial - [REDACTED] 400mg vial - [REDACTED]	10mg/ml soln in vial, 2 x 10ml=£349.25; 50ml=£873.15 (24)	-
<b>Drug cost per patient with average 65.4 kg weight</b>	Year 1 annual cost = [REDACTED] Year 2+ annual cost = [REDACTED]	£3,492.6/annum assuming one dose only £6985.20/annum assuming two doses	-
<b>Administration cost</b>	£154 per infusion (14 in Year 1 and 13 in Year 2 onwards) £2,156 (Year 1) £2,002 (Year 2+)	£693 (2 X £346.50 per 5.5hr infusion) for one dose of £1000mg £1386 for 2 doses	-
<b>Total drug costs</b>	[REDACTED] For simplicity assume: £6627 per year (i.e. £6961 x 0.33 and £6464 x 0.67) to cover over 3 years treatment, i.e.£552/month. Same monthly cost used for 5-year duration although this will slightly over estimate the monthly cost	£4,185.60 per year for one dose	-
Cumulative cost by end of Year 1 (assumes 10 pts per month recruited) = 120 pts	[REDACTED]	£502,272 (assumes 1 dose per patient)	[REDACTED]
Cumulative cost by end of Year 2 (assumes 10 pts per month recruited) = 240 pts	[REDACTED]	1,004,544 (assumes 1 dose per patient)	[REDACTED]
Cumulative cost by end of Year 3 (assumes 10 pts per month recruited) = 360 pts	[REDACTED]	£3,013,632 (assumes 2 doses per patient)	[REDACTED]
Cumulative cost by end of Year 4 (assumes 5 pts per month recruited) = 420 pts	[REDACTED]	3,515,904 (assumes 2 doses per patient)	[REDACTED]
Cumulative cost by end of Year 5 (assumes 5 pts per month recruited) = 480 pts	[REDACTED]	6,027,264 (assumes 3 doses per patient)	[REDACTED]

## Conclusion

Belimumab is an innovative medicine for a debilitating disease where there is a clear unmet need– it was specifically developed to target an underlying pathology of SLE and has demonstrated efficacy where several other biologics have failed. Our proposed target population is small, easily identifiable and is limited to those with the most severe/refractory disease.

Recognising the Appraisal Committee's concerns regarding uncertainty in the evidence base we are proposing that the Committee consider a positive recommendation whilst evidence generation is ongoing. This is a feasible proposal; the registry is already successfully implemented and is supported by leading SLE experts; it will have clinical controls in place to ensure the quality, consistency and independency of data; sufficient numbers of patients should be recruited and the outcome measures are validated and will provide evidence to address some of the uncertainty and help inform a future decision. In addition, over the proposed evidence generation period the cost effectiveness analyses comparing belimumab with SoC show that belimumab should be considered an efficient use of NHS resources. Moreover, GSK are sharing the cost by providing belimumab at a discounted price and by contributing to the funding of the registry, which includes the funding of the additional analyses of the data.

We would therefore ask the Appraisal Committee to reconsider the draft negative guidance taking into account GSK's proposal and allow this subgroup of SLE patients with uncontrolled disease access to another licensed treatment option with proven efficacy.

## Reference List

- (1) NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. **Appraisal consultation document - Belimumab for treating active autoantibody-positive systemic lupus erythematosus.** <http://guidance.nice.org.uk/TA/Wave25/12>
- (2) GlaxoSmithKline. **Response to Appraisal Consultation Document (ACD) Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (SLE).** 13-8-2013.
- (3) NHS England. **Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults September 2013 A13/PS** [www.england.nhs.uk/wp-content/uploads/2013/09/a13-psa.pdf](http://www.england.nhs.uk/wp-content/uploads/2013/09/a13-psa.pdf). 2013.
- (4) Bruce IN, On behalf of the British Isles Lupus Assessment Group. **BILAG Biologics Prospective Cohort: The Use of Novel Biological Therapies in the Treatment of Systemic Lupus Erythematosus (SLE).** Version 1.4. 7-3-2011.
- (5) Hay EM, Bacon PA, Gordon C, Isenberg DA, Maddison P, Snaith ML et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. *Q J Med* 1993; 86(7):447-458.
- (6) McElhone K, Abbott J, Shelmerdine J, Bruce IN, Ahmad Y, Gordon C et al. Development and validation of a disease-specific health-related quality of life measure, the LupusQoL, for adults with systemic lupus erythematosus. *Arthritis Rheum.* 2007; 57[6], 972-979.
- (7) Wailoo A, Davis S, Tosh J. The incorporation of health benefits in cost utility analysis using the EQ-5D. REPORT BY THE DECISION SUPPORT UNIT 15-11-2010.
- (8) Ginzler EM, Wallace DJ, Merrill JT, Furie RA, Stohl W, Chatham WW et al. Disease Control and Safety of Belimumab Plus Standard Therapy Over 7 Years in Patients with Systemic Lupus Erythematosus. *J Rheumatol.* 2014; 41(2):300-309.
- (9) Collins C, Narayan S, Dall'Era M, Dennis G, Oglesby A, Mcguire et al. Outcomes Associated with Belimumab in Patients with Systemic Lupus Erythematosus in Clinical Practice Settings: Results from an Observational Cohort Study in the United States. *ACR.* 2012.
- (10) Schwarting A, Carnarius H, Moore-Ramdin L, Koscielny V. Outcomes in patients with systemic lupus erythematosus (SLE) who were treated with Belimumab: Results of an observational study in Germany (OBSErve). *41st Conference of the German Society of Rheumatology.* 2013.
- (11) Personal Communication from UK BILAG Registry Clinical Research Assistant. 2014.
- (12) The EuroQoL Group. EuroQoL--a new facility for the measurement of health-related quality of life. The EuroQoL Group", *Health Policy.* 1990; 16:(3) 199-208.
- (13) Ibanez D, Gladman DD, Urowitz MB. Adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K is a predictor of outcome in SLE. *J Rheumatol* 2005; 32(5):824-827.
- (14) Lopez R, Davidson J, Beeby M, Egger P, Isenberg D. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort.

*Rheumatology*; 2012; 51: 491-498.

- (15) Merrill JT. Long-Term Safety Profile of Belimumab Plus Standard Therapy in Patients With Systemic Lupus Erythematosus. *Arthritis and Rheum* 64[10], 3364-3373. 2012.
- (16) Duxbury B, Combesure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. *Lupus* 2013; 22(14):1489-1503.
- (17) Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B et al. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French Autoimmunity and Rituximab registry. *Arthritis Rheum* 2010; 62(8):2458-2466.
- (18) Merrill J, Buyon J, Furie R, Latinis K, Gordon C, Hsieh HJ et al. Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). *Lupus* 2011; 20(7):709-716.
- (19) Witt M, Grunke M, Proft Fea, on behalf of the German Registry of Autoimmune Diseases (GRAID) Investigators. Clinical outcomes and safety of rituximab treatment for patients with systemic lupus erythematosus (SLE) - results from a nationwide cohort in Germany (GRAID). *Lupus*. 2013; 22: 1142-1149
- (20) Sutcliffe N, Clarke AE, Taylor R, Frost C, Isenberg DA. Total costs and predictors of costs in patients with systemic lupus erythematosus. *Rheumatology*. 2001; 40(1):37-47.
- (21) Jönssen A. Direct and indirect costs for patients with systemic lupus erythematosus in national cohorts in Sweden. *Arthritis Rheum*. 2013; 65, S752.
- (22) Gouveia M, Borges M, Augusto Mea. Cost-Effectiveness and Cost-Utility Analysis of belimumab for the treatment of Patients with Systemic Lupus Erythematosus. *Value Health*. 2013;16: A384.
- (23) Turchetti G, Pierotti F, Palla I et al. Assessment of the economic impact of belimumab for the treatment of systemic lupus erythematosus in the Italian Setting: a cost-effectiveness analysis. *Value Health*. 2013; 16: A564.
- (24) Monthly Index of Medical Specialities (MIMS). Haymarket Medical Media; 2011.

## Appendix 1

### Ongoing Belimumab Clinical Trials in Systemic Lupus Erythematosus

- BEL112233: A Multi-Center, Continuation Trial of Belimumab, a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE) who Completed the Phase 3 Protocol HGS1006-C1056 in the United States. NCT00724867  
Reporting: 2016, Interim analysis planned 2014
- BEL112234: A Multi-Center, Continuation Trial of Belimumab, a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE) who Completed the Phase 3 Protocol HGS1006-C1056 or HGS1006-C1057. NCT00712933  
Reporting 2016, Interim analysis planned 2014
- LBSL99: A Multi-Center, Open-Label, Continuation Trial of LymphoStat-B™ Antibody (Monoclonal Anti-BLyS Antibody) in Subjects with Systemic Lupus Erythematosus (SLE) who Completed the Phase 2 Protocol LBSL02. NCT00583362  
Reporting 2016-17, Interim analyses have been undertaken and published(8;15)
- BASE: Belimumab Assessment of Safety in SLE. A Randomized, Double-Blind, Placebo-Controlled 52 Week Study to Assess Adverse Events of Special Interest in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Receiving Belimumab. NCT01705977.  
Reporting: 2019
- (BLISS-SC) A Study of Belimumab Administered Subcutaneously in Subjects with Systemic Lupus Erythematosus (SLE). NCT01484496.  
Reporting: 2015
- BEL115470: A Phase 4, Multi-Center, Randomized, Open-Label Study to Evaluate the Effect of BENLYSTA™ (belimumab; HGS1006) on Vaccine Responses in Subjects with Systemic Lupus Erythematosus (SLE). NCT01597492  
Reporting 2015-16
- BEL113750: GSK1550188. A 52 Week Study of Belimumab versus Placebo in the Treatment of Subjects with SLE Located in Northeast Asia. NCT01345253  
Reporting 2016
- EMBRACE BEL115471: Efficacy and Safety of Belimumab in Lupus Subjects of Black Race. NCT01632241.  
Reporting TBC
- SABLE SLE Registry: A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive SLE Treated with or without BENLYSTA® (belimumab). NCT01729455.  
Reporting TBC

- (PLUTO: Pediatric Lupus Trial Of Belimumab) BEL114055: GSK1550188. A Multi-Center, Randomized Parallel group, Placebo-Controlled Double-Blind Trial to Evaluate the Safety, Efficacy, and Pharmacokinetics of Belimumab, A Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE). NCT01649765.  
Reporting TBC

BENLYSTA™(belimumab) Pregnancy Registry. NCT01532310.  
Reporting TBC

- BEL114333: A Multicenter, Continuation Study of Belimumab in Subjects with SLE who Completed the Phase III Study BEL113750 in Northeast Asia. NCT01597622.  
Reporting TBC
- (BLISS-LN) Belimumab Study in Patients with Biopsy Proven Lupus Nephritis GSK Study BEL114054 (HGS Study C1121). NCT01639339.  
Reporting TBC

NOTE: All reporting dates are predictions and are subject to change

## **Appendix 2**

### **Summary of cost-effectiveness assuming a maximum three year treatment duration**

Provided below are the results from the health economic analysis for our proposed target (high disease activity) SLE subgroup incorporating a treatment continuation criterion (SS score decrease of  $\geq 4$ ) after six months treatment and applying a treatment duration with belimumab of three years (lower range base case) for the situation where the Appraisal Committee consider a positive recommendation “with further evidence generation” with an anticipated review of the real-life efficacy, safety and cost-effectiveness evidence at the time of guidance review.

All ICERs quoted in this appendix incorporate the drug acquisition cost discount detailed in our latest proposed patient access scheme which was approved by the DoH in October 2012.

#### **Methodology**

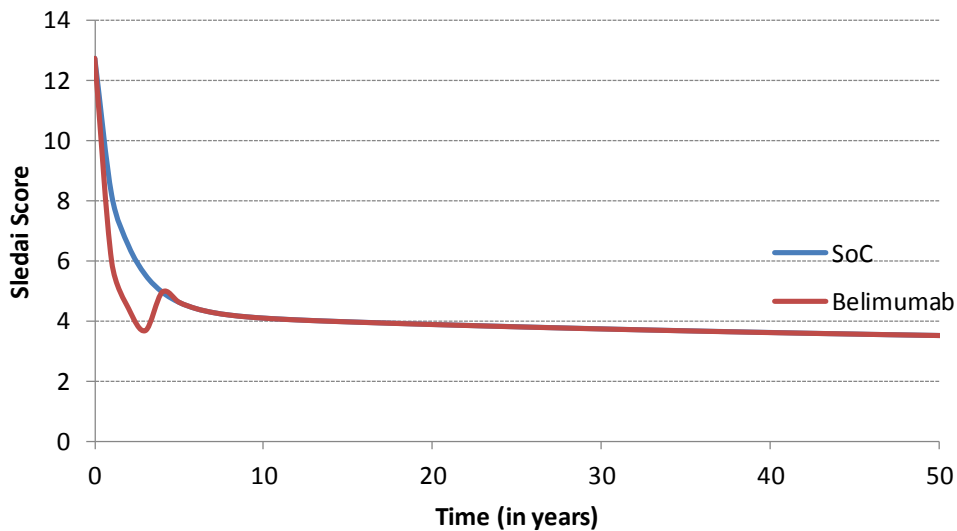
All analyses described in this appendix relate to the health economic model supplied to NICE with our original submission in April 2011. The key assumptions described for our original base case still apply to the analyses presented in this document with two key differences. Firstly, a maximum treatment duration of three to five years for belimumab is now applied to provide a revised base case range; the original base case had allowed up to a lifetime duration with belimumab treatment. However with our restricted belimumab treatment durations the model still provides estimates of cost-effectiveness over a lifetime horizon. This shorten maximum belimumab treatment duration range is assumed in the model to identify the estimated level of cost-effectiveness of belimumab during the proposed period that real-life data could be collected. Secondly, in the absence of published longer term data on withdrawal rate for patients receiving belimumab for our target population, the Appraisal Committee considered the ERG’s suggested annual withdrawal rate of 11.7% to be the most appropriate to use in the modelling. In the modelling for our base case range in these additional analyses we have used a withdrawal rate of 8% as observed in the pooled BLISS studies for Year 1 and a rate of 11.7% thereafter.

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 in this appendix is an explanation of the impact in the model of the incorporation of a maximum belimumab treatment duration of three years (lower base case range). This explanation is also relevant for the cost-effectiveness analyses presented in Appendix 3 for a belimumab treatment duration of five years (upper base case range).

A patient who has not withdrawn early due to reasons related to natural discontinuation, and who successfully completes three years of belimumab treatment, is switched to continue to receive standard of care (SoC) treatments only from the start of the fourth 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 3 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.

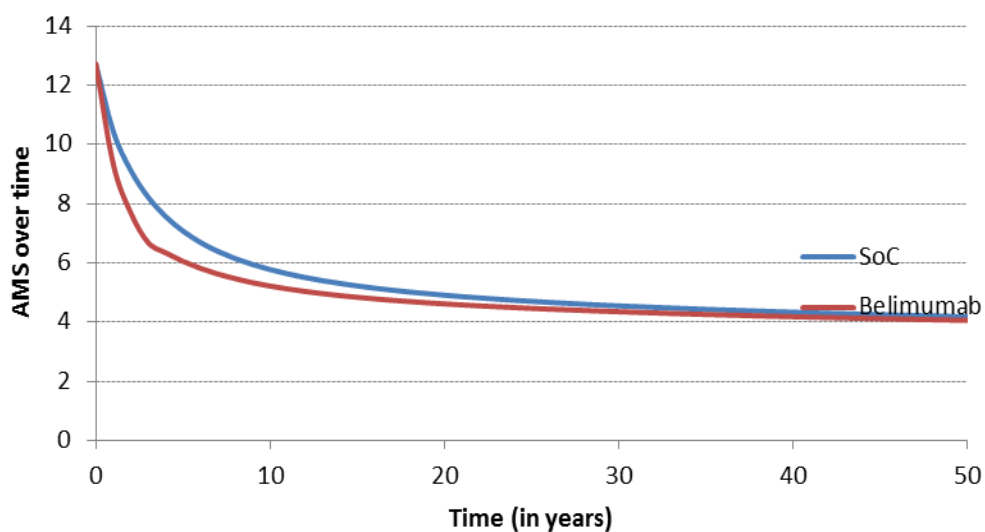
The adjusted (average) SLEDAI score (AMS) for 50,000 simulated patients is shown in Figure A2.1 over time for those patients who remain alive. It is clear from the graph that patients who are treated with belimumab (in addition to SoC) have a larger reduction in SS score than patients who are treated with SoC alone over the first three years.

**Figure A2.1. 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 (AMS) score over time (Figure A2.2). As this AMS is included in the natural history of disease model for organ damage and the mortality model there will be some carry-over benefit on organ damage and survival of these higher SS scores during belimumab treatment, but this beneficial effect diminishes over time

**Figure A2.2. 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 three years of belimumab treatment will lead to a decreased steroid dose over this time period and a decreased risk for organ damage. The 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
<b>Covariates</b>												
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

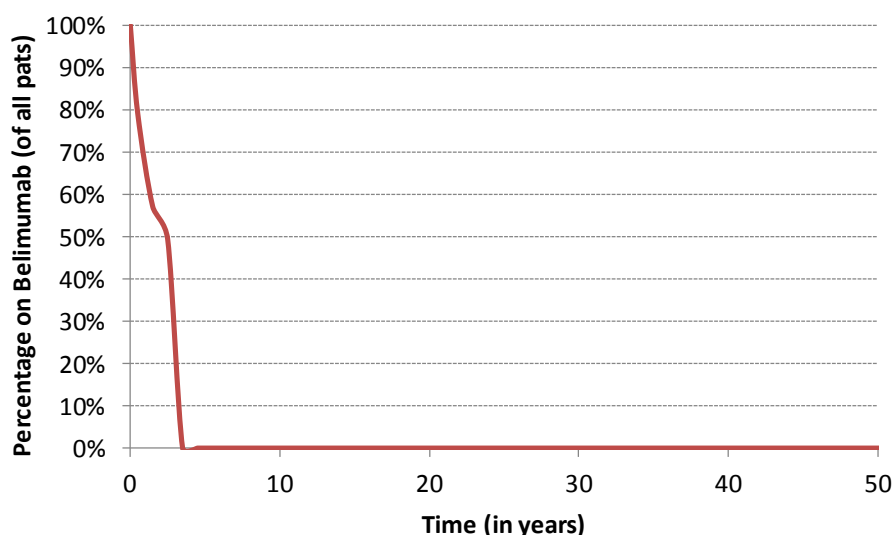
CV = cardiovascular, MSK = musculoskeletal, NP = neuropsychiatric, PV = peripheral vascular, GI = gastrointestinal, GF = Gonadal Failure, Loglog = loglogistic, Exp = exponential, AAP = Anticardiolipid antibodies, LAP = Lupus anticoagulant positive, AMS = average mean SLEDAI up to current time, CAPD = cumulative average prednisone dose up to current time, Seros = serositis, Parametric 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 – 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

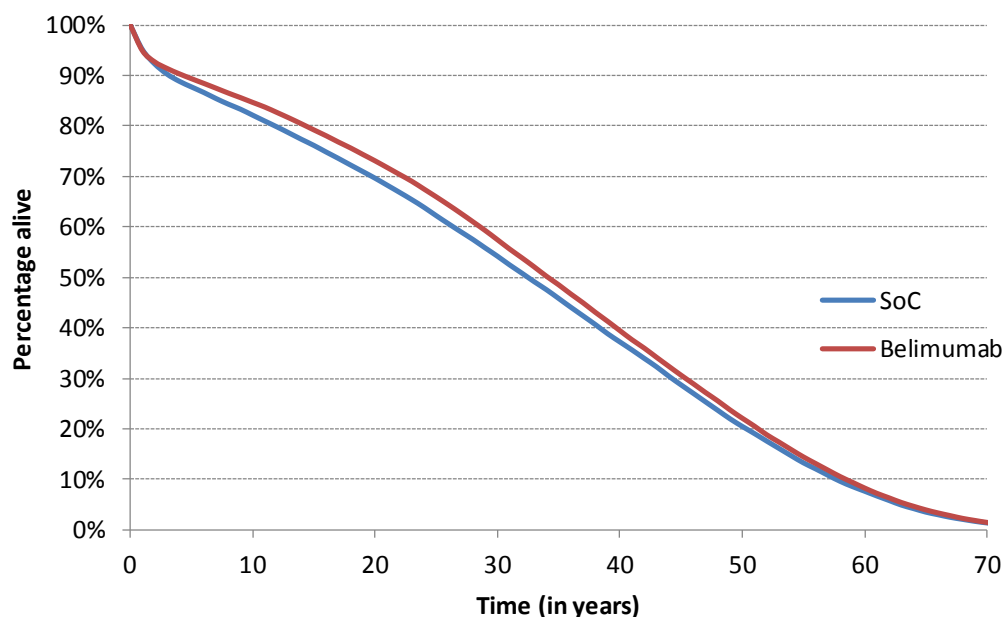
The discontinuation of patients on belimumab is shown in Figure A2.3 for the maximum three year treatment duration. The steep fall in patients continuing with belimumab in the first year is caused by those patients not satisfying the treatment continuation criterion at 24 weeks and hence moving to SoC in the model. After the maximum belimumab treatment duration all patients have switched to receiving SoC treatments only and the corresponding SS scores but continue in the belimumab arm of the model.

**Figure A2.3 Discontinuation from belimumab (includes death) for a three-year maximum belimumab treatment duration – 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 A2.4). 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 A2.4. 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

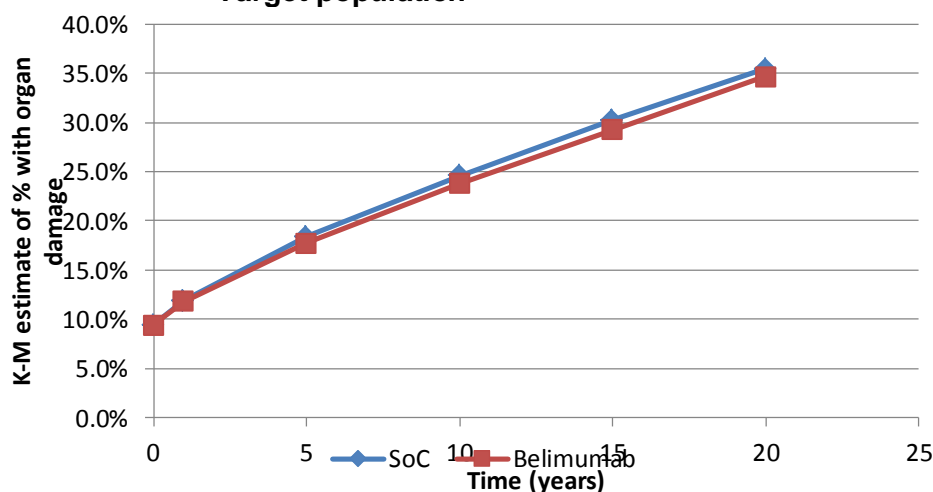
As belimumab patients have an estimated longer life expectancy, the exposure to the risk of organ damage is increased for belimumab patients, hence, for eight of the organs (diabetes, gastrointestinal, malignancy, musculoskeletal, neuropsychiatric and ocular, premature gonadal failure, and skin), the percentage of damage occurrence is similar or higher than for SoC (see Table A2.4). However, for the cardiovascular, peripheral vascular, pulmonary and renal systems, fewer patients on belimumab develop damage compared with 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%	22.4%	-1.4%
Diabetes	17.9%	18.8%	0.9%
Gastrointestinal	22.1%	23.0%	0.9%
Malignancy	32.0%	32.7%	0.8%
Musculoskeletal	48.5%	48.9%	0.4%
Neuropsychiatric	44.7%	45.5%	0.8%
Ocular	35.1%	35.8%	0.7%
Peripheral vascular	21.5%	21.4%	-0.2%
Premature gonadal failure	7.2%	7.3%	0.0%
Pulmonary	39.9%	37.6%	-2.3%
Renal	24.3%	20.9%	-3.3%
Skin	7.9%	7.8%	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. This is illustrated in a Kaplan-Meier plot of neuropsychiatric damage censoring for death (Figure A2.5).

**Figure A2.5. Kaplan-Meier plot of the proportion of patients alive with neuropsychiatric 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 systems, 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	5.31	-0.29
Diabetes	2.64	2.82	0.18
Gastrointestinal	4.62	5.00	0.38
Malignancy	4.39	4.60	0.22
Musculoskeletal	11.24	11.68	0.44
Neuropsychiatric	11.17	11.57	0.40
Ocular	7.88	8.11	0.23
Peripheral vascular	3.66	3.74	0.08
Premature gonadal failure	1.77	1.80	0.02
Pulmonary	9.87	9.33	-0.55
Renal	5.38	4.68	-0.70
Skin	2.47	2.56	0.09

Table A2.6 summarises the main outcome results for the base case lower range including a belimumab treatment duration of three years. As demonstrated previously in Figure A2.4, 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 1.4 years longer, have a reduction in average mean SLEDAI score of -0.4, and a similar total SLICC organ damage score at death compared with SoC patients (Table A2.6). Treatment with belimumab in this subgroup provides an estimated additional 0.6 life years and 0.5 QALYs (discounted at 3.5%).

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

	SoC	Belimumab	Difference
Age at Death	66.2	67.6	1.4
SLICC at Death	4.1	4.1	-0.1
AMS	5.5	5.1	-0.4
Average monthly steroid cumulative dose	228.1	219.2	-8.9
Life Years (undiscounted)	31.93	33.36	1.4
Life Years (discounted at 3.5%)	17.05	17.63	0.6
QALYs (undiscounted)	17.31	18.23	0.9
QALYs (discounted at 3.5%)	9.81	10.26	0.5

All the additional cost effectiveness analyses discussed in this appendix incorporate the discount on vial price offered in our revised PAS. Yearly drug acquisition costs for belimumab when the PAS drug discount scheme is considered are presented in the Table A2.7 below.

**Table A2.7. Unit costs (with PAS) 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 studies UK target population	Year 1 annual cost = XXXXX Year 2 annual cost = XXXXX	The PAS vial costs are XXXXX and XXXXX for the 120 mg and 400 mg 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	£2,156 (Year 1) £2,002 (Year 2+)	£154 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
<b>Total Year 1 costs</b>	XXXXX	
<b>Total Subsequent Year costs</b>	XXXXX	

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, 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 XXXXXXXXX of the total absolute cost difference of XXXXX

**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	£28,511	£628	£628	XXXXX
Belimumab drug acquisition	£0	XXXXX	XXXXX	XXXXX	XXXXX
Belimumab administration	£0	XXXXX	XXXXX	XXXXX	XXXXX
<b>Organ damage costs</b>					
Cardiovascular	£1,838	£1,692	-£146	£146	XXXXX
Diabetes	£2,493	£2,619	£127	£127	XXXXX
Gastrointestinal	£359	£375	£16	£16	XXXXX
Malignancy	£998	£1,007	£9	£9	XXXXX
Musculoskeletal	£9,758	£9,956	£198	£198	XXXXX
Neuropsychiatric	£6,434	£6,571	£138	£138	XXXXX
Ocular	£392	£395	£3	£3	XXXXX
Peripheral vascular	£1,380	£1,364	-£16	£16	XXXXX

Discounted	SoC	Belimumab	Difference	Absolute difference	% absolute difference
Premature gonadal failure	£0	£0	£0	£0	XXXXX
Pulmonary	£42,692	£39,381	-£3,312	£3,312	XXXXX
Renal	£11,139	£9,479	-£1,660	£1,660	XXXXX
Skin	£0	£0	£0	£0	XXXXX
<b>Sum of organ damage costs</b>	£77,483	£72,840	-£4,643	-	
<b>Total direct costs</b>	£105,366	XXXXX	XXXXX	XXXXX	100.0%

Table A2.9 summarises the results for the revised base case analysis incorporating the revised 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 XXXXX, with 0.6 added life years, or 0.5 added QALYs, discounted at 3.5%, resulting in an ICER of XXXXX per QALY gained.

**Table A2.9. Discounted base case results with the revised 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	XXXXX	17.65	10.26	XXXXX	0.59	0.45	XXXXX

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

## Sensitivity Analyses

The deterministic sensitivity analyses and PSA conducted for this base case were identical to those documented in our original submission with our base case which included up to lifetime duration of belimumab treatment.

### Univariate Sensitivity Analyses Results

Tornado diagrams for the ICERs, QALYs and Costs resulting from the univariate sensitivity analyses are presented in Figures A2.6, A2.7, A2.8 and Tables A2.10, A2.11, and A2.12 respectively.

The main drivers of cost-effectiveness in the base case modeling assuming up to three years of treatment with belimumab, 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 pulmonary organ damage is also an important driver of the model results. The greater the reduction in AMS with belimumab, the lower the incidence of pulmonary organ damage with belimumab compared with SoC and consequently the lower the incremental costs leading to more favourable ICERs.

The effect of the constant and log age at the current visit in the pulmonary and neuropsychiatric natural history of disease models also have an important effect either on the incremental costs and/or 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 (negative correlation) between both coefficients. 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 explains why the lower values for some of the latter analyses are above the base case value. In summary, caution should be used when interpreting the univariate results due to the correlation between several model parameters. The PSA acknowledges this correlation by drawing from multivariate normal distributions with covariance matrices.

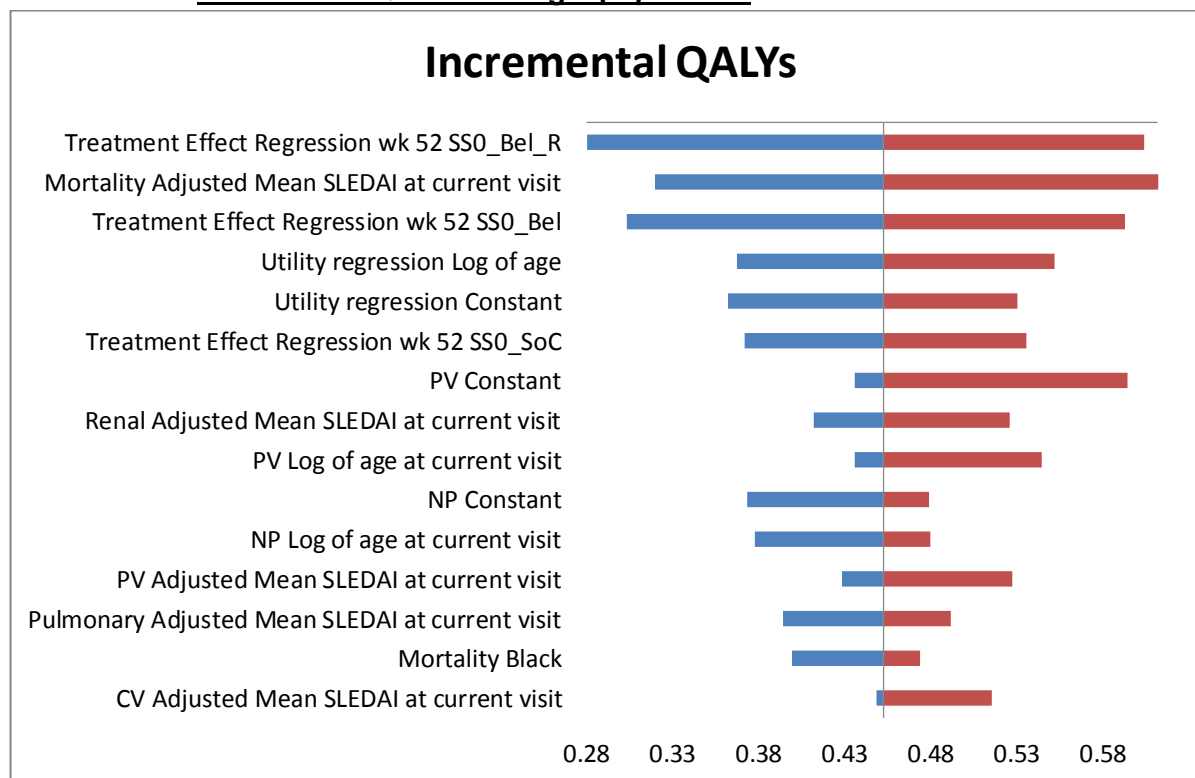
The ICERs yielded from the univariate sensitivity analyses ranged from XXXXX to XXXXX per QALY gained.

**Figure A2.6. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on ICERs Incorporating the PAS – Target population**

**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 <b>all</b> 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 at current visit from the natural history neuropsychiatric model	0.61	0.03	1.23
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	Adjusted Mean SLEDAI coefficient at current visit from the natural history renal model	0.32	0.23	0.41
7	Constant coefficient from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
8	Coefficient of Log of age from the "clean" utility regression	-0.15	-0.18	-0.10
9	Constant coefficient in "clean" utility regression model	1.30	1.15	1.43
10	Coefficient of log of age at current visit from the natural history diabetes model	2.25	1.16	3.35
11	Constant coefficient from the natural history diabetes model	-14.66	-19.14	-10.29
12	Coefficient of log of age at current visit from the natural history pulmonary model	1.23	0.59	1.92
13	Constant coefficient from the natural history renal model	-8.29	-9.01	-7.56
14	Constant coefficient from the natural history malignancy model	-4.81	-6.05	-3.53
15	Coefficient of log of age at current visit from the natural history peripheral vascular model	1.16	0.43	1.89

**Figure A2.7 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 tornado 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	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
3	Coefficient for <b>all</b> belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
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	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
7	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
8	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history renal model	0.32	0.23	0.41
9	Coefficient for log of age at current visit in natural history peripheral vascular model	1.16	0.43	1.89
10	Constant coefficient from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
11	Coefficient for log of age at current visit in natural history neuropsychiatric model	0.61	0.03	1.23
12	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
13	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history pulmonary model	0.14	0.06	0.22
14	Coefficient for black in the mortality model	0.78	0.24	1.33
15	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history cardiovascular model	-0.21	-0.34	-0.07

**Figure A2.8. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental costs with PAS – Target population**

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

Variable ID	Variable	Base value	Lower Bound	Upper Bound
1	Coefficient Adjusted Mean SLEDAI at current visit from the mortality model	0.21	0.09	0.33
2	Coefficient for Adjusted Mean SLEDAI at current visit 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	Constant coefficient in the natural history diabetes model	-14.66	-19.14	-10.29
5	Log of age at current visit coefficient in natural history peripheral vascular model	1.16	0.43	1.89
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	Constant coefficient from the natural history pulmonary model	-9.27	-11.78	-6.86
9	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
10	Coefficient for renal damage at previous visit from the mortality model	0.65	0.16	1.19
11	Adjusted Mean SLEDAI at current visit coefficient from the renal model	0.32	0.23	0.41
12	Coefficient for <b>all</b> belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
13	Adjusted Mean SLEDAI at current visit coefficient from the natural history peripheral vascular model	0.17	0.02	0.31
14	Coefficient for log of age at current visit from the natural history neuropsychiatric model	0.61	0.03	1.23
15	Adjusted Constant coefficient in the natural history Disease Activity Model	3.0	2.20	3.93

### Probabilistic Sensitivity Analyses (PSA) Results

The results for the probabilistic sensitivity analyses are presented in the form of a scatter plot (Figure A2.9) and a cost-effectiveness acceptability curve (Figure A2.10) below.

#### Figure A2.9. Scatter plot of the PSA with PAS - Target population

## Figure A2.10. Acceptability curve of PSA with PAS - Target population

The PSA results show that at a willingness to pay of £20,000 per QALY gained, there is a [REDACTED] probability that belimumab is cost-effective compared to SoC. With a willingness to pay of £30,000 per QALY gained, there is a [REDACTED] probability that belimumab is cost-effective compared to SoC.

### Scenario Analyses

The following scenario analyses were considered relevant for this additional analysis:

1. An alternative maximum treatment duration for belimumab of four years has also been examined as this sits within the base case range and may be the duration agreed with NICE for a suitable period of evidence generation.
2. An analysis was provided for when the more stringent treatment continuation criterion was considered. In order to continue treatment with belimumab, patients would need to show a reduction in SELENA-SLEDAI (SS) score of at least 6 points after 24 weeks treatment.
3. The effect of excluding the treatment continuation criterion in the model has also 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.

4. The effect of assuming an annual withdrawal rate of 8% as per pooled BLISS trials has been investigated.
5. As requested by the Appraisal Committee during discussions at previous Appraisal Committee Meetings, an analysis was conducted which assumed that belimumab non-responders (based on treatment discontinuation criterion of SLEDAI score <4 points at 24 weeks) continue with the average SLEDAI score of SoC non-responders after six months and belimumab responders, who withdraw for reasons other than due to lack of efficacy later, take the SLEDAI score of SoC responders.

The results of the scenario analyses are presented in Table A1.13 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
Base Case (lower range): 3 year belimumab treatment duration	Time horizon = lifetime; 3 year belimumab treatment duration; treatment continuation criterion defined as SS reduction $\geq 4$ at week 24; adjusted natural history model; annual withdrawal rate of 8% Year 1 and 11.7% for Year 2 onwards; health effects discount rate of 3.5%	XXXXX	0.59	0.45	XXXXX
More stringent treatment continuation criterion	As base case (lower range) but with treatment continuation criterion at 24 weeks of SS score of $\geq 6$	XXXXX	0.56	0.42	XXXXX
Treatment continuation criterion excluded	As base case (lower range) but with treatment continuation criterion at 24 weeks excluded	XXXXX	0.58	0.44	XXXXX
4 year belimumab treatment duration	As base case but with a 4 year maximum belimumab treatment duration		0.69	0.52	
Assuming an annual withdrawal rate of 8% as per pooled BLISS trials	As base case (lower range) but assuming an annual withdrawal rate of 8% for belimumab patients for every year.	XXXXX	0.61	0.46	XXXXX
Belimumab non-responders take SLEDAI score of SoC non-responders	Time horizon = lifetime; 3 year belimumab treatment duration; treatment continuation criterion defined as SS reduction $\geq 4$ at week 24; adjusted natural history model; belimumab non-responders take average SLEDAI score of SoC non-responders and belimumab responders, who withdraw for reasons other than stopping rule, take the SLEDAI score of SoC responders.	XXXXX	0.44	0.36	XXXXX

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

Excluding the treatment continuation rule from the cost-effectiveness analysis had the largest impact on the ICER, increasing the base ICER by nearly £6000 per QALY to [REDACTED] per QALY gained.

In contract incorporating the more stringent treatment continuation rule into the model decreased the base case ICER by approximately £1,800 per QALY to [REDACTED] per QALY.

When a maximum of 4 years treatment with belimumab was considered, the ICER yielded was [REDACTED] per QALY gained, £3,389 per QALY than the base case (lower range ICER).

Assuming an annual discontinuation rate of 8% yielded an ICER of [REDACTED] per QALY, only £314 per QALY higher than the base case (lower range) ICER.

The appraisal committee's requested additional analysis in which belimumab non-responders took the SoC non-responders' average SLEDAI score after 24 weeks yielded an ICER of [REDACTED] per QALY, just under £4,000 per QALY higher than the base case (lower range) ICER.

## Summary

Incorporating the PAS, resulted in a base case ICER of [REDACTED] per QALY gained, assuming a maximum of three years treatment with belimumab in the model (base case lower range). Univariate sensitivity analyses and scenario analyses ranged from [REDACTED] to [REDACTED] per QALY gained. Variables and assumptions which had the greatest impact on the ICER comprised the degree of benefit seen on SS score with belimumab and the coefficient for average mean SLEDAI included in the natural history pulmonary model.

### Appendix 3

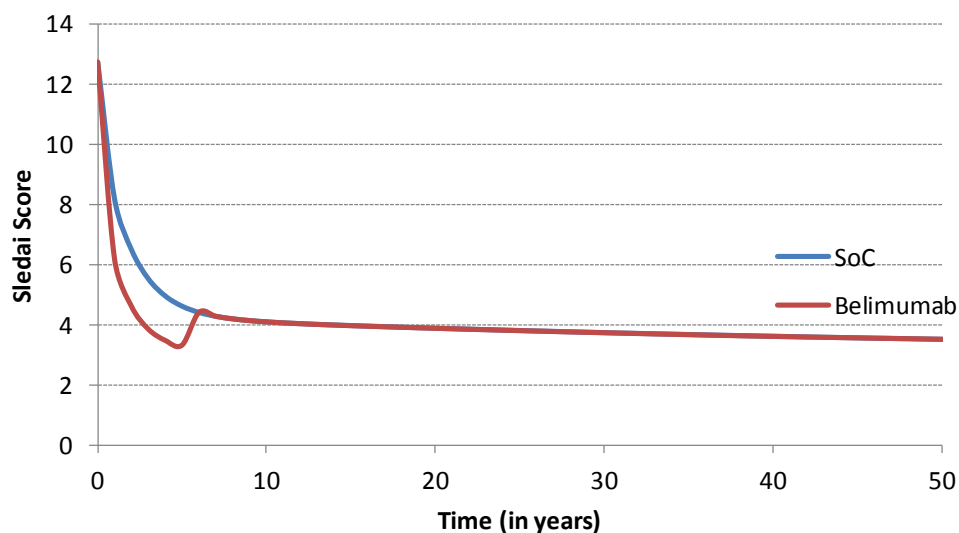
#### Summary of cost-effectiveness assuming a maximum five year belimumab treatment duration

The methodology employed in this cost-effectiveness analysis is the same as that detailed in Appendix 2. The only difference is the assumption of a maximum belimumab treatment duration of five years, therefore only the results which relate to this change in assumption are presented. The summary tables relating to the natural history of disease models are not provided again in this appendix.

#### Results

The adjusted SLEDAI score (AMS) over time for 50,000 simulated patients is shown in Figure A3.1 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 five years.

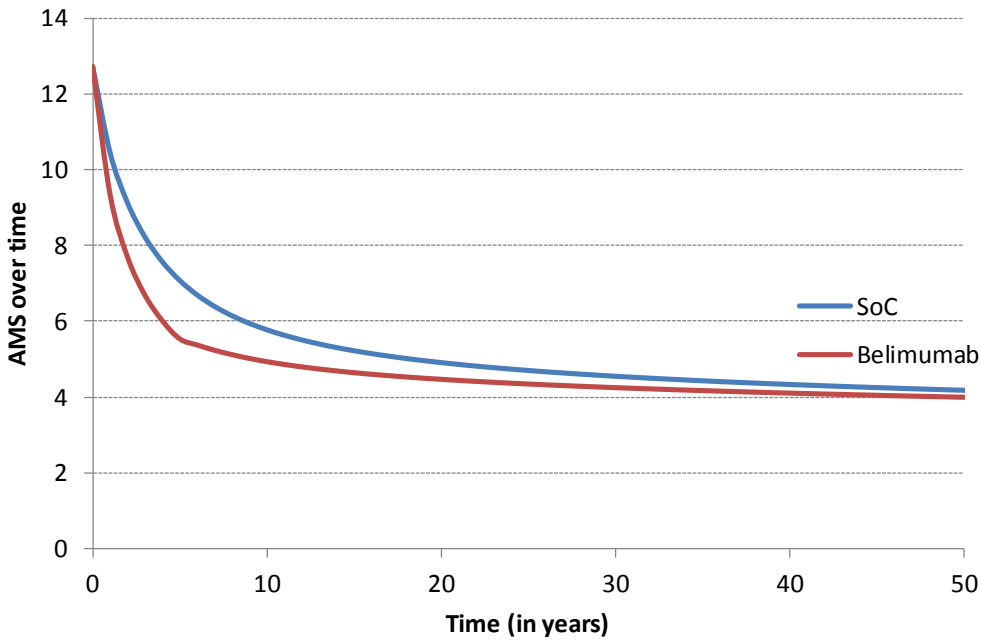
**Figure A3.1. AMS score over time for 50,000 patients simulated – High disease activity (Target) population.**



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 A3.2).



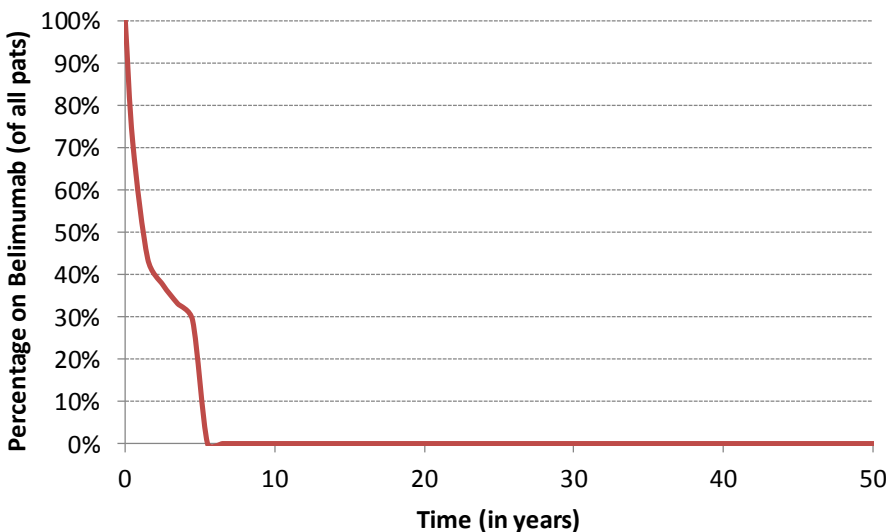
**Figure A3.2. Adjusted Mean SLEDAI (AMS) over time censored for death - Target population.**



The lower disease activity for belimumab patients over five years of treatment will lead to a decreased steroid dose over this time period and a decreased risk for organ damage.

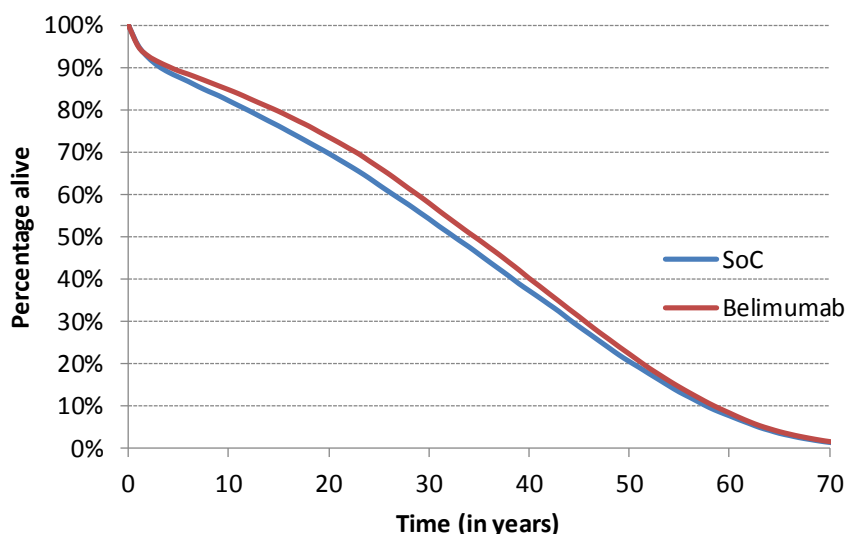
The discontinuation of patients on belimumab is shown in Figure A3.3 for the maximum five year belimumab treatment duration.

**Figure A3.3 Discontinuation from belimumab (includes death) for maximum of five years belimumab treatment duration – Target population**



As seen for the analysis presented in Appendix 2 assuming a maximum of three years of belimumab treatment, the survival over time is improved for belimumab patients compared with patients on SoC (Figure A3.4) and again 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.

**Figure A3.4. Survival of patients over time – Target population**



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, premature gonadal failure, ocular and skin), the percentage of damage occurrence is similar or higher than for SoC (Table A3.1). However, for the cardiovascular, peripheral vascular, pulmonary and renal systems, fewer patients on belimumab develop damage compared with SoC.

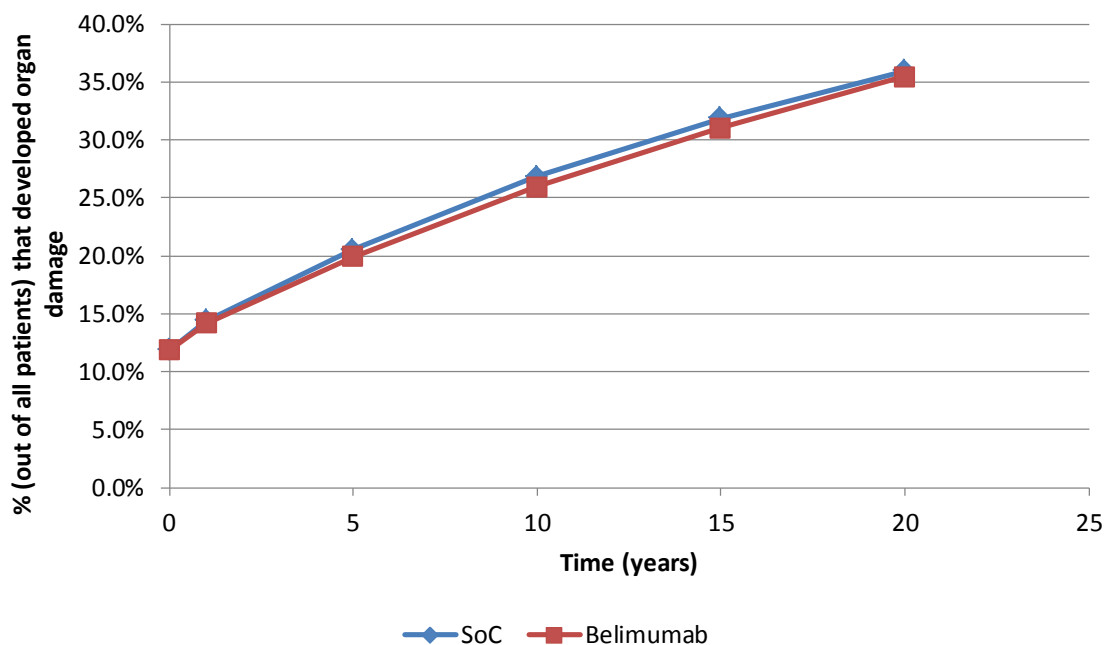
**Table A3.1. Organ damage occurrence for SLE patients until death - Target population**

	SoC	Belimumab	Difference
Cardiovascular	23.9%	21.9%	-2.0%
Diabetes	17.9%	18.7%	0.8%
Gastrointestinal	22.1%	24.0%	1.9%
Malignancy	32.0%	33.4%	1.4%
Musculoskeletal	48.5%	48.9%	0.4%
Neuropsychiatric	44.7%	45.8%	1.1%
Ocular	35.1%	35.8%	0.6%
Peripheral vascular	21.5%	20.9%	-0.7%
Premature gonadal failure	7.2%	7.2%	-0.1%
Pulmonary	39.9%	37.6%	-2.3%
Renal	24.3%	20.3%	-3.9%
Skin	7.9%	7.8%	0.0%

As seen for the maximum three-year belimumab treatment analysis, belimumab is estimated to reduce the risk of organ damage for the cardiovascular, peripheral vascular, pulmonary and renal organ systems, and this damage will occur later in belimumab patients. 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, see for example Figure A3.5 below which presents the Kaplan-Meier plot of musculoskeletal damage censored for death.

**Figure A3.5. 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 systems, the duration of damage for most other organ systems is increased due to the prolonged life-expectancy (Table A3.2).

**Table A3.2. Average duration (yrs) of organ damage – Target Population**

	SoC	Belimumab	Difference
Cardiovascular	5.60	5.25	-0.35
Diabetes	2.64	2.84	0.20
Gastrointestinal	4.62	5.23	0.61
Malignancy	4.39	4.74	0.36
Musculoskeletal	11.24	11.77	0.53
Neuropsychiatric	11.17	11.73	0.56
Ocular	7.88	8.15	0.28
Peripheral vascular	3.66	3.62	-0.04
Premature gonadal failure	1.77	1.80	0.02
Pulmonary	9.87	9.39	-0.48
Renal	5.38	4.53	-0.85
Skin	2.47	2.59	0.12

Table A3.3 summarises the main outcome results for the base case upper range including a maximum belimumab treatment duration of five years. As demonstrated previously in Figure A3.4, belimumab patients have an estimated increased life-expectancy. The model predicts that belimumab-treated patients live on average 1.8 years longer, have a reduction in average mean SLEDAI score of -0.5, and a similar total SLICC organ damage score at death compared with SoC patients. Treatment with belimumab in this subgroup of SLE patients provides an estimated additional 0.7 life years and 0.5 QALYs (discounted at 3.5%).

**Table A3.3. Summary of health economic outcomes – Target population**

	SoC	Belimumab	Difference
Age at Death	66.2	68.0	1.8
SLICC at Death	4.1	4.1	-0.1
AMS	5.5	4.96	-0.5
Average monthly steroid cumulative dose	228.1	216.8	-11.3
Life Years (undiscounted)	31.93	33.73	1.8
Life Years (discounted at 3.5%)	17.05	17.78	0.73
QALYs (undiscounted)	17.31	18.44	1.1
QALYs (discounted at 3.5%)	9.81	10.35	0.54

Table A3.4 below summarises disaggregated costs from the model. For both treatment groups, the organ damage costs are the highest component of the total cost, and similar to the maximum three year treatment duration analysis, the organ damage costs are slightly lower for belimumab-treated patients due to the benefits on the pulmonary and renal systems. Again, the main difference in costs is caused by belimumab acquisition and administration, amounting to **XXXXX** of the total absolute cost difference of **XXXXX**.

**Table A3.4. 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	£28,531	£648	£648	2.8%
Belimumab drug acquisition	£0	<b>XXXXX</b>	£11,545	<b>XXXXX</b>	<b>XXXXX</b>
Belimumab administration	£0	<b>XXXXX</b>	£5,180	<b>XXXXX</b>	<b>XXXXX</b>
<b>Organ damage costs</b>					<b>XXXXX</b>
Cardiovascular	£1,838	£1,666	-£172	£172	
Diabetes	£2,493	£2,625	£133	£133	<b>XXXXX</b>
Gastrointestinal	£359	£387	£27	£27	<b>XXXXX</b>
Malignancy	£998	£1,021	£23	£23	<b>XXXXX</b>
Musculoskeletal	£9,758	£10,001	£243	£243	<b>XXXXX</b>
Neuropsychiatric	£6,434	£6,632	£198	£198	<b>XXXXX</b>
Ocular	£392	£391	-£1	£1	

Discounted	SoC	Belimumab	Difference	Absolute difference	% absolute difference
Peripheral vascular	£1,380	£1,323	-£57	£57	XXXXX
Premature gonadal failure	£0	£0	£0	£0	XXXXX
Pulmonary	£42,692	£39,565	-£3,127	£3127	XXXXX
Renal	£11,139	£9,167	-£1,972	£1972	XXXXX
Skin	£0	£0	£0	£0	XXXXX
<b>Sum of organ damage costs</b>	£77,483	£72,778	-£4,705	£5,953	
<b>Total direct costs</b>	£105,366	XXXXX	XXXXX	XXXXX	100.0%

Table A3.5 summarises the cost-effectiveness results. Belimumab-treated patients are estimated to live longer and due to their increased life expectancy and to the belimumab acquisition and administration costs the total costs of managing SLE patients with highly active disease are higher than for SoC patients. The incremental costs are XXXXX, with 0.73 added life years, or 0.54 added QALYs, discounted at 3.5%, resulting in an ICER of XXXXX per QALY gained.

**Table A3.5. Discounted of base case (upper range) results with the revised 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	XXXXX	17.78	10.35	XXXXX	0.73	0.54	XXXXX

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

## Sensitivity Analyses

### Univariate Sensitivity Analyses Results

Tornado diagrams for the ICERs, QALYs and Costs resulting from the univariate sensitivity analyses are presented in Figures A3.6, A3.7, A3.8 and Tables A3.9, A3.10, and A3.11 respectively.

The ICERs yielded from the univariate sensitivity analyses ranged from XXXXX to XXXXX per QALY gained. The main drivers of cost-effectiveness from these univariate sensitivity analyses for the upper range base case assuming a maximum belimumab treatment duration of 5 years are similar to those reported in Appendix 2 for the maximum three-year belimumab treatment duration (lower range base case). Again, 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. Another important driver of the model is the effect of the AMS on pulmonary organ damage. The greater the reduction in AMS with belimumab, the lower the incidence of pulmonary organ damage with belimumab compared with SoC and consequently the lower the incremental costs leading to more favourable ICERs.

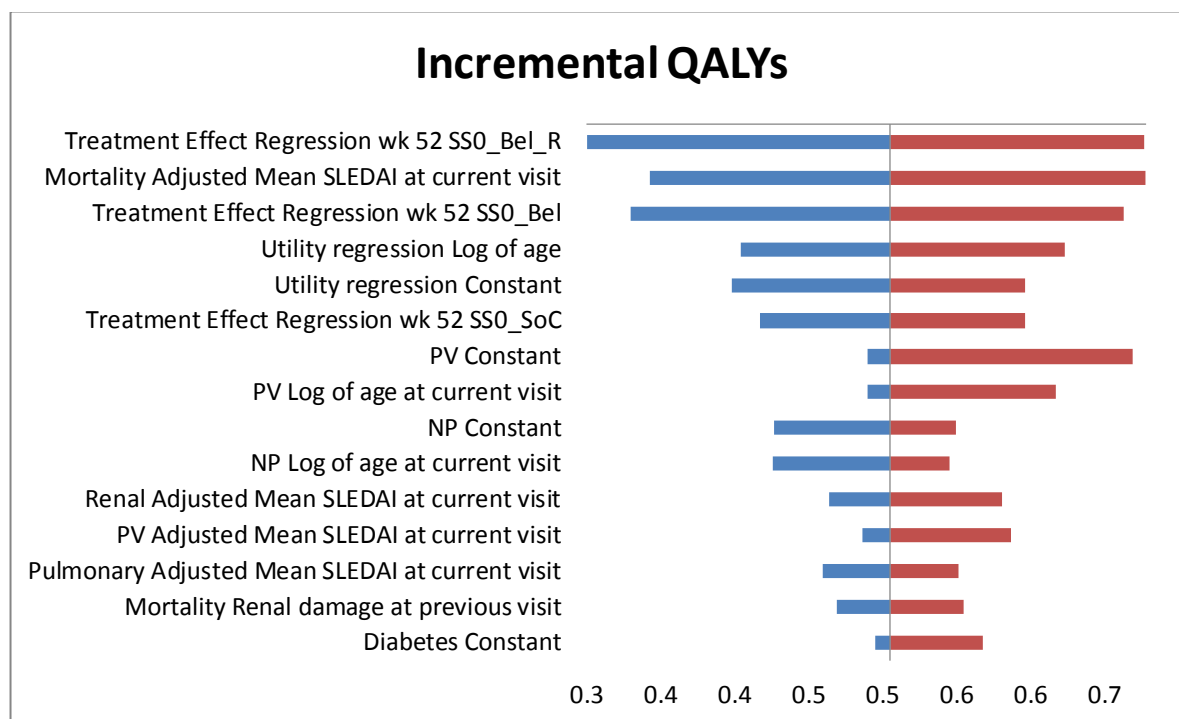
The effect of the constant and log age at the current visit in the pulmonary natural history of disease models also have an important effect either on the incremental costs and/or the ICER as discussed in Appendix 2.

**Figure A3.6. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on ICERs Incorporating the PAS – Target population**

**Table A3.6. 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 <b>all</b> 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
5	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
5	Coefficient of Log of age from the "clean" utility regression	-0.15	-0.18	-0.10
6	Constant coefficient in "clean" utility regression model	1.30	1.15	1.43
7	Adjusted Mean SLEDAI coefficient at current visit from the natural history renal model	0.32	0.23	0.41
8	Coefficient of log of age at current visit from the natural history neuropsychiatric model	0.61	0.03	1.23
9	Constant coefficient from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
10	Coefficient of log of age at current visit from the natural history diabetes model	2.25	1.16	3.35
11	Constant coefficient from the natural history diabetes model	-14.66	-19.14	-10.29
12	Coefficient of log of age at current visit from the natural history pulmonary model	1.23	0.59	1.92
13	Constant coefficient from the natural history renal model	-8.29	-9.01	-7.56
14	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history cardiovascular model	-0.21	-0.34	-0.07
15	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33

**Figure A3.7 Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental QALYs – Target population**



Note: Table A3.7 below details the variables identified as numbers in this tornado plot.

**Table A3.7. 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	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
3	Coefficient for <b>all</b> belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
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	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
7	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
8	Coefficient for log of age at current visit in natural history peripheral vascular model	1.16	0.43	1.89
9	Constant coefficient from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
10	Coefficient for log of age at current visit in natural history neuropsychiatric model	0.61	0.03	1.23
11	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history renal model	0.32	0.23	0.41
12	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
13	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history pulmonary model	0.14	0.06	0.22
14	Coefficient for renal damage at previous visit from the mortality model	0.65	0.16	1.19
15	Constant coefficient from the natural history diabetes model	-14.66	-19.14	-10.29

**Figure A3.8. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental costs with PAS – Target population**

**Table A3.8. Description of key variables with the largest impact on Incremental costs**

<b>Variable ID</b>	<b>Variable</b>	<b>Base value</b>	<b>Lower Bound</b>	<b>Upper Bound</b>
1	Coefficient Adjusted Mean SLEDAI at current visit from the mortality model	0.21	0.09	0.33
2	Coefficient for Adjusted Mean SLEDAI at current visit 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	Constant coefficient in the natural history diabetes model	-14.66	-19.14	-10.29
5	Log of age coefficient at current visit in natural history diabetes model	2.25	1.16	3.35
6	Log of age at current visit coefficient in natural history peripheral vascular model	1.16	0.43	1.89
7	Log of age at current visit coefficient in natural history pulmonary model	1.23	0.59	1.92
8	Constant coefficient from the natural history pulmonary model	-9.27	-11.78	-6.86
9	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
10	Coefficient for renal damage at previous visit from the mortality model	0.65	0.16	1.19
11	Adjusted Constant coefficient in the natural history Disease Activity Model	3.0	2.20	3.93
12	Coefficient for <b>all</b> belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
13	Adjusted Mean SLEDAI at current visit coefficient from the renal model	0.32	0.23	0.41
14	Coefficient for any infection at time of death at current visit from the mortality model	0.74	-0.01	1.53
15	Constant coefficient from the natural history malignancy model	-4.81	-6.05	-3.53



## Probabilistic Sensitivity Analyses (PSA) Results

The results for the probabilistic sensitivity analyses are presented as a scatter plot (Figure A3.9) and a cost-effectiveness acceptability curve (Figure A3.10) below.

### Figure A3.9. Scatter plot of the PSA with PAS - Target population

### Figure A3.10. Acceptability curve of PSA with PAS - Target population

The PSA results show that at a willingness to pay of £20,000 per QALY gained, there is a [REDACTED] probability that belimumab is cost-effective compared to SoC. With a willingness to pay of £30,000 per QALY gained, there is an [REDACTED] probability that belimumab is cost-effective compared to SoC.

## Scenario Analyses

The following scenario analyses were considered relevant for this additional analysis:

1. An analysis was provided for when the more stringent treatment continuation criterion was considered. In order to continue treatment with belimumab, patients would need to show a reduction in SS score of at least 6 points after 24 weeks treatment.
2. The effect of excluding the treatment continuation criterion in the model has also 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.
3. An analysis was conducted which assumed that belimumab non-responders (based on treatment discontinuation criterion of decrease in SLEDAI score <4 points at 24 weeks) continue with the average SLEDAI score of SoC non-responders after six months and belimumab responders who withdraw for reasons other than lack of efficacy take the SLEDAI score of SoC responders after time of withdrawal from belimumab.

The results of the scenario analyses are presented in Table A3.9 below.

**Table A3.9. 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
Base Case (upper range): 5 year belimumab treatment duration	Time horizon = lifetime; 5 year belimumab treatment duration; treatment continuation criterion defined as SS reduction $\geq 4$ at week 24; adjusted natural history model; annual withdrawal rate of 8% Year 1 and 11.7% for Year 2 onwards; health effects discount rate of 3.5%	XXXXX	0.73	0.54	XXXXX
More stringent treatment continuation criterion	As base case (upper range) but with treatment continuation criterion at 24 weeks of SS score of $\geq 6$	XXXXX	0.65	0.49	XXXXX
Treatment continuation criterion excluded	As base case (upper range) but with treatment continuation criterion at 24 weeks excluded	XXXXX	0.69	0.52	XXXXX
Assuming an annual withdrawal rate of 8% as per pooled BLISS trials	As base case (upper range) but with annual withdrawal rate of 8% for belimumab patients for every year	XXXXX	0.75	0.56	XXXXX
Belimumab non-responders take SLEDAI score of SoC non-responders	Time horizon = lifetime; 5 year belimumab treatment duration; treatment continuation criterion defined as SS reduction $\geq 4$ at week 24; adjusted natural history model; belimumab non-responders take average SLEDAI score of SoC non-responders and belimumab responders, who withdraw for reasons other than lack of efficacy or response, take the SLEDAI score of SoC responders.	XXXXX	0.55	0.43	XXXXX

The various alternative scenarios investigated resulted in ICERs ranging from XXXXX to XXXXX per QALY gained compared with the base case (upper range) ICER of XXXXX per QALY gained.

Excluding the treatment continuation rule from the cost-effectiveness analysis and changing the assumptions for SoC SS score when the belimumab patients stop taking belimumab and return to SoC both had the largest impact on the ICERs and were similar, increasing the base case (upper range) ICER by approximately £6,000 per QALY to XXXXX and XXXXX per QALY gained, respectively.

In contrast, incorporating the more stringent treatment continuation rule into the model decreased the base case (upper range) ICER by just under £3,000 per QALY to XXXXX per QALY.

Assuming an annual discontinuation rate of 8% yielded an ICER of XXXXX per QALY, approximately £1,000 per QALY higher than the base case (upper range) ICER.

## Summary

Incorporating the latest PAS, the cost-effectiveness analysis for the base case upper range assuming a maximum of five years treatment with belimumab resulted in an ICER of [REDACTED] per QALY gained. Univariate sensitivity analyses and scenario analyses ranged from [REDACTED] to [REDACTED] per QALY gained. Variables and assumptions which had the greatest impact on the ICER comprised the degree of benefit seen on SS score with belimumab and the coefficient for average mean SLEDAI included in the natural history pulmonary model.

**BILAG Biologics Prospective Cohort:  
The Use of Novel Biological Therapies in the Treatment of  
Systemic Lupus Erythematosus (SLE).**

**(Lay title: Long-term Safety of New Treatments in the Management of SLE)**

Professor Ian N Bruce  
Professor and Honorary Consultant in Rheumatology  
**Arthritis Research UK Epidemiology Unit (formerly the arc Epidemiology Unit),**  
The University of Manchester

On behalf of the British Isles Lupus Assessment Group

## Table of Contents

BILAG Biologics Prospective Cohort: .....	1
The Use of Novel Biological Therapies in the Treatment of Systemic Lupus Erythematosus (SLE). .....	1
Table of Contents .....	2
1. Background .....	4
2. Rationale for the Establishment of a Biologics Prospective Cohort for SLE ....	7
3. Methods.....	7
3.1. Aims.....	7
3.1.1. Infection: .....	7
3.1.2. Efficacy .....	8
3.1.3. Sequencing .....	8
3.2. Design .....	8
3.2.1. Exposed cohort .....	9
3.2.2. Non-exposed cohort.....	10
4. Statistics, sample size and power calculations.....	11
5. Auditing the conduct of the study and research governance.....	14
6. Summary Study flow charts .....	14
7. Baseline data.....	17
7.1. Patient Identification (to be stored separately for confidentiality) .....	17
7.2. Data Collected to appear in cohort study.....	17
7.3. Consultant and nurse collected information (see current version of the Consultant data collection Questionnaire) .....	18
7.4. Patient collected information (see current version of the Patient data collection Questionnaire).....	19
7.5. Laboratory investigations .....	19
8. Follow-up data.....	20
8.1. Consultant Follow-up .....	20
8.2. Postal questionnaire to patients and patient diaries .....	21
9. Analysis .....	22
9.1. Primary endpoint for evaluation.....	22
9.2. Secondary endpoints for evaluation .....	22
9.2.1. Safety.....	23
9.2.2. Efficacy .....	23
9.3. Hypotheses to test .....	23
9.4. Analytic approach .....	23

9.5.	Interim Analyses .....	24
10.	Roles of interested parties .....	24
10.1.	Role of pharmaceutical companies .....	24
10.2.	Role of BILAG .....	24

## 1. Background

There have been very few major advances in the treatment of SLE over the past 35 years. In the past 5 years however, there has been an explosion of interest in developing new molecules for the treatment of SLE. A number of approaches have been proposed and are currently in various stages of development including B-cell depleting therapies, IL6 and IL10 blockade as well as inhibition of co-stimulatory molecules, TNF-blockade and lymphodepletion. As these drugs become available for diseases such as RA, off-licence use in SLE is already underway and it is likely that several of these products will gain licences for use in SLE over the next 5 years. However, clinical trials are limited by patient numbers and study duration and therefore are under powered to study potentially important adverse events. In addition, clinical trials tend to exclude patients who have been exposed to other biological therapies in the past and therefore the potential medium-term interactions between various therapeutic approaches cannot be adequately studied.

There have been a number of biologic therapies that have been used in the treatment of SLE on an exceptional, occasional basis; case reports for these therapies include abatacept, infliximab (Hayat et al. 2007; Hayat & Uppal 2007) and etanercept (Micheloud et al. 2006; Takahashi, Naniwa, & Banno 2008). There are currently a number of trials underway examining the safety and efficacy of these therapies, in addition to a number of other biologic therapies.

In addition to these occasionally used biologics, rituximab has been more frequently used successfully in the treatment of SLE patients. Rituximab, an anti-CD20 molecule in open label studies shows good efficacy for the treatment of SLE (Cambridge et al. 2008; Jonsdottir et al. 2008; Leandro et al. 2005; Ng et al. 2007). However, repeat treatment is often required, **after a varying interval**, and there is evidence that when B cells recover and reconstitute, they may have a more naïve phenotype (Anolik et al. 2007). The long-term consequences of these changes, as well as what happens when additional novel therapies are used thereafter, are areas which require study. In addition, rituximab is associated with the development of a Human Anti-Chimeric Antibodies (HACA) response which can blunt the efficacy of subsequent therapies. Again, whether these antibodies have any cross reactivity with other more humanised molecules (e.g. ocrelizumab) remains to be determined and in particular, their influence on efficacy and adverse events to further therapies requires to be known.

Belimumab is a fully human monoclonal antibody that binds to and inhibits the action of soluble human B lymphocyte stimulator (BLyS). Two Phase III trials using belimumab have also recently been reported. In BLISS-52, 865 SLE patients were randomised to either placebo, belimumab 1mg per kg or belimumab 10mg per kg **given monthly**. The response at 52 weeks, was achieved by 46.3% of placebo treated patients compared to 51.4% with belimumab 1mg per kg and 57.6% with belimumab 10mg per kg ( $p=0.013$  and  $0.0006$  respectively) (Trial watch 2009). A second Phase III trial (BLISS-76) randomised 819 patients with active SLE to placebo, 1mg/kg or 10mg/kg of belimumab. At 52 weeks the % of patients achieving the SRI was 33.8% with placebo, 40.6% with 1mg/kg ( $p=0.10$  vs placebo) and 43.2% with 10mg/kg ( $p=0.021$  vs placebo). (Human Genome Sciences 2009; Trial watch 2009)

Epratuzumab is an anti-CD22 molecule which reduces B-cell numbers by approximately 35-44%. A recent Phase IIB clinical trial compared epratuzumab to placebo in patients with SLE over a 12-week period. The primary end point in this trial was a composite end point with improvement in BILAG scores and no worsening SLEDAI or the Physicians Global Assessment. Using this novel end-point, the treatment advantage of epratuzumab over placebo reached 24.9% at week 12. (Trial watch 2009; UCB Pharmaceuticals 2009)

Abatacept a CTLA4-Ig, licensed for use in RA, reduces co-stimulation also reported a negative trial against a primary outcome of reduced lupus flares. A secondary analysis within the trial did however suggest that patients with arthritis may significantly improve using this agent. (Merrill et al. 2008; Trial watch 2009)

A successful model for carrying out such research has been pioneered by the British Society for Rheumatology (BSR) in establishing the BSR Biologics Prospective Cohort (BSRBR) in rheumatoid arthritis. This is a long-term observational study designed and powered to study the development of uncommon long-term adverse events to anti-TNF therapy (principally the development of lymphoproliferative disorders) in RA patients. Although the BSRBR is powered to detect an increase in risk of lymphoma, this wealth of data has been able to address a number of additional questions relating to the safety of these relatively new drugs, including rates of serious infections and the effects of switching between agents (Dixon et al.



2006;Hyrich et al. 2008). The BSRBR is now being extended to capture data on RA patients receiving rituximab.

The model has also been adopted by the British Association of Dermatologists (BAD) who have recently also established a similar prospective cohort study (the British Association of Dermatologists' Biologics Intervention Register, BADBIR) for patients with severe psoriasis, with the main difference being that all data is being collected electronically using secure web-based systems. These studies are likely to become the norm in the UK for following patients treated with biological agents and are now considered the gold standard for collecting real life long-term safety data. The prospective cohort design allows the long-term safety and efficacy of the therapy to be monitored in real life situations, something that cannot be determined from short-term clinical trials in selected groups of patients.

SLE is a less common disease than either RA or psoriasis. In addition, any study to be established at this time would be an open-label cohort study of patients being treated for an off-licence indication. The limiting factor in doing medium to long term studies of, for example, rituximab in a single centre is numbers and a UK-wide registry would significantly increase the statistical power to study efficacy, safety and biomarker changes in patients receiving these treatments in a 'real world' clinical setting. Also, the small numbers of other drugs precludes any specific conclusions to be drawn from "anecdotal" reporting.

The British Isles Lupus Assessment Group (BILAG) represents a consortium of 10 rheumatology centres across Great Britain who share a specific commitment to the study of SLE. Collaborative work involving this group has led to the development and validation of the original BILAG disease activity instrument (Hay et al. 1993) and current collaborative studies are underway to validate the BILAG 2004 instrument (Isenberg et al. 2005). Other collaborative work has included the CYAZ trial, the LASER study of cardiovascular disease in SLE and the development of the LupusQoL (McElhone et al. 2007), as well as work collaborating with the BSR – Lupus Special Interest Group (BSR-LSIG), the UK Juvenile SLE Group and the Renal Association. .

## **2. Rationale for the Establishment of a Biologics Prospective Cohort for SLE**

We propose to establish a BILAG Biologics Prospective Cohort. Considerable expertise in establishing and maintaining such prospective registries is already available in the University of Manchester **Arthritis Research UK** Epidemiology Unit where both the BSRBR and the BADBIR are being hosted. In the first phase of the BILAG Biologics Prospective Cohort we aim to study clinical response, adverse events and post-treatment biomarker changes in patients receiving biologic agents for the routine management of their SLE. The initial registry would collect data on the safety of the therapy, with hospitalisation for infection as a primary endpoint, in addition to efficacy data (using the BILAG 2004 instrument) to study global and organ specific efficacy of biologic therapies in SLE. Data will also be collected on adverse events post-treatment, particularly according to whether the treating physician continues to co-prescribe concomitant immunosuppressive therapy. In the post-treatment phase the development of HACA antibodies would be determined as would characteristics of the B-cell population as it is reconstituted. In addition, predictors of response-non-response will be studied.

As previously mentioned, there are a number of other biologic agents that are used for the treatment of SLE, including abatacept, infliximab and etanercept, with further drugs such as alemtuzumab, ocrelizumab, belimumab and tocilizumab being used in the near future. The cohort will be set up to include the registration and follow up of patients treated with these additional biologic agents.

## **3. Methods**

The BILAG Biologics Prospective Cohort will be established as an independent investigator-led prospective cohort study with the BILAG group acting as the Steering committee.

### **3.1. Aims**

#### **3.1.1. Infection:**

The primary aim of establishing the BILAG Biologics Prospective Cohort is to ascertain whether using biologics in the ***routine*** treatment of SLE is associated with an increased risk of being hospitalised for infection, compared to SLE patients with similar disease activity receiving conventional therapies.

### 3.1.2. Efficacy

The secondary purpose of the BILAG Biologics Prospective Cohort is to determine the long-term efficacy of biological therapies in the treatment of SLE.

### 3.1.3. Sequencing

A number of subsidiary questions will also be addressed if sufficient data is collected from additional biologic agents, which include the evaluation of differences between these agents, multiple agents concurrently or in sequence in terms of serious adverse effects.

The BILAG Biologics Prospective Cohort will also correct for the influence of potential confounding variables on these outcomes, with data collected on SLE severity, alcohol and smoking and concomitant medications and comorbidities.

## 3.2. Design

This is a prospective cohort study consisting of two cohorts of patients all of whom will be treated by their consultant according to clinical need and according to the consultant's decision in their usual clinical setting. Patients treated with biological therapies (any and not exclusively those mentioned above) will be recruited along with a control group with similar disease characteristics but exposed only to non-biological systemic therapies. Further patients initiating treatment on additional biologic agents will also be included. These patients need following up, and even in small numbers, a UK-wide effort through the BILAG Biologics Prospective Cohort presents the ideal opportunity in which to do this. The protocol will be submitted for MREC approval. Analysis will take into account switching from the control group to a biologic agent, and switching between agents.

The cohort will be modelled on the existing BSRBR and the BADBIR and co-located at Manchester University. Clinicians from the 10 rheumatology centres that make up BILAG will recruit all patients that they treat, commencing treatment with a biologic intervention, that satisfy the inclusion criteria and who consent to take part. Additional collaborating clinicians from the BSR Special Interest Group, the Renal Association and the UK Juvenile SLE Group nationally, will also become recruiting sites and will recruit patients in the same manner.

The cohort aims to recruit all patients from the BILAG centres, and other collaborating sites, receiving **any** biologic therapy, until the required cohort size has

been attained. Numbers required need to be achievable and sufficient to enable worthwhile comparisons to be made. It is anticipated that 220 will be required in the biological intervention cohort and 220 controls.

Following registration, for the duration of the study, the BILAG Biologics Prospective Cohort will approach participating consultants, or their delegated contact, to update the records of all patients whether or not they continue on therapy. This will be captured primarily as web-based data entry. Consultants, or their nominated, trained deputy, will be able to view data on their patients and add to this without unnecessary repetition. Paper forms will be available as a substitute for those unable to use a web-based system.

The co-ordinating centre will mail patients with paper forms to gain additional information on their quality of life, lifestyle habits, medication and any health care problems according to the protocol. Where responses from patients or physicians are delayed there will be repeated reminders and phone calls if necessary to ensure the most complete data possible is obtained. This will take the form of a reminder postcard at 2 weeks and a follow-up phone call at 4 weeks if no response is obtained.

When formal follow-up of the last patients entered in the study is complete, BILAG Biologics Prospective Cohort will continue to link the study to the **NHS-IC (formerly the Office for National Statistics) who will process the data and will provide cancer and death information**. Patient data will need to be acquired and stored with patient specific information. This will be pseudonymised (e.g. patient number) to protect confidentiality.

### **3.2.1. Exposed cohort**

#### **Inclusion Criteria**

1. Patients commencing treatment with a biological agent within the previous 12 months for their SLE at the clinical decision of their treating consultant
2. Patients age 5 years or older
3. a) Willingness and ability to give informed consent for long-term follow-up and access to all medical records (patients 16 years old or older)

**or**

- b) Willingness and ability of parents to give informed consent for their child and willingness and ability of child to give assent

### **Exclusion Criteria**

1. Patients with exposure to the biologic agent prompting registration more than 12 months before entry
2. Unwilling or unable to provide informed consent

### **Repeat treatments**

**In routine care, biologics therapies will usually be administered in one of two different methods: as a regular injection / infusion throughout the therapeutic course, or as an intermittent / episodic therapy, for example with some rituximab regimes. In some situations, therefore, a patient will be given the treatment in an intermittent way and a re-treatment will be indicated by a flare of their disease. As the primary aim of the study is to examine the safety of the biologic therapies, when compared to conventional treatments, in patients who flare, and therefore require a retreatment with a biologic in this way, their “study clock” will be reset to time 0, and will receive 3, 6 and 12 monthly post-treatment follow-ups as a newly recruited patient would.**

**Similarly, patients who switch from conventional therapy to the biologics group, or who switch from one biologic therapy to another, due to lack of efficacy or toxicity issues, for example, will also have their “study clock” reset to zero to ensure the safety of the newly prescribed biologic can be ascertained, with the appropriate statistical adjustment for such time varying data.**

### **3.2.2. Non-exposed cohort**

Many patients with similar disease activity will also be started on more traditional interventions e.g. azathioprine, mycophenolate mofetil, cyclophosphamide etc. A control group will be recruited and will consist of SLE patients from the BILAG centres who are being initiated on standard therapy, including azathioprine, Mycophenolate mofetil (MMF) or cyclophosphamide for active SLE. This will allow us to adjust any future analysis for factors associated with severe SLE of an equivalent level of severity to that for which biologics would be employed.

### **Inclusion Criteria**

1. Patients **newly** commencing treatment with a non-biological, immunosuppressive agent, such as azathioprine, MMF or cyclophosphamide for their SLE at the clinical decision of their treating consultant
2. Patients age 5 years or older
3. a) Willingness and ability to give informed consent for long-term follow-up and access to all medical records (patients 16 years old or older)

**or**

- b) Willingness and ability of parents to give informed consent for their child and willingness and ability of child to give assent

### **Exclusion Criteria**

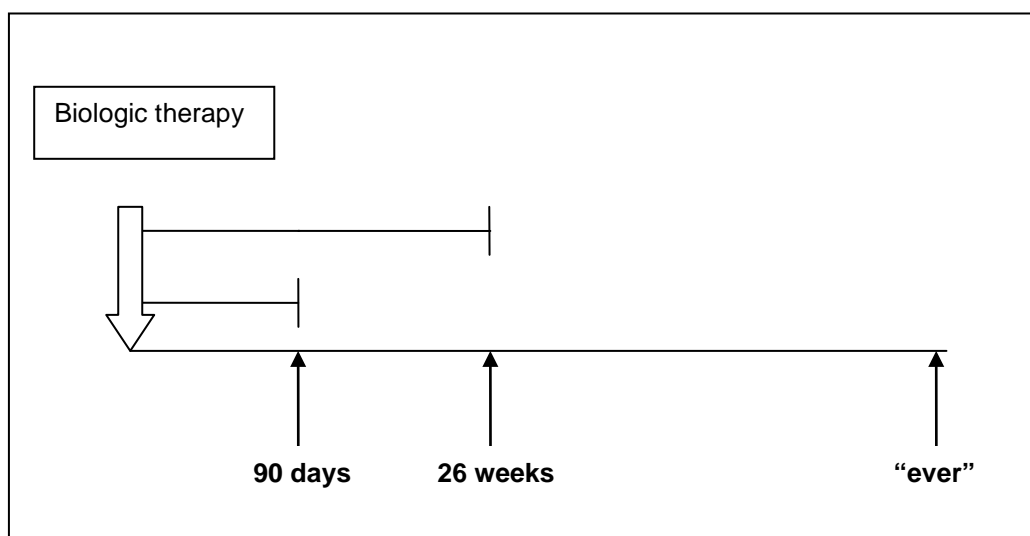
1. Patients with any prior exposure to biologic agents

If for clinical reasons a 'control' is subsequently started on a biological therapy then he/she would switch from the control cohort into the biological cohort.

## **4. Statistics, sample size and power calculations**

The initial analyses will consist of comparisons in baseline status between the individuals in the treatment cohorts. For the purposes of analysis (initially) follow-up time will be censored in both cohorts if there is switching to another class of biologic therapy and censored in the standard therapy group if there is switching to a biologic agent. The adverse events of interest are calculated per person time of follow-up, after the start of therapy. Depending on the events, separate analyses are undertaken (i) restricting consideration to time on drug, which include the period within 90 days of last injection (ii) within 26 weeks and (iii) all person time following start of therapy (see figure below). Standard time-dependent regression analyses will be undertaken to compare event rates between groups after adjusting for baseline and other

differences.



**Figure 1:**

The primary comparison to consider is whether, compared to other immune therapies, biologics are associated with a doubling of the risk of being hospitalised for infection. This is an important and well recognised serious adverse event (SAE) that can occur in the context of SLE therapy. Secondary analyses will include factors related to both the safety and efficacy of the therapy.

### **Safety**

Secondary outcomes relating to the safety of the therapy will include

- All SAEs on therapy
- Mortality (all cause)

### **Efficacy**

Secondary outcomes relating to the safety of the therapy will include

- Initial clinical response data and predictors of response
- Damage accrual over 3-5 years of follow-up
- Additional outcomes based on biomarker and immune function studies.

A review of the current literature reveals a range of rates that have been suggested for hospitalisation for infection in SLE. In 2 MMF trials (vs. other immunosuppressive regimes), which may be of relevance to the current considerations, rates of hospitalisation for infection in patients taking immunosuppression for lupus nephritis specifically were 5% over 6 months and 10% over 72 months (Contreas et al. 2004;Ginzler et al. 2005). In addition Houssiau et al in the ELNT trial (cyclophosphamide and azathioprine exposure) 17% of patients were admitted over a 41-month period with infection (Houssiau et al. 2002).

In cohort studies of SLE, a 1992 study (Petri & Genovese 1992) suggested 9% per annum were admitted for infection while an estimate from Bosch et al suggests 9% hospitalisations over 2 years (Bosch et al. 2006) and in the Toronto cohort approx 13% were admitted over a 5 years period (Gladman et al. 2002). Two recent trials of contraception in SLE followed subjects for 12 months. In each trial 4-6 % of patients per annum were admitted for infection. In one trial there was a particularly high incidence of infection in one subgroup which may have skewed the results upward. However the trials were of milder SLE patients.

Therefore, taking a conservative view and considering the ELNT trial as well as the Bosch, Gladman and Contreras studies (Bosch, Guilabert, Pallares, Cerveral, Ramos-Casals, Bove, Ingelmo, & Font 2006;Contreas, Pardo, Leclercq, Lenz, Tozman, O'Nan, & Roth 2004;Gladman, Hussain, Ibanez, & Urowitz 2002) in particular as showing the lower end of the range, our sample size is based on a rate of 10% of patients being admitted for infection over a 3-year period. Using this rate of infection admissions in the control group, 220 patients per group would be needed to demonstrate a doubling of the rate of admissions in the biological agent exposed patients over a 3 year period with 80% power at the 5% level. If the rates are closer to 15% over 3 years then 130 patients per group will achieve sufficient power (see appendix 1).

These are conservative estimates and if numbers of admissions are considered (i.e. multiple admissions per patient) then power is greater, however this data is difficult to estimate from the literature. Similarly, if the absolute rates are higher in SLE overall, then the sample size will be reduced.

We would estimate that once operational approximately 75 patients per year will be recruited to each arm in each of the first 3 years. Once established then we estimate approximately 100 patients per annum thereafter. We would plan initially to follow patients for the first 3 years after first exposure to a new biological agent with extended follow-up the subject of future plans.

Given the anticipated recruitment rates, we aim to recruit the relevant numbers in the first 3-4 years of the registry and within 4-6 years will have adequate follow-up data to perform a primary analysis.



Patients recruited newly exposed to other biologic agents (for example infliximab, etanercept, abatacept or alemtuzumab) will also be recruited following the same sample size and power calculations, although these will be less frequent due to the current policy of occasional, exceptional prescribing of these agents in this patient group. It is however important to follow-up these patients within the BILAGBR as the long term safety and efficacy of other biologic therapy in SLE requires monitoring, regardless of the numbers initially receiving the therapy. The fact that many of these will be used after rituximab means that valuable data will be recorded on whether specific “sequences” of biologic therapy have any obvious adverse events.

## 5. Auditing the conduct of the study and research governance

The following coordinated program will ensure quality control

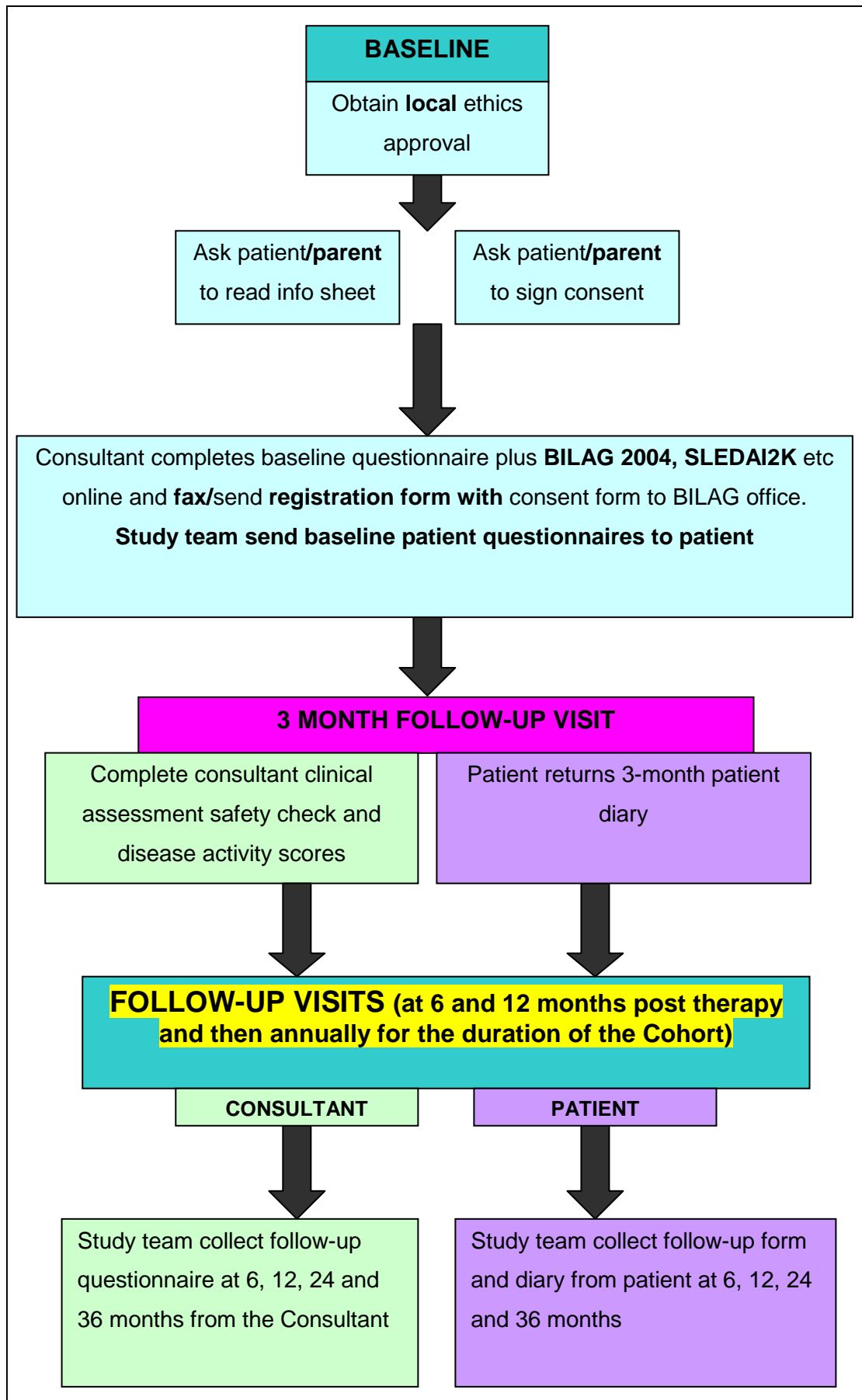
1. Training of staff
2. Online manual will be provided for clinicians to send in quality data, including worksheets for collection of data
3. Quality checks will be made for all data received (i.e. scanning for completeness, errors and database examined for inconsistencies.)
4. Selected serious adverse events (SAEs) will be checked against a set of predefined validation criteria

## 6. Summary Study flow charts

Data captured	Time post therapy					
	Baseline	3 months	6 months	12 months	24 months	36 months
Consent	✓					
Patient ID	✓					
Clinical assessment	✓	✓	✓	✓	✓	✓
Co-morbidities	✓					
Concomitant medications	✓	✓	✓	✓	✓	✓
Pregnancy*	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓
<b>SLE details</b>						
BILAG Index 2004	✓	✓	✓	✓	✓	✓
SLEDAI-2K	✓	✓	✓	✓	✓	✓
SLICC Damage Index	✓			✓	✓	✓
Prior therapy	✓					
<b>Patient Questionnaire</b>						
EuroQol / EQ5D	✓	✓	✓	✓	✓	✓
SF-36	✓	✓	✓	✓	✓	✓
LupusQoL	✓	✓	✓	✓	✓	✓

Patient diary	✓	✓	✓	✓	✓	✓
Employment	✓	✓	✓	✓	✓	✓
Drinking	✓	✓	✓	✓	✓	✓
Smoking	✓	✓	✓	✓	✓	✓
Women's health	✓	✓	✓	✓	✓	✓
<b><u>Bloods (drawn at routine monitoring time points only)</u></b>						
Basic laboratory values, e.g. Auto antibody profiles Complement fractions Total cholesterol HDL Fasting blood glucose ESR/CRP Immunoglobulins Serology	✓					
DNA	✓					
mRNA	✓		✓			
Plasma	✓	✓	✓	✓		
serum	✓	✓	✓	✓		
<b><u>Urine (from routinely collected samples)</u></b>	✓	✓	✓	✓		

\*Pregnancy: Specific prompts in the consultant follow-up forms with additional questionnaires if yes to follow specific outcome.



## **7. Baseline data**

It will be necessary to collect comprehensive baseline data to allow us to adjust for potential confounders in the analysis. To protect the confidentiality of participants, a unique patient identifier will be assigned to each patient on registration. Each participant's identifiable data will then be stored separately from the data to be stored in the cohort study.

Ascertainment of data will be from a combination of methods: patient interview and examination by their doctor or a trained deputy, e.g. research nurse, patient questionnaire and patient diaries. Data will be entered online by the patient's doctor (or allocated trained deputy) using a secure web-based data entry system. The patient's record will be identified by the unique study ID only.

### **7.1. Patient Identification (to be stored separately for confidentiality)**

- Surname
- Forenames
- Address
- Telephone number
- Gender
- Date of Birth
- NHS number (Chi number Scotland) (health and care number Northern Ireland)
- Hospital unit number if above not known
- Lead Consultant(s) for their SLE
- Code for Centre

### **7.2. Data Collected to appear in cohort study**

- Patient identification unique number
- Code for centre
- Gender
- Ethnicity
- Date of Birth
- Date of registration
- Employment status

### **7.3. Consultant and nurse collected information (see current version of the Consultant data collection Questionnaire)**

- Baseline examination – to include blood pressure, height, weight, BMI and waist circumference
- Comprehensive SLE details – to include ACR criteria met and timing of diagnosis
- Biologic therapy data (in treatment cohort only) – to include organ system responsible for treatment, previous treatments and reasons for biologics treatment
- Baseline activity of SLE and health status – to include use of BILAG 2004 Index (Isenberg, Rahman, Allen, Farewell, Akil, Bruce, D'Cruz, Griffiths, Khamashta, Maddison, McHugh, Snaith, Teh, Yee, Zoma, & Gordon 2005), SLEDAI 2K (Gladman, Ibanez, & Urowitz 2002), SLICC/ACR Damage Index (Gladman et al. 1996)
- Current and prior therapy – to include exposure to non-biologic immunosuppressive drugs, Glucocorticoid exposure from time of SLE diagnosis, Antimalarials, NSAIDS
- Risk factors for infection – to include hepatitis B, hepatitis C, leg ulcers, catheterisation, hyposplenism, splenectomy
- Vaccination history
- Medical history and co-morbidity data - to include angina, heart attack, stroke, epilepsy, asthma, renal disease, raised creatinine, immunodeficiency syndromes (for full list see current version of the questionnaire)
- Concomitant medications
- Results from routine laboratory tests within the previous 6 months, to include:
  - Auto antibody profiles
    - ANA, Ds DNA, Ro, La, Sm, RNP, Scl-70, Centromere
  - Complement fractions
    - C3, C4
  - Total cholesterol
  - HDL
  - Fasting blood glucose
  - ESR/CRP
  - Immunoglobulins

#### **7.4. Patient collected information (see current versions of the Patient data collection Questionnaires)**

- Health status and quality of life data to be collected to include instruments such as:
  - EQ5D (2 mins) (The EuroQol Group 1990)
  - SF-36 (10 mins)
  - LupusQoL (10 mins) (McElhone, Abbott, Shelmerdine, Bruce, Ahmad, Gordon, Peers, Isenberg, Ferenkeh-Koroma, Griffiths, Akil, Maddison, & Teh 2007)
  - lifestyle questionnaire (10 mins)
    - Smoking status
    - Alcohol consumption
    - Women's health
  - patient diary recording hospital admissions, visits to outpatients and medications

#### **7.5. Laboratory investigations**

Biological samples will be collected from each patient and the BILAG group will coordinate the scientific questions that can be addressed using the relevant material.

A DNA repository will also be established for pharmacogenetic analysis in particular we are interested in predictors of severity and clinical response. Such genes reported to alter phenotype and clinical response in SLE include, complement pathway genes, mannose binding lectin, FCgamma receptor 2A and 3A as well as interferon responsive genes.

DNA will be collected at baseline only, with bloods for serum analysis collected at baseline and at 3, 6 and 12 months post therapy. These blood samples will be taken at the same time as routine bloods are taken. If the patient is not due a routine blood test, then no blood will be collected for that visit and the blood will be collected at the next routine blood test. The patient will be given the opportunity to opt into this separately from the rest of the study.

A urine sample is routinely taken from SLE patients as part of standard of care screening for nephritis and possible infection, the residual sample will also be saved at baseline and at 3, 6 and 12 months post therapy from each patient. This sample will therefore be aliquoted from a routine urine sample. If the patient is unable to

provide a routine urine sample, then no urine will be collected from the patient at this visit and the urine will be collected at the next routine appointment.

#### DNA analysis:

Future analyses will involve the analysis of genes with the potential to predict clinical and drug-specific outcomes of SLE, including genes involved in the susceptibility and pathogenesis of SLE as well as genes in the relevant pharmacogenetic pathways. Such genes include complement pathway genes, mannose binding lectin, FCgamma receptor 2A and 3A as well as interferon responsive genes.

Analysis will be undertaken when sufficient samples have been collected and the relevant outcome is known. This work will be performed by investigators within the BILAG group or by investigators collaborating with BLAG.

#### Blood and urine analysis:

The blood and urine will be used to analyse serological and biochemical markers that may predict clinical response and specific clinical outcomes in SLE patients, for example urinary MCP-1 and urinary TGF $\beta$ , and also serum autoantibodies, endothelial microparticles and VEGF.

Analysis will be undertaken when sufficient samples have been collected and the relevant outcome is known. This work will be performed by investigators within the BILAG group or by investigators collaborating with BLAG.

Patients will be given the opportunity to consent to their samples being shared with other collaborating groups. This will allow applications for samples to be considered by the steering group.

## **8. Follow-up data**

Recorded at 3, 6, 12, 24 and 36 months post therapy for the duration of the project. The following data will be collected:

### **8.1. Consultant Follow-up**

- Changes to the patient's biological therapy and reasons for changes
- Change in the patient's concomitant medication
- Information on any adverse events – with prompts for serious infection, infusion reactions, immunological reactions. Adverse events will be classified

according to the new pharmaceutical standard Medical Dictionary for Regulatory Authorities (MedDRA) coding (latest version)

- Current SLE activity and health status
- Vital status
- Pregnancy status
- Results from routine laboratory tests within the previous 6 months, to include(where relevant):
  - Auto antibody profiles
    - ANA, Ds DNA, Ro, La, Sm, RNP, Scl-70, Centromere
  - Complement fractions
    - C3, C4
  - Total cholesterol
  - HDL
  - Fasting blood glucose
  - ESR/CRP
  - Immunoglobulins

## **8.2. Postal questionnaire to patients and patient diaries**

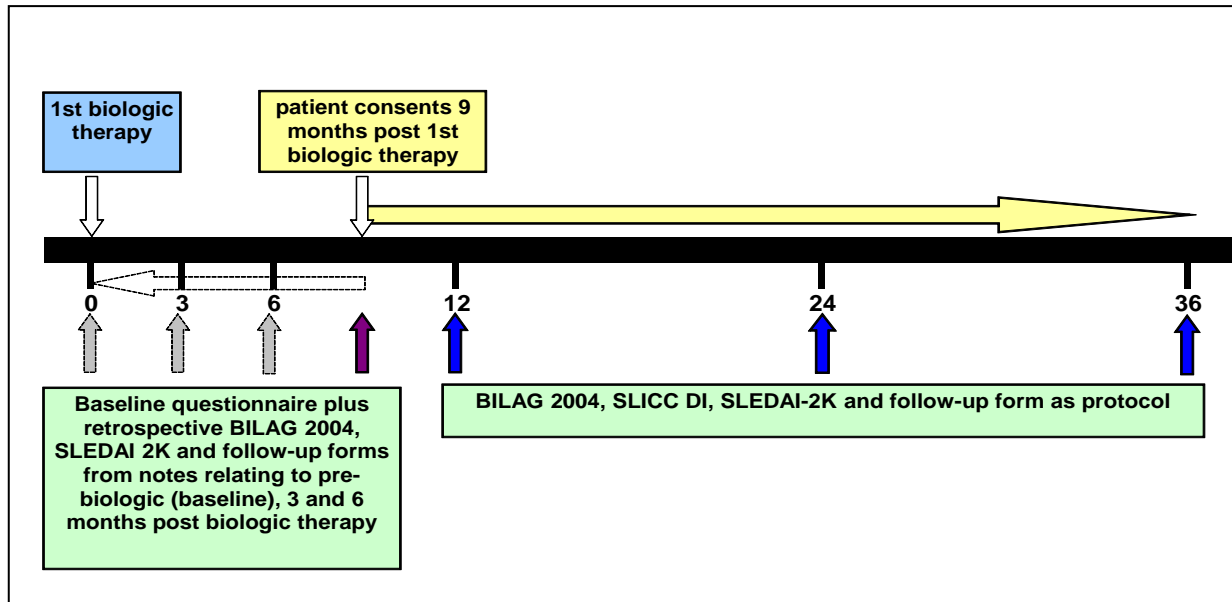
- Health status and quality of life data to be collected to include the instruments such as:
  - EQ5D (The EuroQol Group 1990) (2 mins)
  - SF-36
  - LupusQoL (10 mins) (McElhone, Abbott, Shelmerdine, Bruce, Ahmad, Gordon, Peers, Isenberg, Ferenkeh-Koroma, Griffiths, Akil, Maddison, & Teh 2007)
  - lifestyle questionnaire (10 mins)
- Add any missing data from registration
- Patient diaries
  - New hospital referrals or admissions
  - New medications

## **8.3. Retrospectively recruited patients**

**As described in section 3.2.1., participants are eligible to participate in the study, and be recruited into the biologics arm if they have had their first treatment with a biologic therapy in the last 12 months. Some patients may therefore have been recruited after their 3 and 6 months follow-up visits would have taken place. To ensure that important information is not missed relating**



to the time period immediately after their biologic therapy, the consultant follow-up questionnaire, BILAG 2004 and SLEDAI 2K will be completed from their notes to correspond to the participant's baseline, 3 and 6 months visit, where necessary. The example below outlines this for a patient recruited 9 months post initial biologic therapy



#### 8.4. NHS Information Centre (NHS-IC)

All exposed and control individuals will be “flagged” with the NHS Information Centre and the NHS Central Register for continuous surveillance and notification of mortality and the development of any malignancy. A copy of the death certificate will be obtained for those who die and details of type and site of cancer for those who develop a malignancy will be provided.

### 9. Analysis

#### 9.1. Primary endpoint for evaluation

- Any infection requiring hospitalisation

#### 9.2. Secondary endpoints for evaluation

Secondary endpoints fall into two categories; those to do with the safety of biologic therapy in patients with SLE, and those concerning the efficacy of biologic therapy in SLE patients

### **9.2.1. Safety**

- Serious adverse event (**according to WHO definition**), other than death
- Death and cause of death
- Malignancy

### **9.2.2. Efficacy**

- Clinical response
- Damage

## **9.3. Hypotheses to test**

1. Biologic therapy is associated with an increase in hospitalisation for infection when compared to patients on conventional, non-biologic therapy
  - a. Increased risk is related to the duration of therapy
  - b. Baseline characteristics determine increased risk, especially prior therapy
2. Biologic therapy reduces the disease activity when compared to patients on conventional, non-biologic therapy
3. Biologic therapy reduces the damage accrued when compared to patients on conventional, non-biologic therapy
4. Biologic therapy exposure reduces steroid use over 3 years in SLE
5. Certain longitudinal combinations of treatment carry higher risks
6. Novel genetic and serum/urine biomarkers will predict changes in inflammatory disease burden over time in SLE patients treated with biological therapy.

## **9.4. Analytic approach**

The initial analyses will consist of comparisons in baseline status between the individuals in the treatment cohorts. For the purposes of analysis (initially) follow up time will be censored in the standard therapy cohort if there is switching to a biologic agent. The adverse events of interest are calculated per person time of follow up, following the start of therapy. Depending on the events, separate analyses are undertaken (i) restricting consideration to time on drug, which includes the period within 90 days of last injection (ii) including the window 26 weeks after the last injection and (iii) all person time following start of therapy e.g. malignancy. Time-dependent regression analyses will be undertaken to compare event rates between groups after adjusting for baseline and other differences.

### **9.5. Interim Analyses**

Interim analyses will be undertaken at appropriate intervals when sufficient person years of exposure have been accumulated in the exposed group. Such analyses will be a guide to the ultimate levels of recruitment and length of follow up required. Decisions as to the timing of publications and the need for continued follow up and/or recruitment can only be taken in the light of results from such analyses.

A Data Monitoring and Ethics Committee (DMEC) will be established, analogous to a Data Safety & Monitoring Board established for major clinical trials. The DMEC will be independent of the principal investigators and also of any of the pharmaceutical industries involved, and will have the power to request interim analyses and advise on the timing and nature of any publications. The DMEC will include one epidemiologist, a rheumatologist and a statistician.

### **10. Roles of interested parties**

The University of Manchester will be the sponsor of the BILAG Biologics Prospective Cohort and BILAG will have ownership of the data. The project will be steered by a steering group and data monitoring and ethics committee (DMEC) under the auspices of the BILAG and will operate independently from direct industry involvement.

#### **10.1. Role of pharmaceutical companies**

- Funding
- Access
- Intellectual Property

#### **10.2. Role of BILAG**

BILAG will be the owner of the data that emerge from the study and will form the Steering Committee. The study coordinator will report on a quarterly basis to such committees that the BILAG deem appropriate. The membership of the DMEC will be subject to the approval of BILAG.

## References

Anolik, J. H., Barnard, J., Owen, T., Zheng, B., Kemsheiti, S., Looney, R. J., & Sanz, I. 2007, "Delayed memory B cell recovery in peripheral blood and lymphoid tissue in systemic lupus erythematosus after B cell depletion therapy", *Arthritis Rheum.*, vol. 56, no. 9, pp. 3044-3056.

Bosch, X., Guilabert, A., Pallares, L., Cerveral, R., Ramos-Casals, M., Bove, A., Ingelmo, M., & Font, J. 2006, "Infections in systemic lupus erythematosus: a prospective and controlled study of 110 patients", *Lupus*, vol. 15, no. 9, pp. 584-589.

Cambridge, G., Isenberg, D. A., Edwards, J. C., Leandro, M. J., Migone, T. S., Teodorescu, M., & Stohl, W. 2008, "B cell depletion therapy in systemic lupus erythematosus: relationships among serum B lymphocyte stimulator levels, autoantibody profile and clinical response", *Ann.Rheum.Dis.*, vol. 67, no. 7, pp. 1011-1016.

Contreas, G., Pardo, V., Leclercq, B., Lenz, O., Tozman, E., O'Nan, P., & Roth, D. Sequential therapies for proliferative lupus nephritis. *N Engl J Med.* 350[10], 971-980. 2004.

Ref Type: Generic

Dixon, W. G., Watson, K., Lunt, M., Hyrich, K. L., Silman, A. J., & Symmons, D. P. 2006, "Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register", *Arthritis Rheum.*, vol. 54, no. 8, pp. 2368-2376.

Ginzler, E. M., Dooley, M. A., Aranow, C., Kim, M. Y., Buyon, J., Merrill, J. T., Petri, M., Gilkeson, G. S., Wallace, D. J., Weisman, M. H., & Appel, G. B. 2005, "Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis", *N.Engl.J.Med.*, vol. 353, no. 21, pp. 2219-2228.

Gladman, D., Ginzler, E., Goldsmith, C., Fortin, P., Liang, M., Urowitz, M., Bacon, P., Bombardieri, S., Hanly, J., Hay, E., Isenberg, D., Jones, J., Kalunian, K., Maddison, P., Nived, O., Petri, M., Richter, M., Sanchez-Guerrero, J., Snaith, M., Sturfelt, G., Symmons, D., & Zoma, A. 1996, "The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus", *Arthritis Rheum.*, vol. 39, no. 3, pp. 363-369.

Gladman, D. D., Hussain, F., Ibanez, D., & Urowitz, M. B. 2002, "The nature and outcome of infection in systemic lupus erythematosus", *Lupus*, vol. 11, no. 4, pp. 234-239.

Gladman, D. D., Ibanez, D., & Urowitz, M. B. 2002, "Systemic lupus erythematosus disease activity index 2000", *J.Rheumatol.*, vol. 29, no. 2, pp. 288-291.

Hay, E. M., Bacon, P. A., Gordon, C., Isenberg, D. A., Maddison, P., Snaith, M. L., Symmons, D. P., Viner, N., & Zoma, A. 1993, "The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus", *Q.J.Med.*, vol. 86, no. 7, pp. 447-458.

Hayat, S. J. & Uppal, S. S. 2007, "Therapeutic efficacy and safety profile of infliximab in active systemic lupus erythematosus", *Mod.Rheumatol.*, vol. 17, no. 2, pp. 174-177.

Hayat, S. J., Uppal, S. S., Narayanan Nampoory, M. R., Johny, K. V., Gupta, R., & Al-Oun, M. 2007, "Safety and efficacy of infliximab in a patient with active WHO class IV lupus nephritis", *Clin.Rheumatol.*, vol. 26, no. 6, pp. 973-975.

Houssiau, F. A., Vasconcelos, C., D'Cruz, D., Sebastiani, G. D., Garrido Ed, E. R., Danieli, M. G., Abramovicz, D., Blockmans, D., Mathieu, A., Direskeneli, H., Galeazzi, M., Gul, A., Levy, Y., Petera, P., Popovic, R., Petrovic, R., Sinico, R. A., Cattaneo, R., Font, J., Depresseux, G., Cosyns, J. P., & Cervera, R. 2002, "Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide", *Arthritis Rheum.*, vol. 46, no. 8, pp. 2121-2131.

Human Genome Sciences. Human Genome Sciences and Glaxo Smith Kline announce positive results in second of two Phase 3 trials of BENLYSTA™ in systemic lupus erythematosus. [www.hgsi.com/latest/human-genome-sciences-and-glaxosmithkline-announce-positive-results-in-second-of-two-phase-3-trials-of-benlysta-in-systemic-lupus-erythema.html](http://www.hgsi.com/latest/human-genome-sciences-and-glaxosmithkline-announce-positive-results-in-second-of-two-phase-3-trials-of-benlysta-in-systemic-lupus-erythema.html) , last accessed Nov 28th 2009. 2009.  
Ref Type: Generic

Hyrich, K. L., Lunt, M., Dixon, W. G., Watson, K. D., & Symmons, D. P. 2008, "Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug", *Rheumatology.(Oxford)*, vol. 47, no. 7, pp. 1000-1005.

Isenberg, D. A., Rahman, A., Allen, E., Farewell, V., Akil, M., Bruce, I. N., D'Cruz, D., Griffiths, B., Khamashta, M., Maddison, P., McHugh, N., Snaith, M., Teh, L. S., Yee, C. S., Zoma, A., & Gordon, C. 2005, "BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus", *Rheumatology.(Oxford)*, vol. 44, no. 7, pp. 902-906.

Jonsdottir, T., Gunnarsson, I., Risselada, A., Henriksson, E. W., Klareskog, L., & van Vollenhoven, R. F. 2008, "Treatment of refractory SLE with rituximab plus cyclophosphamide: clinical effects, serological changes, and predictors of response", *Ann.Rheum.Dis.*, vol. 67, no. 3, pp. 330-334.

Leandro, M. J., Cambridge, G., Edwards, J. C., Ehrenstein, M. R., & Isenberg, D. A. 2005, "B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients", *Rheumatology.(Oxford)*, vol. 44, no. 12, pp. 1542-1545.

McElhone, K., Abbott, J., Shelmerdine, J., Bruce, I. N., Ahmad, Y., Gordon, C., Peers, K., Isenberg, D., Ferenkeh-Koroma, A., Griffiths, B., Akil, M., Maddison, P., & Teh, L. S. 2007, "Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus", *Arthritis Rheum.*, vol. 57, no. 6, pp. 972-979.

Merrill, J. T., Neuwelt, C. M., Wallace, D. J., Shanahan, J. C., Latinis, K. M., Oates, J. C., Utset, T. O., Gordon, C., Isenberg, D. A., Hsieh, H. J., Zhang, D., & Brunetta, P. G. 2008, "Efficacy and Safety of Rituximab in Patients with Moderately to Severely Active Systemic Lupus Erythematosus (SLE): Results from the Randomized, Double-

blind Phase II/III Study EXPLORER", *Arthritis and Rheumatism*, vol. 58, no. 12, pp. 4029-4030.

Micheloud, D., Nuno, L., Rodriguez-Mahou, M., Sanchez-Ramon, S., Ortega, M. C., Aguaron, A., Junco, E., Carbone, J., Fernandez-Cruz, E., Carreno, L., & Lopez-Longo, F. J. 2006, "Efficacy and safety of Etanercept, high-dose intravenous gammaglobulin and plasmapheresis combined therapy for lupus diffuse proliferative nephritis complicating pregnancy", *Lupus*, vol. 15, no. 12, pp. 881-885.

Ng, K. P., Cambridge, G., Leandro, M. J., Edwards, J. C., Ehrenstein, M., & Isenberg, D. A. 2007, "B cell depletion therapy in systemic lupus erythematosus: long-term follow-up and predictors of response", *Ann.Rheum.Dis.*, vol. 66, no. 9, pp. 1259-1262.

Petri, M. & Genovese, M. 1992, "Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort", *J Rheumatol.*, vol. 19, no. 10, pp. 1559-1565.

Takahashi, N., Naniwa, T., & Banno, S. 2008, "Successful use of etanercept in the treatment of acute lupus hemophagocytic syndrome", *Mod.Rheumatol.*, vol. 18, no. 1, pp. 72-75.

The EuroQol Group 1990, "EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group", *Health Policy*, vol. 16, no. 3, pp. 199-208.

Trial watch 2009, "Trial watch: BLYS-targeted antibody shows promise in Phase III SLE trial", *Nat.Rev.Drug Discov.*, vol. 8, no. 9, p. 688.

UCB Pharmaceuticals. UCB and Immunomedics announce positive results for epratuzumab phase IIb study in systemic lupus erythematosus (SLE). [www.ucb.com/media-room/newsdetail/?det=1337304](http://www.ucb.com/media-room/newsdetail/?det=1337304) . 2009.

Ref Type: Generic

## Appendix 1

<b>Disease in unexposed</b>	<b>Relative risk</b>	<b>unexposed</b>	<b>exposed</b>	<b>Total</b>
5%	2	474	474	948
10%	2	219	219	438
15%	2	133	133	266
20%	2	91	91	182

Using stat calc (epi info) 95% confidence level 80% power 1 to 1 ratio in each cohort

**Single Technology Appraisal (STA)**

**Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (ID416)**

Dear [REDACTED],

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have now had an opportunity to take a look at the submission received in May 2014 by GlaxoSmithKline. The ERG would like further clarification relating to the cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm on 24<sup>th</sup> September**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under '**commercial in confidence**' in turquoise, and all information submitted under '**academic in confidence**' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Ian Watson, Technical Lead ([ian.watson@nice.org.uk](mailto:ian.watson@nice.org.uk)) and Zoe Garrett, Technical Adviser ([zoe.garrett@nice.org.uk](mailto:zoe.garrett@nice.org.uk)). Any procedural questions should be addressed to Kate Moore, Project Manager ([kate.moore@nice.org.uk](mailto:kate.moore@nice.org.uk)) in the first instance.

Yours sincerely

**Helen Knight**  
Associate Director – Appraisals  
Centre for Health Technology Evaluation



Encl. checklist for in confidence information

**Clarification on cost-effectiveness data**

A1. The revised model contains additional regression parameters for the modelling of the SS score at week 52. Please provide the functional forms for the following four hypothetical patients for the values that would be entered into the regression for the dependent and explanatory variables as functions of the regression parameters to be estimated;

- A SoC non-responder with a baseline SS score of 12 and a 52 week SS score of 9
- A SoC responder with a baseline SS score of 12 and a 52 week SS score of 6
- A belimumab non-responder with a baseline SS score of 12 and a 52 week SS score of 9
- A belimumab responder with a baseline SS score of 12 and a 52 week SS score of 6

For instance, in effect the first patient might be something along the lines of:

$$9 = 12 * [1 + \beta_{\text{SoC}} * 1 + \beta_{\text{SoC\_R}} * 1 + \beta_{\text{Bel}} * 0 + \beta_{\text{Bel\_R}} * 0]$$

Or re-arranging:

$$[(9/12) - 1] = \beta_{\text{SoC}} * 1 + \beta_{\text{SoC\_R}} * 1 + \beta_{\text{Bel}} * 0 + \beta_{\text{Bel\_R}} * 0$$

Please also outline whether this regression analysis was a simple OLS linear regression or took some other form.

A2. The additional regression parameters for the modelling of the SS score at week 52 appear to suggest the following for SoC responders and for belimumab responders.

- SoC effect =  $SS0_{\text{SoC}} + SS0_{\text{SoC\_R}} = -0.25359 - 0.14358 = -0.39717$
- Belimumab effect =  $SS0_{\text{Bel}} + SS0_{\text{Bel\_R}} = -0.34346 - 0.28001 = -0.62347$

Please clarify, if this is the correct interpretation of the parameters; i.e. that on average a SoC responder experiences a 39.7% reduction in SS scores by week

52 and on average a belimumab responder experiences a 62.3% reduction in SS scores by week 52?

- A3. Please clarify whether the SS regression with the parameter estimates  $-0.25359$ ,  $-0.14358$ ,  $-0.34346$  and  $-0.28001$  is estimated using only data from the target population?

**Single Technology Appraisal (STA)**

**Belimumab for the treatment of active autoantibody-positive systemic lupus  
erythematosus (ID416)**

**GlaxoSmithKline UK Response to Clarification on Cost-Effectiveness Data – 23/09/14**

A1. The revised model contains additional regression parameters for the modelling of the SS score at week 52. Please provide the functional forms for the following four hypothetical patients for the values that would be entered into the regression for the dependent and explanatory variables as functions of the regression parameters to be estimated;

- A SoC non-responder with a baseline SS score of 12 and a 52 week SS score of 9
- A SoC responder with a baseline SS score of 12 and a 52 week SS score of 6
- A belimumab non-responder with a baseline SS score of 12 and a 52 week SS score of 9
- A belimumab responder with a baseline SS score of 12 and a 52 week SS score of 6

For instance, in effect the first patient might be something along the lines of:

$$9 = 12 * [1 + \beta_{SoC} * 1 + \beta_{SoC\_R} * 1 + \beta_{Bel} * 0 + \beta_{Bel\_R} * 0]$$

Or re-arranging:

$$[(9/12) - 1] = \beta_{SoC} * 1 + \beta_{SoC\_R} * 1 + \beta_{Bel} * 0 + \beta_{Bel\_R} * 0$$

Please also outline whether this regression analysis was a simple OLS linear regression or took some other form.

***The week 52 SS score is a result of the regression and baseline SS score. SoC responder status is not modelled, instead the original regression is used:***

$$SS_{52} = SS_0 + \beta_{SOC} * SS_0 = SS_0 * (1 + \beta_{SOC}) = SS_0 * (1 - 0.349)$$

***In the case of a 12 point score at baseline for a SoC patient, irrespective of responder status, its 52 week score will be:***

$$SS_{52} = 12 * (1 - 0.349) = 7.81$$

***The new regression analysis is used for a belimumab non-responder, who gets withdrawn from treatment (which automatically happens when using the responder rule SS reduction  $\geq 4$  at week 24). This patient's SS score after 52 weeks is based on the following regression analysis:***

$$SS_{52} = SS_0 + \beta_{SOC\_NR} * SS_0 = SS_0 * (1 + \beta_{SOC\_NR}) = SS_0 * (1 - 0.254)$$

***In the case of a 12 point score at baseline for a belimumab non-responder, its 52 week score will be***

$$SS_{52} = 12 * (1 - 0.254) = 8.95$$

***For a belimumab responder, the original regression is again used:***

$$SS_{52} = SS_0 + \beta_{BEL} + \beta_{BEL\_R} = SS_0 * (1 + \beta_{BEL} + \beta_{BEL\_R}) = SS_0 * (1 - 0.343 - 0.280)$$

***In the case of a 12 point score at baseline for a belimumab responder, its 52 week score will be***

$$SS_{52} = 12 * (1 - 0.343 - 0.280) = 4.52$$

A2. The additional regression parameters for the modelling of the SS score at week 52 appear to suggest the following for SoC responders and for belimumab responders.

- SoC effect =  $SS_0\_SoC + SS_0\_SoC\_R = -0.25359 - 0.14358 = -0.39717$
- Belimumab effect =  $SS_0\_Bel + SS_0\_Bel\_R = -0.34346 - 0.28001 = -0.62347$

Please clarify, if this is the correct interpretation of the parameters; i.e. that on average a SoC responder experiences a 39.7% reduction in SS scores by week 52 and on average a belimumab responder experiences a 62.3% reduction in SS scores by week 52?

***Yes, this is the correct interpretation for SoC and belimumab responders. However please note that SoC response status is not modelled. Instead, the average SoC in total (combining SoC responders and non-responders) from the original regression is used: 34.9% reduction on average for SoC.***

- A3.** Please clarify whether the SS regression with the parameter estimates  $-0.25359$ ,  $-0.14358$ ,  $-0.34346$  and  $-0.28001$  is estimated using only data from the target population?

***Yes, these regression parameters are based on data using the target population only.***



## **Title of Report: Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus**

Produced by: Warwick Evidence

Lead author: Ewen Cummins

Co-authors: Martin Connock  
Aileen Clarke  
Paul Sutcliffe

**Correspondence to:** Dr Paul Sutcliffe  
Associate Professor  
Deputy Director for Warwick Evidence  
Populations, Evidence and Technologies  
Division of Health Sciences  
Warwick Medical School  
University of Warwick  
Coventry CV4 7AL

Tel: 02476 150189

Fax: 02476 528375

Email: [p.a.sutcliffe@warwick.ac.uk](mailto:p.a.sutcliffe@warwick.ac.uk)

**Date completed:** 2 October 2014

**Source of funding:** This report was commissioned by the NIHR HTA Programme as project number ID416.

**Competing interests:** None.

**Rider on responsibility for report:** The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme, who commissioned the report.

**Acknowledgements:** Thank you to Professor Caroline Gordon for her valuable clinical comments.

## **ERG report on GSK submission for belimumab of the 9<sup>th</sup> May 2014**

### **ERG brief**

NICE requested that the ERG:

- Identify whether given the assumptions stated by the manufacturer, the ICERs presented in their new submission are correct.
- Correct any errors identified in the revised model and analyses in the new submission.
- Review the additional analysis that assumes a different SLEDAI score for belimumab non-responders and whether this addresses the uncertainty identified in the original ERG report.
- Undertake additional analyses varying the assumed maximum duration of belimumab treatment to reflect the previous discussions of the assessment committee.

The following provides this, coupled with some comment about the value of information and the GSK budget impact section.

### **GSK submission of 9<sup>th</sup> May 2014**

GSK proposes that patients should be treated with belimumab for a minimum of three years, though the proposal goes on to suggest up to five years data collection may be required. During this time further data would be collected on “real-life” efficacy, safety and quality of life.

The GSK submission presents analyses that:

- Restrict the patient population to those with low complement and anti-dsDNA and a baseline SLEDAI (SS) score of at least 10.
- Assume that treatment will be withdrawn at week 24 among non-responders; i.e. those not achieving a reduction of at least 4 SS points at week 24.
- Have a natural discontinuation rate of 8% in the first year of treatment, and 11.7% thereafter among belimumab 24 week responders.
- Assume a maximum treatment duration of 3 years or of 5 years.
- Assume that those discontinuing belimumab treatment revert to the mean SS score of the control arm (SoC).
- Have a lifetime horizon.

A range of scenario analyses are also presented.

- A maximum treatment duration of 4 years.
- Excluding the treatment continuation rule at 24 weeks.
- Applying a more stringent treatment continuation rule of a reduction at least 6 SS points at week 24.

- Assuming an 8% discontinuation rate among belimumab 24 week responders.
- Assuming that belimumab week 24 non-responders adopt the SS score of SoC week 24 non-responders, due to them having belimumab treatment withdrawn. This is also coupled with an assumption that those discontinuing belimumab treatment for other reasons adopt the SS score of SoC week 24 responders. This analysis requires a revised SS regression as outlined below.

Table 1: Change in SS scores between baseline and 52 weeks: Target population

	Old	New
$\beta_{\text{SoC}}$	-34.9%	-25.4%
$\beta_{\text{SoC Responder}}$	..	-14.4%
$\beta_{\text{Belimumab}}$	-34.3%	-34.3%
$\beta_{\text{Belimumab Responder}}$	-28.0%	-28.0%

All parameters in both regressions were significant at the 1% level. The estimates in Table 1 show that the pooled average change in the SS score between baseline and 52 weeks for the SoC arm was a drop of 34.9%. Due to the model implementation within the visual basic, this parameter is retained within the revised model for the SoC arm.

Within the belimumab arm, among those discontinuing due to non-response at week 24 their SS score is modelled as differing from that in the SoC arm by -25.4% minus -34.3% = +9.5% of their baseline SS score. In other words a belimumab non responder with a baseline SS score of 15 is modelled as being  $15 * 9.5\% = 1.43$  SS points worse than the SS score in the pooled SoC arm. Similarly, among those responders discontinuing after week 24 their SS score is modelled as differing from that in the SoC arm by -25.4% plus -14.4% minus -34.3% = -4.9% of their baseline SS score. In other words a belimumab responder with a baseline SS score of 15 who ceases treatment is modelled as being  $15 * 4.9\% = 0.74$  SS points better than the SS score in the pooled SoC arm.

The following results are from ERG model re-runs. These present more detail but differ very slightly from those of the GSK submission of the 9<sup>th</sup> of May. The reasons for the discrepancies are unclear, but the discrepancies are extremely minor and are typically less than £10 either way on the ICER.

Note that the belimumab costs include both the drug cost and the administration cost, with administration costs being a quite significant ■■■ of these. Overall survival figures are presented as undiscounted life years (LY), while the quality adjusted life years (QALYs) and cost figures are discounted at 3.5%.



The results are presented for analyses that assume a maximum treatment duration of 3 years, 4 years and 5 years, with the results of the sensitivity analyses being presented for analyses that assume a maximum treatment duration of 3 years and 5 years (see Table 2).

Table 2: GSK submission cost effectiveness estimates

	SoC			Belimumab				Net effects			
	LY	QALY	Cost	LY	QALY	Belimumab	Cost	LY	QALY	Cost	ICER
3 year	31.93	9.81	██████	33.36	10.26	██████	██████	1.42	0.45	██████	██████
no resp. rule	31.93	9.81	██████	33.31	10.25	██████	██████	1.37	0.44	██████	██████
6pt resp. rule	31.93	9.81	██████	33.23	10.22	██████	██████	1.30	0.41	██████	██████
8% disc.	31.93	9.81	██████	33.39	10.27	██████	██████	1.46	0.46	██████	██████
alt disc.	31.93	9.81	██████	33.09	10.17	██████	██████	1.16	0.36	██████	██████
4 year	31.93	9.81	██████	33.63	10.33	██████	██████	1.70	0.52	██████	██████
5 year	31.93	9.81	██████	33.73	10.35	██████	██████	1.80	0.54	██████	██████
no resp. rule	31.93	9.81	██████	33.62	10.33	██████	██████	1.68	0.52	██████	██████
6pt resp. rule	31.93	9.81	██████	33.50	10.29	██████	██████	1.57	0.48	██████	██████
8% disc.	31.93	9.81	██████	33.80	10.37	██████	██████	1.87	0.56	██████	██████
alt disc.	31.93	9.81	██████	33.38	10.24	██████	██████	1.45	0.43	██████	██████

**ERG comments: The value of information**

The GSK proposal is that further data be collected in order to better inform the cost effectiveness estimates made for belimumab.

The primary question to be addressed would appear to be whether the proposed data collection is an efficient use of NHS resources. The expected cost effectiveness of treating patients with belimumab for three to five years and then ceasing their treatment does not answer this question.

It can be argued that answering this question requires an Expected Value of Sample Information (EVSI) analysis. Any formal EVSI analysis using the current model would be require it to be placed in the context of the other structural uncertainties, both those which can be quantified and those that cannot. The submission also does not demonstrate how the anticipated sample size is likely to be an optimal or an efficient use of NHS resources.

The submission is vague about what will happen to patients treated with belimumab should the NHS still conclude after three to five years’ data collection that belimumab is not cost effective. It mentions that “an appropriate strategy” would be agreed and that GSK would continue to “offer belimumab at the discounted PAS price for those patients remaining on belimumab”. This appears to suggest that those remaining on belimumab at the end of the data collection period would continue to be treated

with belimumab, with the drug and administration costs of this being borne by the NHS. This throws into question the relevance of the three and five year maximum treatment durations that have been modelled.

There may also be a question as to whether agreeing to the data collection proposal could set a precedent for other STAs. Manufacturer of other drugs that have been rejected during the STA process on cost effectiveness grounds might similarly argue that further data collection should be undertaken, with the NHS funding the drug and administration costs during the data collection periods.

### **ERG comments: Modelling the week 52 SS scores for those stopping belimumab treatment**

Within the model patients in the belimumab arm cease treatment for two reasons.

- Non-response, defined as a reduction in the SS score at 24 weeks of less than 4 points, at which point the model assumes that treatment is withdrawn.
- Discontinuation for other unspecified reasons

The 9 May 2014 GSK submission states that:

*As requested by the Appraisal Committee during discussions at previous Appraisal Committee Meetings, an analysis was conducted which assumed that belimumab non-responders (based on treatment discontinuation criterion of SLEDAI score <4 points at 24 weeks) continue with the average SLEDAI score of SoC non-responders after six months and belimumab responders, who withdraw for reasons other than due to lack of efficacy later, take the SLEDAI score of SoC responders.*

The ERG recalls discussions at previous Appraisal Committee Meetings requesting that belimumab non-responders continue with the average SLEDAI score of SoC non-responders after six months. The ERG does not recall discussions at previous Appraisal Committee Meetings requesting that belimumab responders, who withdraw for reasons other than due to lack of efficacy later, take the SLEDAI score of SoC responders.

Section 4.21 of the ACD<sup>1</sup> only discusses the treatment of patients receiving belimumab whose disease did not respond to treatment at 24 weeks, further noting that:

*alternative scenarios exploring the impact on the ICER with respect to the assumed mean benefit experienced by the patients whose disease did not respond to treatment in the belimumab group would help to better reflect the level of uncertainty.*

---

<sup>1</sup> <http://www.nice.org.uk/guidance/gid-tag273/resources/systemic-lupus-erythematosus-active-belimumab-appraisal-consultation-document>

The Summary of Appraisal Committee's key conclusions of the ACD also noted that:

*The Committee noted the ERG comments that, for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, it was assumed that at week 52 they had the mean benefit observed in the standard care group. The Committee concluded that GSK's approach may have overestimated the treatment effect of belimumab.*

In the light of the above, it does not appear justified for GSK to assert that the Appraisal Committee requested that belimumab responders, who withdraw for reasons other than due to lack of efficacy later, take the SLEDAI score of SoC responders.

But there is an arithmetic difficulty that arises from assuming that belimumab non-responders continue with the average SLEDAI score of SoC non-responders after six months. This value lies below the average SLEDAI score pooled across SoC non-responders and SoC responders. The model could simulate belimumab responders who withdraw for reasons other than due to lack of efficacy as then taking the SLEDAI score pooled across SoC non-responders and SoC responders. But doing so would mean that when all belimumab patients had withdrawn from treatment the average SLEDAI score among them would lie below the average SLEDAI score in the SoC arm.

In the opinion of the ERG, the most reasonable assumption that can be made is that made by the manufacturer: belimumab responders who discontinue treatment should adopt the mean SLEDAI score of SoC responders.

The ERG has cross checked the implementation of the revised model that applies the mean SoC non-responder SLEDAI score to belimumab non-responders and the mean SoC responder SLEDAI score to belimumab responders who discontinue treatment by:

- Examination of the changes to the visual basic code of the model.
- Examination of the model outputs, with scenario analyses of 0% of the belimumab arm being responders and 100% of the belimumab arm being responders but all ceasing treatment at the end of the first year<sup>2</sup>.
- Changing the parameter values within the excel worksheets while retaining the visual basic code of the revised model such that this should result in the same model outputs as the original model.

---

<sup>2</sup> This has only been explored by simplifying the model to equalise baseline characteristics such that all are female, white, age 40 and have a baseline SS score of 15 with a maximum treatment duration of 5 years. This was implemented within the *Subgroup\_BLISS\_Data* worksheet by setting cells P64=396, P78=0, Q7:Q28=0, Q29=396, Q30:Q62=0, Q185:Q199=0, Q200=196, Q201:Q215=0. The responder probabilities within cells AR9:AR30 were also all set to either 0% or 100%. The resulting difference between cells BS31 and BR31 in the *Results* worksheet correspond to those calculated by  $15 * inputSSRed4$  and  $15 * inputSSRed5$ , depending upon whether responders or non-responders were being examined.

These all suggest that the revisions to the model work as intended, given the stated assumptions.

### ERG modelling using the revised model

In the opinion of the ERG the revised model is most in line with that requested by the assessment committee. A number of additional analyses are presented below:

- Longer maximum durations of belimumab treatment, due to it being unclear whether patients would have their treatment guillotined at an arbitrary time point. Note that these retain an assumption of an 11.7% annual discontinuation rate among belimumab responders.
- Applying the original 2.0577 intercept value for the natural history model for the evolution of the SS score as drawn from the John Hopkins University cohort rather than the 3.0 value.
- An 8% discontinuation rate rather than the 11.7% that was drawn from the phase II extension trial<sup>3</sup>. This is to reflect the concerns expressed about the discontinuation rate among SLE sufferers with very active disease who respond well to belimumab possibly being lower than that observed on average during the phase II extension trial. GSK also notes that patients that need to stay on belimumab for long periods of time are likely to be those with very severe disease who are demonstrating significant benefits with belimumab.
- Assuming a cost function that is flat in the SS score<sup>4</sup> due to the previously concerns around both the method of the cost function deviation and the possibility of it double counting costs.
- For the 10 year and lifetime maximum treatment duration scenarios, the original modelling of those discontinuing belimumab having the mean SS score of the SoC arm, pooled between responders and non-responders.

Table 3: Additional ERG analyses: 3 year maximum treatment duration

	Δ Cost	Δ QALY	ICER
Base case	██████	0.360	██████
JHU SS model intercept	██████	0.339	██████
8% discontinuation	██████	0.368	██████
Same SS costs	██████	0.360	██████

<sup>3</sup> Implemented within the model in the *Treatment\_Effect* worksheet by setting cell L34=8%.

<sup>4</sup> Implemented within the model in the *Other\_Cost\_Inputs* worksheet by setting cells C35:C54 to be equal to cell C34.

Table 4: Additional ERG analyses: 5 year maximum treatment duration

	$\Delta$ Cost	$\Delta$ QALY	ICER
Base case	██████	0.430	██████
JHU SS model intercept	██████	0.406	██████
8% discontinuation	██████	0.444	██████
Same SS costs	██████	0.430	██████

Table 5: Additional ERG analyses: 10 year maximum treatment duration

	$\Delta$ Cost	$\Delta$ QALY	ICER
Base case	██████	0.518	██████
JHU SS model intercept	██████	0.452	██████
8% discontinuation	██████	0.559	██████
Same SS costs	██████	0.518	██████
Original model	██████	0.650	██████

Table 6: Additional ERG analyses: lifetime maximum treatment duration

	$\Delta$ Cost	$\Delta$ QALY	ICER
Base case	██████	0.563	██████
JHU SS model intercept	██████	0.462	██████
8% discontinuation	██████	0.646	██████
Same SS costs	██████	0.563	██████
Original model	██████	0.708	██████

Tables 3 to 6 present the deterministic estimates. The submitted model presented the means and standard errors of the revised regression equation for the modelling of week 52 SS scores, but the implementation of these within the submitted model is only deterministic.

It would be relatively simple to use the means and standard errors to make these elements probabilistic. But this might not be reasonable if there is a high degree of correlation between the estimates, as seems probable.

The current deterministic model, being built upon the structure of the original model, also adds the parameters of the revised regression to the parameters of the original regression. It is not clear whether it would be reasonable for the probabilistic modelling to add probabilistically implemented parameters from the revised regression to probabilistically implemented parameters from the original regression.

The concern about the correlation between the parameter estimates is sufficient for it to be questionable to undertake probabilistic modelling given the information currently available to the ERG. These are key parameters within the modelling, and characterisation of the uncertainty around the cost effectiveness estimates requires an accurate characterisation of the uncertainty around these parameters.

### ***Budget impact section***

The budget impact section is not entirely transparent. But based upon an administration cost of £154 for belimumab and £346 for rituximab<sup>5</sup> with 10 new patients incident each month during the first three years and 5 new patients incident each month during years 4 and 5 appears to suggest the following assumptions as in Table 7 or something akin to them have been made by GSK regarding the average number of rituximab doses.

Note that within Table 7 one dose of rituximab is taken to be 1000mg. Due to the dosing schedule for belimumab and the spread of incident patients over the year, this appears to have been assumed to result in around an average 7.21 administrations of belimumab during the first year.

The rituximab dosing schedules required to replicate the GSK figures appear peculiar, particularly in years 3 and 5. The ERG is also unclear about the source of the £346 for rituximab.

### **Conclusions**

In conclusion:

- The GSK costs effectiveness estimates are in line with the assumptions made and input values
- The GSK cost effectiveness estimates mainly range between around [REDACTED] and [REDACTED] per QALY
- An additional GSK analyses that address committee concerns about the modelling of belimumab non-responders worsen the cost effectiveness estimates to between [REDACTED] and [REDACTED] per QALY
- The GSK cost effectiveness estimates assume that all belimumab treatment will stop at either 3, 4 or 5 years which may limit their relevance
- The economics of the proposed data collection exercise might be better or more formally addressed through an Expected Value of Sample Information (EVSI) analysis
- ERG analysis using the original model with no limit to the maximum duration of belimumab treatment yields a cost effectiveness estimate of [REDACTED] per QALY
- ERG analyses using the revised model that addresses the handling of belimumab non-

---

<sup>5</sup> The text of Table 3 of the GSK submission suggests that this cost is applied for each vial, with a patient requiring two vials so two administration costs per 1000mg dose. It appears that the budget figures given do not assume this, and only assume that one £346 administration cost is incurred per 1000mg dose of rituximab.

responders yield cost effectiveness estimates of between around ■ and ■ per QALY

- The ERG has not been able to reproduce the GSK budget impact figures without making what appear to be peculiar assumptions

Table 7: ERG attempted replication of GSK Table 3: Summary of Estimated Budget Impact

	Belimumab				Rituximab				Net
	Doses	Drug	Admin	Total	Doses	Drug	Admin	Total	
Year 1									
Patients incident in year 1 (120)	7.2		£133,333		2	£419,112	£83,160	£502,272	
Year total			£133,333			£419,112	£83,160	£502,272	
Cumulative total			£133,333			£419,112	£83,160	£502,272	
Year 2									
Patients incident in year 1 (120)	13		£240,240		0	£0	£0	£0	
Patients incident in year 2 (120)	7.2		£133,333		2	£419,112	£83,160	£502,272	
Year total			£373,573			£419,112	£83,160	£502,272	
Cumulative total			£506,906			£838,224	£166,320	£1,004,544	
Year 3									
Patients incident in year 1 (120)	13		£240,240		2	£419,112	£83,160	£502,272	
Patients incident in year 2 (120)	13		£240,240		2	£419,112	£83,160	£502,272	
Patients incident in year 3 (120)	7.2		£133,333		4	£838,224	£166,320	£1,004,544	
Year total			£613,813			£1,676,448	£332,640	£2,009,088	
Cumulative total			£1,120,720			£2,514,672	£498,960	£3,013,632	
Year 4									
Patients incident in year 1 (120)	13		£240,240		0	£0	£0	£0	
Patients incident in year 2 (120)	13		£240,240		0	£0	£0	£0	
Patients incident in year 3 (120)	13		£240,240		1	£209,556	£41,580	£251,136	
Patients incident in year 4 (60)	7.2		£66,667		2	£209,556	£41,580	£251,136	
Year total			£787,387			£419,112	£83,160	£502,272	
Cumulative total			£1,908,106			£2,933,784	£582,120	£3,515,904	
Year 5									
Patients incident in year 1 (120)	13		£240,240		1	£209,556	£41,580	£251,136	
Patients incident in year 2 (120)	13		£240,240		3	£628,668	£124,740	£753,408	
Patients incident in year 3 (120)	13		£240,240		3	£628,668	£124,740	£753,408	
Patients incident in year 4 (60)	13		£120,120		3	£314,334	£62,370	£376,704	
Patients incident in year 5 (60)	7.2		£66,667		3	£314,334	£62,370	£376,704	
Year total			£907,507			£2,095,560	£415,800	£2,511,360	
Cumulative total			£2,815,613			£5,029,344	£997,920	£6,027,264	



**FURTHER EVIDENCE COLLECTION AND THE REIMBURSEMENT  
DECISION OF BELIMUMAB**

REPORT BY THE DECISION SUPPORT UNIT

1 October 2014

Eldon Spackman<sup>1</sup>

<sup>1</sup>Centre for Health Economics, University of York

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street  
Sheffield, S1 4DA

Tel (+44) (0)114 222 0734

E-mail [dsuadmin@sheffield.ac.uk](mailto:dsuadmin@sheffield.ac.uk)

Website [www.nicedsu.org.uk](http://www.nicedsu.org.uk)

Twitter [@NICE\\_DSU](https://twitter.com/NICE_DSU)

## **ABOUT THE DECISION SUPPORT UNIT**

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information [www.nicedsu.org.uk](http://www.nicedsu.org.uk)

The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

### **Acknowledgements**

The DSU would like to thank Emily Sutton and Ian Bruce from BILAG register for providing details of the register.

## EXECUTIVE SUMMARY

In the previous appraisal consultation document (ACD) the Committee did not recommend belimumab for treating active autoantibody-positive systemic lupus erythematosus (SLE). The Committee found that although there was some evidence of clinical effectiveness, belimumab was not cost-effective compared to standard of care using the patient access scheme price.

In the ACD the Committee also considered the manufacturer's suggestion that if belimumab was recommended for use in the NHS then real world evidence could be collected on the efficacy and safety of belimumab through a UK registry. The Committee determined that insufficient details were provided about the suggested data collection using the registry, and that "it could not reasonably expect belimumab to provide likely net benefits for all patients in the NHS while the research is carried out, and therefore that it could not accept the company's proposal" (4.28, [ACD 2013](#)).<sup>1</sup>

The manufacturer has now submitted more details on their proposed data collection. They proposed to use an established UK biologics registry for SLE and collect real world data on effectiveness, safety and quality of life on all patients prescribed belimumab following UK clinical practice over at least three years. The manufacturer provided details on data collection for many of the uncertainties raised in the previous ACD as well as collecting other data the manufacturer believes will demonstrate the benefits of belimumab.

The NICE Decision Support Unit (DSU) was asked to i) review the manufacturer's proposal, ii) discuss how the research proposal will address the uncertainties outlined in the ACD, iii) discuss any needed improvements to the data collection, iv) provide advice on the data available and how this data might be used to inform a final decision, and v) make recommendations for other research if appropriate.

The DSU found that the proposal accurately described the BILAG registry and some of the data that could be used to resolve the Committee's uncertainty, but the proposal did not provide important details such as whether a comparison with rituximab will be possible if belimumab receives a positive recommendation or details about how to adjust for selection bias. The proposal discusses many of the uncertainties outlined in the ACD but it is unlikely that the long-term comparative data needed to answer some of the important questions linking short-term data to organ damage and survival will be available. The DSU provide information on 15 ongoing studies of belimumab for SLE. The information being collected

in these ongoing studies overlaps much of the data proposed by the manufacturer to be collected in the BILAG registry. The DSU also review the NICE methods guide for making ‘only in research’ decisions and discuss how the information provided should be used to inform a decision.

The DSU concluded that the proposed evidence collection might be valuable in collecting data on adherence to the proposed stopping rule as stopping rules are not being used in any other country. However, comparisons with rituximab are unlikely to be robust and uncertainties requiring long-term data collections such as treatment effect maintenance or organ damage are unlikely to be adequate. Fortunately, a number of other studies are currently ongoing which may be better positioned to resolve the uncertainties raised by the Committee. The DSU also provides a framework and suggests methods and evidence to support the Committee in making an OIR or AWR decision.

## CONTENTS

<b>1. INTRODUCTION.....</b>	<b>7</b>
<b>2. METHODS FOR MAKING REIMBURSEMENT DECISIONS WITH EVIDENCE COLLECTION .....</b>	<b>9</b>
<b>3. THE BILAG BIOLOGICS PROSPECTIVE COHORT .....</b>	<b>12</b>
<b>4. REVIEW OF THE MANUFACTURER’S PROPOSAL .....</b>	<b>14</b>
4.1. EVIDENCE COLLECTION .....	14
4.2. IRRECOVERABLE COSTS .....	19
<b>5. MAKING REIMBURSEMENT DECISIONS WITH EVIDENCE COLLECTION</b>	<b>21</b>
<b>6. CONCLUSIONS .....</b>	<b>24</b>
<b>7. REFERENCES.....</b>	<b>25</b>
<b>APPENDIX.....</b>	<b>26</b>
A.1 DATA COLLECTED IN BILAG .....	26
A.2 ONGOING TRIALS WITH BELIMUMAB .....	28

## TABLES AND FIGURES

<i>Table 1 Uncertainties and ongoing trials.....</i>	<i>18</i>
<i>Table 2 Types and categories of guidance.....</i>	<i>23</i>
 <i>Figure 1 Cumulative incremental net health effects of belimumab compared to SOC.....</i>	 <i>19</i>

## **ABBREVIATIONS AND DEFINITIONS**

ACD	Appraisal consultation document
ACR	American College of Rheumatology
AWR	Approval with research
BILAG	British Isles Lupus Assessment Group
BSRBR	British Society for Rheumatology Biologics Registry
DSU	Decision Support Unit
ERG	Evidence review group
FACIT	Functional assessment of chronic illness therapy
ICER	Incremental cost-effectiveness ratio
NHE	Net health effect
NHS	National health system
NICE	National Institute of Health and Care Excellence
OIR	Only in research
QALY	Quality adjusted life-year
RCT	Randomised controlled trial
SAE	Serious adverse event
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic lupus erythematosus disease activity index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SOC	Standard of care
UK	United Kingdom

## 1. INTRODUCTION

Belimumab for active autoantibody-positive systemic lupus erythematosus (SLE) was submitted for review to the National Institute for Health and Care Excellence (NICE) in 2011. The fourth appraisal consultation document (ACD) was published by the Appraisal Committee in June 2013 ([ACD 2013](#)).<sup>1</sup> After consideration of the evidence submitted by the manufacturer and the views of non-manufacturer consultees, commentators, clinical specialists and patient experts, the committee did not recommend belimumab. The committee concluded that there was some evidence of clinical effectiveness compared with standard of care, but did not consider belimumab a cost-effective use of limited NHS resources. Cost-effectiveness was based on a confidential price of belimumab agreed with the Department of Health through the patient access scheme. The committee also concluded that there was uncertainty around the evidence submitted by the manufacturer.

In the ACD of June 2013, the manufacturer proposed that if belimumab was recommended by the Appraisal Committee then the NHS would be able to recruit people with SLE to the British Isles Lupus Assessment Group (BILAG) registry and collect real world evidence on safety and efficacy of belimumab to address the key uncertainties. The committee did not consider that sufficient details were provided. The Committee listed a few of their concerns with the proposal including, i) the degree to which the registry would be able to resolve the key uncertainties, ii) what data would be collected, iii) what the funding arrangements for the registry would be, iv) when an evaluation of the outcomes of the registry would be available, and iv) what would happen with patients who were still being treated with belimumab at the end of the evaluation period if the results are disappointing.

Importantly, the Committee did not consider it likely that belimumab would fulfil the NICE Methods Guide requirement for an ‘only in research’ recommendation that belimumab “have a reasonable prospect of providing benefits to the patients in a cost-effective way”.

Following the ACD the manufacturer has resubmitted their proposal to utilise the BILAG registry. They proposed to generate real-life data for belimumab as prescribed in UK clinical practice for the treatment of SLE patients with highly active disease despite current standard of care over at least three years. The manufacturer stated that collection of the real-life data will help confirm some of the assumptions used in the health economic model and address some of the concerns the Committee raised about the uncertainty of the evidence. At the same time the manufacturer also submitted a revised health economic analysis. The new

health economic analysis has been reviewed by the Evidence Review Group and the results of this analysis will be important for determining the need for further evidence collection.

### ***This review***

The purpose of this report is to assist the Committee in making reimbursement decisions with evidence development. The DSU was asked to,

1. Review the registry documents submitted
2. Provide a description of how the proposal will address the uncertainties identified in the ACD
3. Provide comments on the suitability of the data collection proposed and any necessary changes
4. Provide a description of how the information available could be used by the Committee to make a decision on each of the criterion outlined in the methods guide
5. Make recommendations for any further research outside of the register that could address the uncertainties identified in the ACD

The sections below begin with a description of the methods for making reimbursement decisions with evidence collection using the NICE Methods Guide and other published literature. This is followed by a description of the BILAG registry, a review of the uncertainties identified from the ACD and the manufacturer's proposal and then a description of how the evidence might be used to make a reimbursement decision with evidence.



## **2. METHODS FOR MAKING REIMBURSEMENT DECISIONS WITH EVIDENCE COLLECTION**

The 2013 NICE Methods Guide states that when the clinical effectiveness evidence or the impact on other health outcomes is absent, weak or uncertain that the appraisal committee may recommend that the technology is only used in patients participating in data collection (only in research, OIR) or may recommend the treatment for all patients while data collection is undertaken only in some (approval with research, AWR) (Section 6.4.1, [NICE Methods Guide 2013](#)).<sup>2</sup>

There are three broad areas for consideration when making such a decision: i) the expected cost-effectiveness (i.e. the current estimate of the mean ICER) and population net health effects (including benefits, harms and NHS costs); ii) whether there are significant costs which will be committed and cannot be recovered once the therapy is recommended (i.e. irrecoverable costs); and iii) the need for evidence and whether the type of research required can be conducted.

The population net health or “the likely net benefits for all NHS patients of use only in a research setting during the time the recommended research is being conducted”<sup>2</sup> is determined by the cost-effectiveness. Recommending a treatment that is cost-effective improves the population net health. However, recommending a treatment that is not cost-effective decreases the population net health as other more cost-effective treatments must be displaced to fund the new treatment. This decrease in the population net health might be considered appropriate in the short term if, because of this decrease, further evidence can be collected which will lead to better decisions and therefore better health in the future. The consideration of cost-effectiveness has been previously discussed by the committee and will be re-evaluated given the additional evidence provided by the manufacturer and reviewed by the Evidence Review Group. No further evidence on the cost-effectiveness of belimumab will be presented in this report. This report will discuss the implications of the committee’s judgement about cost-effectiveness on decisions for reimbursement with or without evidence collection.

The NICE Methods Guide also states that Committee will consider whether there are “irrecoverable costs from introducing the technology”.<sup>2</sup> Irrecoverable costs are those which once committed cannot be recovered should guidance be revised at a later date. In most NICE appraisals these are included in the expected costs of a technology. These types of cost

are commonly thought of as capital expenditure on equipment or facilities which have a long life expectancy. They might also include the resources required to implement guidance, to train staff to use a new health technology, the cost of changing delivery or a period of learning where outcomes are lower. Although these costs are incurred ‘up-front’ they tend to be included in the NICE assessments as if they are paid per patient treated over the life time of the equipment or facility. This common assumption will have no effect, so long as guidance is certain not to change during this period. However, if it is possible that initial approval might be withdrawn at some point, then, although future patients will no longer use the technology, these upfront costs cannot be recovered. Therefore, the possibility that ‘approval’ or ‘approval with research’ might be reconsidered after research reports, for example, and the impact this would have on expected costs needs to be considered, i.e. it may be better to withhold approval and avoid commitment of resources until the uncertainty is resolved.

When considering an OIR or AWR decision a number of factors with regards to the value and collection of the additional evidence must be considered. To determine the value of additional evidence requires judgements about: i) how uncertain a decision to recommend or reject a treatment might be, based on the estimates of expected cost-effectiveness; and ii) whether the scale of the likely consequences of this uncertainty might justify further research. If the potential benefits of further research are unlikely to justify the costs, then a judgement that more research does not seem worthwhile rules out the need for OIR or AWR decisions. If the potential benefits of further research seem likely to justify the costs, then further consideration should be made about the likelihood that research will be conducted, when the results are likely to be available and how much uncertainty is likely to be resolved.

The next consideration with regards to the evidence collection is whether research is possible given the recommendation decision. This requires an assessment of what type of evidence is needed and a judgement of whether the research required can be conducted while the technology is recommended or not. For example, if the evidence that is needed will require experimental research design, then recommending a treatment may make an RCT infeasible. If the evidence that is needed is to understand clinical practice, then the treatment may need to be recommended to capture the appropriate data.

The next important consideration is whether the decision uncertainty is likely to resolve over time. Decision uncertainty takes into account more than the magnitude of the variation around an estimate; it accounts for the impact of that variation on the decision problem. Given that other things are going to change while the research is being conducted, it is

important to consider whether any likely changes might render the results of the evidence collection less valuable or entirely redundant. Decision uncertainty might resolve over time if the technology or a comparator is likely to change its price, if a new technology is likely to enter the market or if other research is already underway. Changes in prices not only influence expected cost-effectiveness but also uncertainty and the potential benefits of research to future patients, e.g., if the price of a technology expected to be cost-effective is likely to fall significantly just before research reports the potential benefits will not be realised because approval of the technology will be less uncertain and there may be much less or little to gain from the results of the research. Similarly, an immediate reduction in price could resolve all the decision uncertainty and turn any decision to a positive recommendation. The entry of a new technology may make the existing technology that is expected to be cost-effective obsolete (no longer the most cost-effective alternative). Even when it does not, it will tend to change the relative cost-effectiveness of the alternatives, influencing how uncertain a decision to approve the original treatment will be for future patients and the potential gains from research. Research which is already underway, commissioned or likely to be undertaken whether in the UK or elsewhere, is relevant for two reasons. Firstly, if it is research based in the UK then guidance might impact on recruitment and the successful completion of this research. Secondly, when this research reports there is a chance that it will change the estimates of cost-effectiveness and resolve some of the current uncertainties. In other words, there is little to be gained by recommending OIR or AWR if the uncertainty is likely to be resolved in the near future when other research reports. The value of the additional evidence determined previously should then be considered given that some of the decision uncertainty may resolve over time.

An overall judgement about whether the benefits of research are greater than the costs will take into account the potential benefits of research, whether the benefits are likely to be realized and the likely impact of the other sources of uncertainty on the longer term benefits of research.

Finally a judgement should be made about whether the benefits of recommending the treatment are greater than the costs. This decision combines the opportunity costs of approval assessed from the cost-effectiveness analysis and any costs that are irrecoverably committed by approval weighed against the expected benefits to future patients.

### 3. THE BILAG BIOLOGICS PROSPECTIVE COHORT

The BILAG Biologics Prospective Cohort began recruitment in September 2010 and is a prospective observational cohort study of patients with SLE who are starting treatment with a biologic drug or a conventional, non-biologic therapy. The study aims to recruit 220 patients into the biologic treatment group and a further 220 patients into the conventional, non-biologic therapy cohort ([BILAG BR](#)).<sup>3</sup> As of September 2014, 235 participants had been recruited to the biologic cohort and 44 to the control cohort. Patients in the control cohort had a mean follow-up of 12 months and maximum follow-up of 36 months. Most patients, 222, in the biologic cohort were prescribed rituximab with a mean follow-up of 15 months and a maximum of 46 months; 10 patients were receiving belimumab with a mean follow-up of 12 months and a maximum of 24 months and 3 patients were receiving other biologics.

The primary aim of the BILAG BR is to ascertain whether using biologics in the routine treatment of SLE is associated with an increased risk of hospitalisation for infection, compared to SLE patients with similar disease activity receiving conventional therapies. The secondary purpose of the BILAG Biologics Prospective Cohort is to determine the long-term efficacy of biological therapies in the treatment of SLE.

Comprehensive data is collected at baseline, from the clinic team and the patient, including data on disease diagnosis and activity, risk factors for infection and routine laboratory results. Follow-up data is collected at 3, 6, 12, 24 and 36 months to include any changes in medications, adverse events, hospitalisations for infections, disease activity and quality of life along with biological samples for biomarker analysis. Appendix A.1 provides the full list of data points being collected in BILAG.

The primary measure of effectiveness is the systemic lupus erythematosus disease activity index 2000 (SLEDAI 2K). As of September 2014, 90-95% of the biologics cohort and 85%-90% of the control cohort had reported SLEDAI 2K at 6 months. At 12 months there was more than 70% reporting in both cohorts, with many of the patients still inside the “visit window”.

Eligibility Criteria ([BILAG 2010](#))<sup>4</sup>

- Diagnosis of SLE (4 or more ACR criteria)
- Age 5 years and over
- Willingness to give informed consent
- Newly commencing a biologic drug or started within the preceding 12 months

or

- Newly commencing conventional, non-biologic immunosuppressive therapy and never taken a biologic drug

Additionally rituximab will only be funded for use in SLE where the following criteria are met ([Policy statement for rituximab](#))<sup>5</sup>:

- Diagnosis of SLE (fulfilling either ACR or SLICC criteria)
- Active disease (defined as at least one BILAG A score and/or 2B score, or a SLEDAI-2K score > 6)
- Failure to respond or having adverse events to, two or more standard immunosuppressive therapies (one of which must be either mycophenolate mofetil or cyclophosphamide, unless contraindicated) in combination with corticosteroids.
- All patients must be managed at, or in collaboration with a centre commissioned to provide specialised services that has expertise in the assessment and management of SLE.
- All patients receiving rituximab for SLE must be registered with the BILAG Biologics Register

## **4. REVIEW OF THE MANUFACTURER’S PROPOSAL**

### **4.1. EVIDENCE COLLECTION**

The manufacturer GlaxoSmithKline submitted a proposal to collect additional evidence to resolve the uncertainties raised by the Committee. It was proposed that real world data be collected for belimumab on effectiveness, safety and quality of life, as well as relative effectiveness data for rituximab in the BILAG registry over a minimum of three years.

In Table 1 of the manufacturer’s submission the proposed data collection is summarized. This table indicates the area of uncertainty to be addressed and the data available from the BILAG registry.

Firstly the manufacturer identified discontinuation rates as being uncertain. The ERG analysis used seven years of data available on the discontinuation of belimumab. The manufacturer proposed to collect the distribution of cumulative treatment duration over 3 to 5 years, the percent of patients with each discontinuation reason and the percent re-starting belimumab. Additionally the manufacturer is undertaking large registry and extension studies that would be useful in assessing discontinuation, including a continuation trial for subjects that completed protocol HGS1006-C1056/C1057 (Table 1). This continuation study is expected to complete in 2015 and has 733 patients of which some are in the UK (Appendix A.2).

The manufacturer also proposed to report the standard of care in England and Wales in response to the Committee’s uncertainty about the extent to which standard care in belimumab trials represented UK clinical practice. This is currently being collected in the BILAG registry and the reporting of this evidence does not depend on the recommendation of belimumab.

In response to the Committee’s conclusion that “the effect of belimumab on the full range of manifestations of systemic lupus erythematosus was uncertain”, the manufacturer suggested collecting data on the percent of patients with the different manifestations. This will not provide data on the effect by manifestation, as requested by the Committee. As discussed below the population size is unlikely to provide sufficient patient numbers to estimate treatment effects by manifestation subgroups in BILAG, although, a number of much larger studies are ongoing. Alternatively, data across trials might be combined to increase the power of subgroup analyses to estimate relative efficacy by manifestation.

Besides providing data to resolve the uncertainties raised by the committee, the manufacturer suggests that additional data could be provided on whether some health benefits such as fatigue and steroid sparing have been underestimated in the randomised controlled trials. The benefits of changes in fatigue were considered in the ACD. In the ACD the Committee noted that “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” and stated that “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”. There was no indication from the Committee that they considered the measurement of fatigue was uncertain. In the case of the steroid sparing effect the manufacturer references two observational studies one from the US and one from Germany that demonstrate positive results. Additionally SABLE is a large ongoing study which will collect data on both fatigue and concomitant SLE medication.

The manufacturer proposed to test adherence to the stopping rule using the SLEDAI-2K score at the start and after 6 months and assessing discontinuation of non-responders. As any stopping rule recommended by the Committee would be specific to the UK, ongoing registries outside of the UK would not provide this evidence.

In the ACD the Committee concluded that there was still some uncertainty in the evidence about whether it was appropriate to assume that treatment effect was maintained over time. Current evidence is from a 7-year open label phase II extension study. The manufacturer proposed to collect the mean SLEDAI-2K score and mean change in SLEDAI-2K score over 3 to 5 years. Unfortunately the 3 to 5 year timeframe will not provide any data beyond the 7 years of data which is already available. Currently ongoing continuation trials and registries are likely to provide more robust data than BILAG given the timeframe and sample size. No randomised controlled data is available or proposed beyond 52 weeks although the SABLE study does have a non-randomised control arm (Appendix A.2).

To understand the development of organ damage over time the manufacturer proposed to collect prevalence of each type of organ damage over 3 to 5 years using the SLICC and BILAG scores. The manufacturer states that “a longer follow-up period (5+ years) would provide more informative data”, this is because minimal organ damage is expected to occur within 5 years. The SABLE study is also collecting SLICC scores for 5 years in a larger population and is currently ongoing.

Finally the manufacturer suggested collecting data on serious adverse events (death, hospitalisation for infection, malignancy and other SAEs) while on belimumab and after

having stopped belimumab to assess the rebound phenomenon. Currently ongoing is the ‘Belimumab treatment holiday and treatment re-start study in lupus patients’. This study will assess the effect of a 24-week withdrawal followed by a 28-week reintroduction. Also the rebound phenomenon will be assessed for subjects who have permanently withdrawn from further belimumab treatment. This trial started in May 2014 and is ongoing in Japan and the Republic of Korea. The primary outcome is the SELENA SLEDAI score at 52 weeks (Appendix).

The manufacturer reported that over 8 months from July 2013 nine rituximab patients were enrolled each month into the biologic arm of BILAG. The manufacturer estimated that 9 to 11 patients would be prescribed belimumab and included in the registry each month. From this it was assumed that 360 patients would be treated with belimumab in BILAG after three years. One of the stated goals of the evidence collection was to provide relative effectiveness data comparing belimumab and rituximab. The manufacturer’s sample size calculation assumes that once belimumab is approved all patients in the biologic cohort arm will be prescribed belimumab. If this is the case there will likely be insufficient data on rituximab to compare with belimumab. Alternately the biologic arm may split the number of patients receiving rituximab and belimumab. In this case fewer belimumab patients are likely to make the comparison with rituximab under powered. Some of the other analyses are also likely to be under powered such as the subgroup analysis by SLE manifestation as mentioned previously.

There are further concerns with the comparison with rituximab given the different definitions of the population and the potential for selection bias. Particularly rituximab is only reimbursed if a patient has failed to respond or having adverse events to, two or more standard immunosuppressive therapies (one of which must be either mycophenolate mofetil or cyclophosphamide, unless contraindicated) in combination with corticosteroids. It is not clear that clinicians will apply the same restrictions to the use of belimumab if it is recommended. There is very likely to be selection bias in any comparison between treatments. The manufacturer in their proposal state that a comparison with rituximab might be possible “assuming a comparable cohort can be identified”. The manufacturer does not provide any pre-specified details on how selection bias might be controlled for, i.e. methods and control variables. However, even pre-specified analyses can be difficult to uphold when the results might change a NICE decision i.e. multiple sclerosis cohort study for beta-interferons (Raftery, BMJ 2010).<sup>6</sup>



There is a good likelihood that if belimumab was used in the BILAG registry that the data proposed for collection by the manufacturer could be collected. As the manufacturer argues, the BILAG registry is an ongoing study already successfully recruiting patients on biologics. However, recruitment to the non-biologic arm is much slower. There is a concern that given the low number of non-biologic patients any comparisons with standard of care will be under powered. There will also be selection bias between standard of care and belimumab populations, which has not been discussed in the manufacturer's proposal.

As discussed throughout there are a number of ongoing studies (Appendix A.2). The phase 3 RCT for subcutaneous formulation is expected to report in 2015 and there will be interim data from the long-term real life multinational SABLE study. This section demonstrates that in most cases the proposed evidence collection is already ongoing in other studies or will be collected in BILAG without a requirement to recommend belimumab. Only evidence on the effect of the proposed treatment stopping rule on the discontinuation rate is not currently ongoing and would benefit from an OIR or AWR decision. It is worth noting that analyses of the British Society for Rheumatology Biologics Registry (BSRBR) indicated that approximately 50% of non-responders remain on biologic therapy at one year after the start of treatment and 25% of non-responders remain on therapy almost 5 years after the start of treatment. NICE guidance states that treatment should not continue at 6 months for non-responders. Currently most of the patients in the BILAG registry are on rituximab, this will provide needed information on the effect of rituximab in an off-label setting. If belimumab is approved then data collection on rituximab is likely to cease. This may be an important consideration for the Committee when weighing the value of evidence.

**Table 1 Uncertainties and ongoing trials**

<b>Identified uncertainties</b>	<b>Source</b>	<b>Ongoing data collection</b>
Discontinuation rate	ACD (4.5) & (4.17)	SABLE
Maintenance of treatment effect over time and progression after stopping treatment	ACD (4.20) & (4.21) / MS Table 1	SABLE
Adherence to stopping rules	MS Table 1	None
Translation of short term delay outcomes into long term survival gains	ACD (4.22)	SABLE
Relative effectiveness of rituximab vs belimumab	ACD (4.13)	None
Effect of rituximab on a range of manifestations	ACD (4.9) / MS Table 1	BILAG
Impact on delay to organ damage	ACD (4.22)	SABLE
What is standard of care	ACD (4.10) / MS Table 1	BILAG
Effect on steroid sparing	ACD (4.11) & (4,12) / MS Table 1	SABLE, A continuation trial HGS1006-C1056, A continuation trial LBSL0, BASE, BLISS-SC
Costs and disutility of damage to different organs	ACD (4.25)	SABLE
Any additional impact of fatigue and QoL	ACD (4.31) / MS Table 1	SABLE, A continuation trial HGS1006-C1056
Safety and rebound phenomenon	ACD (4.17)MS Table 1	Belimumab treatment holiday and treatment re-start study in lupus patients

## 4.2. IRRECOVERABLE COSTS

The manufacturer stated that there should not be any significant irrecoverable costs as no new service infrastructure is needed. Irrecoverable costs also include the period of learning and the negative health consequences of upfront costs if the treatment effects are reversible. A completely reversible treatment effect is one in which treatment effects are lost once treatment is stopped and there are no long-term benefits. This might be compared to a treatment for which long-term benefits are not lost but delayed if treatment is stopped or compared to a treatment (e.g. surgery) for which once taken the expected long-term benefits are completely irreversible. Figure 1 demonstrates the incremental net health effect (NHE) of belimumab in the ERG's base case assuming a threshold of £30,000 per QALY. It shows that for the first five years the health benefits of belimumab are outweighed by the costs and it is not until 28 years when the treatment with belimumab breaks even.

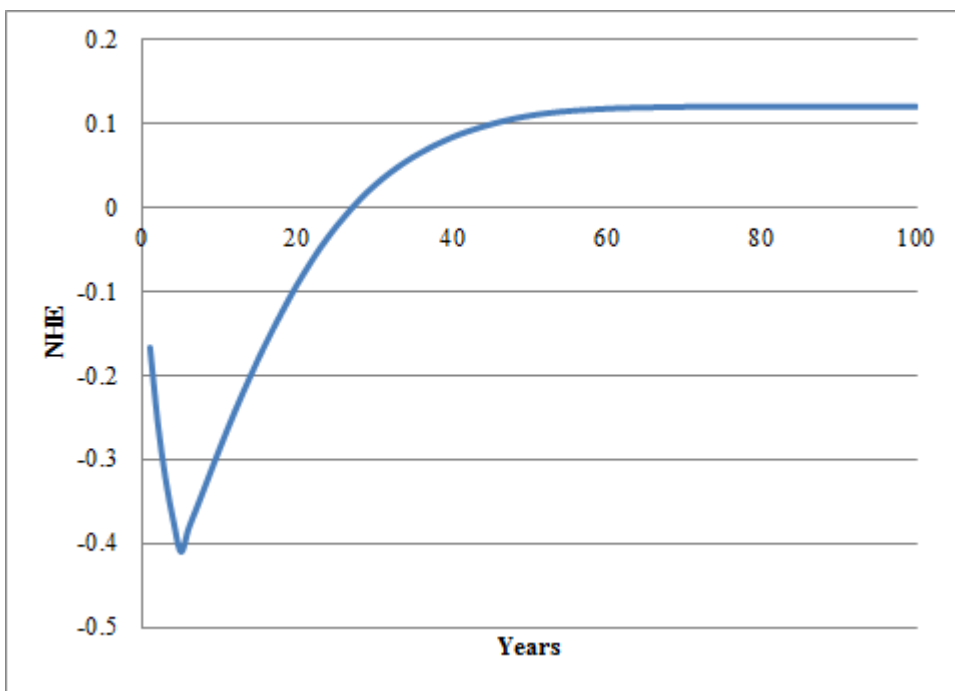


Figure 1 Cumulative incremental net health effects of belimumab compared to SOC<sup>1</sup>

<sup>1</sup> Figure 1 was created by first calculating the net health effects for each treatment at each cycle of the model. Then the difference in net health effects at each cycle were calculated and the cumulative difference in net health effects was plotted over time.

Given the long time horizon until the treatment breaks even, any change in a decision before 52 years may result in patients accumulating most of the costs of belimumab without achieving all of the expected benefits (depending on the Committee's view about reversibility of the treatment effect of belimumab). If the treatment effects are judged to be irreversible then patients who received treatment will be expected to continue to benefit and may still achieve the long-term benefits even if treatment is stopped. Decisions about whether belimumab has irrecoverable costs are likely to rest on the expected magnitude of the learning costs and whether treatment effect is expected to be irreversible.

## 5. MAKING REIMBURSEMENT DECISIONS WITH EVIDENCE COLLECTION

As discussed previously there are three broad areas for consideration when making decisions about evidence collection with or without a recommendation for reimbursement: i) the expected cost-effectiveness ; ii) whether there are irrecoverable costs; and iii) the need/value of evidence and whether the type of research required can be conducted.

More precisely seven important questions have been discussed in Section 2 and need to be considered ([HTA 2012](#)).<sup>7</sup> These questions were determined as part of a framework produced from a recent MRC study. This framework guides decisions of approval and evidence collection and is based on logic and the principles of maximizing health.

1. Is the treatment estimated to be cost-effective based on current evidence?
2. Are there significant irrecoverable costs?
3. Does more research seem worthwhile?
4. Is the research possible with approval (if considered cost-effective) or without approval (if not considered cost-effective)?
5. Will uncertainty resolve over time?
6. Are the benefits of research greater than the costs?
7. Are the benefits of approval greater than the costs?

The answers to these questions can be used to guide appropriate decisions as indicated in Table 2. For example, if belimumab is considered by the committee to be cost-effective, and not to have irrecoverable costs, then most decisions would result in a positive recommendation (approval). The framework suggests the committee may still want to request evidence collection if the benefits of the evidence outweigh the costs of collecting the evidence. Even OIR may still be an option if the evidence is very valuable but cannot be collected if the treatment is in wide spread use from having been recommended.

If belimumab is considered by the committee not to be cost-effective based on current evidence, and not to have irrecoverable costs, then most decisions result in not recommending (reject). The framework suggests that the committee may still want to request evidence collection if the benefits of the evidence on future health are expected to outweigh the costs imposed on society by recommending a treatment that is not cost-effective.

When considering the above questions the following evidence should be considered.

1. The evidence of cost-effectiveness submitted by the manufacturer and reviewed by the ERG.

2. The evidence of irrecoverable costs submitted by the manufacturer and commented on above.
3. The sensitivity analyses provided and whether the uncertainty is likely to influence the decision. Each of the uncertainties for consideration is listed in Table 1, and should be judged individually.
4. The type of evidence that will be most valuable, and whether the collection of that evidence will be limited by a positive or negative recommendation. If for instance the evidence relates to clinical practice then data will be difficult to collect if the treatment is not approved.
5. The number of trials ongoing and the likelihood that the uncertainty around those identified and judged important in question 3 will be resolved without an OIR or AWR decision.
6. The likelihood the data will be collected, be analysed and reported appropriately and that the data will be of sufficient quality to sufficiently resolve the uncertainty (no research will completely resolve uncertainty). If it is decided in question 5 that much of the uncertainty will be resolved from other sources or that the other sources are in a better position to resolve the uncertainty then OIR or AWR decisions are less valuable.
7. The consequences of the early decision versus the benefits of being able to collect data. For example if the treatment is not considered cost-effective, but evidence can only be collected if the treatment is approved then the magnitude of the NHE of recommending a treatment that is not cost-effective must be weighed against the potential benefit of resolving the decision uncertainty.

Table 2 Types and categories of guidance

Assessment	1	2	3	4	5	6	7	Guidance
1	Yes	No	Yes	Yes	Yes/No	Yes	-	AWR 1
2	Yes	No	Yes	Yes	Yes/No	No	-	Approve 1
3	Yes	No	Yes	No	Yes/No	Yes	Yes	Approve 2
4	Yes	No	Yes	No	Yes/No	Yes	No	OIR 1
5	Yes	No	Yes	No	Yes/No	No	-	Approve3
6	Yes	No	No	-	-	-	-	Approve 4
7	No	No	Yes	Yes	Yes/No	Yes	-	OIR 2
8	No	No	Yes	Yes	Yes/No	No	-	Reject 1
9	No	No	Yes	No	Yes/No	Yes	Yes	AWR 2
10	No	No	Yes	No	Yes/No	Yes	No	Reject 2
11	No	No	Yes	No	Yes/No	No	-	Reject 3
12	No	No	No	-	-	-	-	Reject 4
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes	AWR 3
14	Yes	Yes	Yes	Yes	Yes	Yes	No	OIR 3
15	Yes	Yes	Yes	Yes	Yes	No	Yes	Approve 5
16	Yes	Yes	Yes	Yes	Yes	No	No	Reject 5
17	Yes	Yes	Yes	Yes	No	Yes	Yes	AWR 4
18	Yes	Yes	Yes	Yes	No	Yes	No	OIR 4
19	Yes	Yes	Yes	Yes	No	No	-	Approve 6
20	Yes	Yes	Yes	No	Yes	Yes	Yes	Approve 7
21	Yes	Yes	Yes	No	Yes	Yes	No	OIR 5
22	Yes	Yes	Yes	No	Yes	No	Yes	Approve 8
23	Yes	Yes	Yes	No	Yes	No	No	Reject 6
24	Yes	Yes	Yes	No	No	Yes	Yes	Approve 9
25	Yes	Yes	Yes	No	No	Yes	No	OIR 6
26	Yes	Yes	Yes	No	No	No	-	Approve 10
27	Yes	Yes	No	n/a	Yes	n/a	Yes	Approve 11
28	Yes	Yes	No	n/a	Yes	n/a	No	Reject 7
29	Yes	Yes	No	n/a	No	-	-	Approve 12
30	No	Yes	Yes	Yes	Yes/No	Yes	-	OIR 7
31	No	Yes	Yes	Yes	Yes/No	No	-	Reject 8
32	No	Yes	Yes	No	Yes/No	Yes	Yes	AWR 5
33	No	Yes	Yes	No	Yes/No	Yes	No	Reject 9
34	No	Yes	Yes	No	Yes/No	No	-	Reject 10
35	No	Yes	No	-	-	-	-	Reject 11

Part I of the algorithm

Part II of the algorithm

Part III of the algorithm

[HTA 2012](#)<sup>7</sup>

## 6. CONCLUSIONS

It is not the remit of the DSU to make recommendations on the above decisions, but to suggest methods and evidence that may be helpful in making these decisions. The DSU is however able to comment on the proposed data collection. BILAG is an ongoing, well organised registry collecting important data on the biologic (i.e. rituximab) and non-biologic treatment of SLE. A Committee decision to approve with research for belimumab is likely to limit the available data on rituximab and any comparisons between belimumab and rituximab. Furthermore it is unlikely that BILAG will be able to resolve the uncertainties requiring long-term data collection such as organ damage or treatment effect maintenance. Fortunately, many other studies are currently ongoing, including trials to determine the effect of treatment holidays and the rebound effect, and large registries collecting discontinuation data, steroid sparing, and effects on fatigue and quality of life measures.

The evidence discussed has been a qualitative approach for assessing the value of evidence and the trade-off between the reimbursement decision and long-term health improvements from evidence collection, however, more quantitative methods are available to assess the value of information, and the value of evidence collection which might be used in further research.



## 7. REFERENCES

1. NICE. Systemic lupus erythematosus (active) - belimumab: appraisal consultation document. 2013. <http://www.nice.org.uk/guidance/gid-tag273/resources/systemic-lupus-erythematosus-active-belimumab-appraisal-consultation-document>.
2. NICE. Guide to the methods of technology appraisal 2013. <http://publications.nice.org.uk/pmg9>.
3. Centre for Musculoskeletal Research. BILAG Biologics Prospective Cohort. <http://www.inflammation-repair.manchester.ac.uk/Musculoskeletal/research/CfE/pharmacoepidemiology/bilagbr/>.
4. Centre for Musculoskeletal Research. BILAG Biologics Prospective Cohort. [http://www.bilagbr.org/downloads/BILAG%20BR\\_newsletter%20-%20Nov%202010.pdf](http://www.bilagbr.org/downloads/BILAG%20BR_newsletter%20-%20Nov%202010.pdf).
5. NHS England. Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. August 2013. <http://www.england.nhs.uk/wp-content/uploads/2013/10/a13-ps-a.pdf>.
6. Raftery J. Multiple sclerosis risk sharing scheme: a costly failure. *BMJ*. 2010. 3/340.
7. Claxton K, Palmer S, Longworth L, et al. Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. *Health Technology Assessment*. 2012. 16/46/1-342.

## **APPENDIX**

### **A.1 DATA COLLECTED IN BILAG**

#### **Baseline Data**

- Patient identification unique number
- Code for centre
- Gender
- Ethnicity
- Date of Birth
- Date of registration
- Employment status

#### **Consultant and nurse collected information**

- Baseline examination – to include blood pressure, height, weight, BMI and waist circumference
- Comprehensive SLE details – to include ACR criteria met and timing of diagnosis
- Biologic therapy data (in treatment cohort only) – to include organ system responsible for treatment, previous treatments and reasons for biologics treatment
- Baseline activity of SLE and health status – to include use of BILAG 2004 Index, SLEDAI 2K, SLICC/ACR Damage Index
- Current and prior therapy – to include exposure to non-biologic immunosuppressive drugs, Glucocorticoid exposure from time of SLE diagnosis, Antimalarials, NSAIDS
- Risk factors for infection – to include hepatitis B, hepatitis C, leg ulcers, catheterisation, hyposplenism, splenectomy
- Vaccination history
- Medical history and co-morbidity data - to include angina, heart attack, stroke, epilepsy, asthma, renal disease, raised creatinine, immunodeficiency syndromes (for full list see current version of the questionnaire)
- Concomitant medications
- Results from routine laboratory tests within the previous 6 months, to include:
  - o Auto antibody profiles: ANA, Ds DNA, Ro, La, Sm, RNP, Scl-70, Centromere
  - o Complement fractions: C3, C4
  - o Total cholesterol
  - o HDL
  - o Fasting blood glucose

- o ESR/CRP
- o Immunoglobulins

**Patient collected information**

- EQ5D
- SF-36
- LupusQoL
- lifestyle questionnaire: Smoking status, Alcohol consumption, Women's health
- patient diary recording hospital admissions, visits to outpatients and medications

## A.2 ONGOING TRIALS WITH BELIMUMAB

<b>Title</b>	<b>Trial Identifier</b>	<b>Description</b>	<b>Start Date Completion Date</b>	<b>Enrollment</b>	<b>Locations</b>	<b>Study Arms</b>	<b>Outcomes</b>	<b>Population</b>
A Continuation Trial for Subjects With Lupus Who Completed Protocol HGS1006-C1056 in the United States	NCT00724867	This is a long-term continuation study to provide continuing treatment to subjects who completed study HGS1006-C1056 in the United States. This study is to evaluate the long-term safety and efficacy of belimumab (LymphoStat-B™) in subjects with SLE disease.	August 2008 May 2015	268	US, Canada	1. belimumab 1mg/kg IV every 28 days 2. belimumab 10mg/kg IV every 28 days	Assessment of efficacy and biomarkers including: disease activity, anti-dsDNA and serum complement levels, prednisone use, proteinuria level, serum immunoglobulin G, and B-cell subsets. Assessment of efficacy according to the SLICC/ACR Damage Index. Assessment of quality of life according to the following scales: SF-36 Health Survey, and FACIT-Fatigue scale.	Inclusion Criteria: Have completed the HGS1006-C1056 protocol in the United States through Week 72 visit. Be able to receive 1st dose of belimumab for HGS 1006-c1066 four weeks after last dose in HGS1006-c1056.
A Continuation Trial for Subjects With Lupus That Completed Protocol HGS1006-C1056 or HGS1006-C1057	NCT00712933	This trial is a long-term continuation study to provide continuing treatment to subjects with System Lupus Erythematosus (SLE).	June 2008 March 2015	733	28 countries including the United Kingdom	1. belimumab 1mg/kg IV every 28 days 2. belimumab 10mg/kg IV every 28 days	The SLICC/ACR Damage Index will be assessed every 48 weeks and at exit visit.	Inclusion Criteria: Have completed the HGS 1006-C1056 or HGS 1006-C1057 protocol through the Week 72 or Week 48 visits, respectively.
A Continuation	NCT00583362	The purpose of this	November	298	US, Canada	1. belimumab	The efficacy	Inclusion Criteria:

<b>Title</b>	<b>Trial Identifier</b>	<b>Description</b>	<b>Start Date Completion Date</b>	<b>Enrollment</b>	<b>Locations</b>	<b>Study Arms</b>	<b>Outcomes</b>	<b>Population</b>
Trial for Subjects With Systemic Lupus Erythematosus That Have Completed Protocol LBSL02		continuation study to evaluate the long-term safety and efficacy of LymphoStat-B™ in subjects with Systemic Lupus Erythematosus (SLE), that completed study LBSL02 and benefitted from treatment.	2004 May 2016			10mg/kg IV every 28 days	endpoints will include time-to-flare SELENA SLEDAI, PGA, BILAG, reduction in steroid use, biological markers and autoantibodies.	Have completed the LBSL02 trial and achieved a satisfactory response.
Belimumab Assessment of Safety in SLE (BASE)	NCT01705977	52 week RCT comparing placebo (no active medicine) to belimumab. After completion of the 52-week study period, participants will be contacted by phone annually for 4 more years to assess health status	November 2012 January 2023	5000	34 countries not including the UK	1. Placebo plus SOC 2. belimumab 10mg/kg plus SOC	Incidence of mortality, incidence of adverse events, reduction in prednisone dose	Inclusion Criteria: clinical diagnosis of SLE, active SLE disease, autoantibody-positive, on stable SLE treatment
A Study of Belimumab Administered Subcutaneously in Subjects With Systemic Lupus Erythematosus (SLE) (BLISS-SC)	NCT01484496	This is a Phase 3, multi-center, international, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy, safety and tolerability of belimumab administered subcutaneously	November 2011 October 2014	816	31 countries including the UK	1. Placebo plus SOC 2. belimumab 200 mg SC plus standard therapy	SRI response rate, PGA, BILAG B, time to severe flare, reduction in prednisone dose	Inclusion Criteria: 18 years, clinical diagnosis of SLE, active SLE, autoantibody-positive, on stable SLE treatment
A Study to Evaluate the Effect of Belimumab on Vaccine Responses in Subjects With Systemic Lupus Erythematosus (SLE)	NCT01597492	All patients in this study will receive belimumab plus standard therapy for SLE and vaccinations against pneumococcus and tetanus toxoid. Patients will be randomized to receive	May 2012 May 2014	80	US	1. belimumab 10mg/kg IV plus early vaccine 2. belimumab 10mg/kg IV plus late vaccine	Immune Response to Tetanus Toxoid and Pneumococcal Vaccines	Inclusion: diagnosis of SLE, active SLE, autoantibody-positive, levels of antibodies to tetanus toxoid and pneumococcal

<b>Title</b>	<b>Trial Identifier</b>	<b>Description</b>	<b>Start Date Completion Date</b>	<b>Enrollment</b>	<b>Locations</b>	<b>Study Arms</b>	<b>Outcomes</b>	<b>Population</b>
		vaccinations either 4 weeks prior (early vaccination group) or 24 weeks after (late vaccination group) their first belimumab dose. Vaccine response will be assessed 4 weeks after vaccine administration.						vaccine below protective levels
GSK1550188 A 52 Week Study of Belimumab Versus Placebo in the Treatment of Subjects With Systemic Lupus Erythematosus (SLE) Located in Northeast Asia	NCT01345253	Demonstrate the efficacy and safety of belimumab 10mg/kg administered intravenously (IV) every 4 weeks compared to placebo, in patients with SLE when added to standard of care therapy, as measured by the SLE Responder Index (SRI) at 52 weeks, defined by a composite endpoint using SELENA SLEDAI score, Physician's Global Assessment (PGA) and BILAG A and B organ domain scores.	May 2011 January 2015	700	China, Japan, Republic of Korea	1. belimumab 10mg/kg IV 2. Placebo plus SOC	SRI at 52 weeks, SELENA SLEDAI, BILAG, PGA, Days with prednisone, flares	
Efficacy and Safety of Belimumab in Black Race Patients With Systemic Lupus Erythematosus (SLE) (EMBRACE)	NCT01632241	Study participants receive stable standard therapy for lupus in addition to receiving either placebo (no active medicine) or belimumab. The controlled period of the study is 52 weeks.	February 2012 July 2017	816	US, Brazil, Columbia, France, South Africa and UK	1. belimumab 10mg/kg IV 2. Placebo plus SOC	SRI at 52 weeks, time to severe flare, reduction in prednisone dose, Aes	Inclusion Criteria: Black race, diagnosis of SLE, active SLE, autoantibody-positive, on stable SLE treatment

Title	Trial Identifier	Description	Start Date Completion Date	Enrollment	Locations	Study Arms	Outcomes	Population
Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus Registry (SABLE)	NCT01729455	The registry will enroll 2 groups of patients. One group will include patients who are currently taking lupus medicines along with intravenous BENLYSTA (With BENLYSTA). The other group will include patients who are taking lupus medicines but do not take BENLYSTA (Without BENLYSTA). After enrollment, changes in lupus medications, including starting or stopping BENLYSTA, are at the discretion of the physician, and all patients will continue to be followed regardless of changes in their lupus medicines until study completion. Physicians will manage the patient in accordance with their medical judgment and standard of care. Data will be collected at enrollment and at 6 month intervals for 5 years.	February 2013 March 2022	3000	US, Austria, Belgium, Canada, France, Germany, Slovakia	1. belimumab 2. SOC	Incidence of adverse events, change in organ damage, SLICC, change in concomitant SLE medication, change in disease activity, severe flares, quality of life, fatigue, rate of hospitalization	Inclusion Criteria: Diagnosis of active SLE, autoantibody-positive, current SLE treatment
Pediatric Lupus Trial of Belimumab Plus Background	NCT01649765	This is a multi-center study to evaluate the safety, pharmacokinetics, and efficacy of	September 2012 March 2016	100	11 countries including UK	1. 10mg/kg IV monthly belimumab 2. placebo	SRI at 52 weeks, PGA, AEs	Inclusion Criteria: 5 years to 17 years of age, diagnosis of SLE, active

<b>Title</b>	<b>Trial Identifier</b>	<b>Description</b>	<b>Start Date Completion Date</b>	<b>Enrollment</b>	<b>Locations</b>	<b>Study Arms</b>	<b>Outcomes</b>	<b>Population</b>
Standard Therapy (PLUTO)		belimumab intravenous (IV) in pediatric patients 5 to 17 years of age with active systemic lupus erythematosus						SLE, positive anti-nuclear antibody, on stable SLE treatment
Belimumab (BENLYSTA®) Pregnancy Registry	NCT01532310	This global Belimumab Pregnancy Registry will collect prospective data on pregnancies and pregnancy outcomes on a voluntary basis in women with systemic lupus erythematosus (SLE) who have received commercially supplied belimumab within the 4 months prior to and/or during pregnancy. The registry will also evaluate outcomes of infants born to mothers who were exposed to belimumab within the 4 months prior to and/or during pregnancy.	July 2012 May 2019	500	US	1. belimumab	Birth defects, miscarriages, infant outcomes	Inclusion Criteria: Pregnant women supplied belimumab within 4 months prior to and/or during pregnancy
BEL114333, a Continuation Study of BEL113750 in Subjects With Systemic Lupus Erythematosus (SLE) in Northeast Asia, and in Japan Subjects Completing the Open-label	NCT01597622	This study provides subjects who complete the BEL113750 study the option of continuing treatment with belimumab (10 mg/kg intravenously every 4 weeks) for those randomized to belimumab, or the option to begin treatment with	June 2012 January 2016	420	Japan, Republic of Korea	1. 10 mg/kg administered intravenously over 1 hour every 4 weeks	AEs	Inclusion Criteria: Have completed BEL113750 through week 48



<b>Title</b>	<b>Trial Identifier</b>	<b>Description</b>	<b>Start Date Completion Date</b>	<b>Enrollment</b>	<b>Locations</b>	<b>Study Arms</b>	<b>Outcomes</b>	<b>Population</b>
Extension of HGS1006-C1115		belimumab for those randomized to placebo, as an add-on to their standard of care SLE therapy.						
Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis (BLISS-LN)	NCT01639339	The purpose of this study is to evaluate the efficacy, safety, and tolerability of belimumab in adult patients with active lupus nephritis.	July 2012 February 2017	464	17 countries including the UK	1. 10mg/kg IV belimumab plus SOC 2. Placebo plus SOC	Renal response at 104 weeks, AEs	Inclusion Criteria: Diagnosis of SLE, biopsy confirmed active lupus nephritis, autoantibody-positive
Belimumab Treatment Holiday and Treatment Re-start Study in Lupus Patients.	NCT02119156	This study will assess the effect of a 24-week withdrawal followed by a 28-week reintroduction of belimumab 10 mg/kg plus standard of care medications in subjects with stable low systemic lupus erythematosus (SLE) disease activity. Rebound phenomenon will be assessed for subjects who have permanently withdrawn from further belimumab treatment.	May 2014 May 2018	135	Japan, Republic of Korea	1. 6 month treatment holiday then restart belimumab for 6 months 2. 52 weeks belimumab treatment 3. 52 weeks SoC after belimumab treatment	SELENA SLEDAI at 52 weeks, SLE flare index	Inclusion Criteria: Received a minimum of 6 months therapy with 10mg/kg belimumab
A Phase 2B Open-Label, Single-Arm, Repeat-Dose Study to Evaluate the Reliability of an Autoinjector	NCT02124798	The study will assess the use of the disposable autoinjector assembled with the prefilled syringe containing the drug product belimumab with	May 2014 January 2015	100	US	1. Single use, disposable autoinjector	ability to self administer	Inclusion Criteria: Diagnosis of SLE, active SLE, autoantibody-positive, on IV belimumab

Title	Trial Identifier	Description	Start Date Completion Date	Enrollment	Locations	Study Arms	Outcomes	Population
		<p>unit dose strength of 200mg/mL and 1 mL will be given as a once weekly SC dose inside the clinic setting and outside the clinic setting. The study will also assess the safety and tolerability of belimumab administered subcutaneously (SC) via the autoinjector. Subjects will self-administer belimumab SC into the thigh or abdomen using the autoinjector device for 8 weekly doses.</p>						

## 5-Year Analysis of Phase 3 Safety and Organ Damage of belimumab Plus Standard Care in Patients with SLE

### Introduction:

BEL112233 (NCT# 00724867) and BEL112234 (NCT# 00712933) are ongoing multi-centre, phase 3, open-label continuation trials that enrolled patients who completed the BLISS-52 (BEL 110752) and BLISS-76 (BEL110751) trials. Patients voluntarily entered the continuation trials following completion of a parent BLISS trial and received belimumab plus standard SLE care (SC) every 4 weeks, regardless of treatment assignment in the parent trial. Data were pooled (parent data was included for these long-term continuation subjects if these subjects received active treatment, either 1mg/kg or 10mg/kg belimumab in the parent study) and an interim year analysis was conducted (201223) to assess the long-term safety and organ damage of treatment with belimumab in patients with systemic lupus erythematosus (SLE). Subjects receiving 1mg/kg belimumab in the parent study transitioned to a 10mg/kg dose in the extension study.

### Patient Population:

998 patients were eligible to be included in this analysis (enrolled and had at least one dose of belimumab in the extension studies); 268 patients came from BEL112233 and 730 patients came from BEL112234. At baseline, 94.2% were female, 36.3% were Hispanic or Latino, mean age was 38.7 (SD 11.49) years, mean duration of illness was 6.7 (SD 6.24) years and the mean SELENA-SLEDAI score was 8.2 (SD 4.18). 96.6% had anti-double stranded DNA and/or were auto-antibody positive, mean SDI score was 0.7 (SD 1.19). 411 (41.2%) of patients had organ damage (SDI  $\geq 1$ ) at baseline; 585 (58.6%) had no organ damage at baseline.

Concomitant medication use at baseline included: 31.2% anti-malarials+ corticosteroids, 25.3% corticosteroids + anti-malarials + immunosuppressants, 15.8% immunosuppressants + corticosteroids, 13.8% corticosteroids, 6.6% anti-malarials, 3.5% anti-malarials + immunosuppressants, and 2.2% immunosuppressants.

Overall, [redacted] patients withdrew ([redacted] patients are ongoing). The most common reasons for withdrawal included: [redacted] for patient request, [redacted] adverse events, [redacted] investigator decision, [redacted] lack of compliance and [redacted] lack of efficacy.

### Results:

**Adverse Events:** Overall, [redacted] of all patients reported an AE, [redacted] % reported a drug-related AE and [redacted] reported a serious adverse event (SAE) at some time point post-baseline. Table 1 details the frequency of AEs, drug-related AEs, AEs leading to study drug discontinuation and SAE over time.

	Year 0-1 N=998	Year 1-2 N=955	Year 2-3 N=861	Year 3-4 N=734	Year 4-5 N=655	Year 5-6 N=531	Any time post baseline N=998
At least one AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least one Drug-related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least one SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least one AE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 1: AE, drug-related AE, SAE and AE leading to study drug discontinuation reporting by year and for any time post-baseline (year intervals are based on the CRF reported intervals)

The most common drug-related AEs (>5%) by system organ class included: [REDACTED] infections/infestation, [REDACTED] gastrointestinal disorders, [REDACTED] general disorders and administration site conditions.

Of the AEs that resulted in study withdrawal, the most common AEs ( $\geq 3$  subjects) were classified in the following organ system classification: [REDACTED]

Adverse events of special interest that occurred at any time point post baseline included [REDACTED]

SDI Organ Damage: At years 5 -6, the mean change from baseline in SDI score (increase) overall was [REDACTED] (figure 1). ; [REDACTED] of patients reported no increase in SDI score.

When the presence or absence of organ damage at baseline was examined, [REDACTED] of patients without organ damage at baseline had no change in SDI at years 5-6 whereas [REDACTED] of subjects with organ damage at baseline had no change in SDI. Mean change in SDI for both subgroups was [REDACTED] at years 5-6 (figure 2).

*Figure 1: Mean SDI by year (year intervals are based on the CRF reported intervals)*

*Figure 2: Mean Change from baseline in SDI by year, by baseline SDI (year intervals are based on the CRF reported intervals)*

When SDI was examined by elevated SLEDAI score at baseline ( $\geq 10$ ), [REDACTED] had no change in SDI at years 5-6. When SDI was examined for those patients with elevated proteinuria ( $>0.5$  g/L24 hours) at baseline, [REDACTED] had no change in SDI at years 5-6.

Multi-state modeling was performed to estimate the probability of damage after 5 years. For those patients with no damage, the probability of remaining damage free at 5 years was [REDACTED], and for those patients with a damage score of 1, the probability of accruing no further damage after 5 years was [REDACTED].

A Kaplan Meier estimate of median time to first SDI worsening was not calculable, [REDACTED]  
[REDACTED]

### **Conclusion/Discussion:**

This interim analysis of patients with moderate to severe SLE treated with belimumab plus standard SLE care for 5-6 years demonstrated favorable tolerability. These safety results are similar to and extend the findings reported from the phase 2 open-label continuation patients (N=345) (Ginzler et al, *J Rheumatol.* 2014; 41(2):300-309) and are from a larger population (N=998).

In the first analysis of organ damage for patients on belimumab, the rate of accrual of organ damage was [REDACTED]. The rate of damage accrual was [REDACTED] in patients with organ damage at baseline, or those with elevated proteinuria at baseline.

### **Relevance of new organ damage data results to the Benlysta NICE Appraisal**

The summary document titled “5-Year Analysis of Phase 3 Safety and Organ Damage of Belimumab Plus Standard Care in Patients with SLE” presents interim data on the longer term follow-up of safety and of organ damage development for the SLE patients treated with belimumab who were originally enrolled in the two Phase 3 belimumab randomised controlled trials. GSK acknowledges that the target population for belimumab in the UK is a subgroup of these patients who demonstrate highly active disease, defined as low complement, positive anti-double stranded DNA and SELENA-SLEDAI  $\geq 10$  at baseline. Although the majority of results presented in the attached short summary document apply to the broader licensed population, top-line subgroup analysis has been presented for patients with a SELENA-SLEDAI  $\geq 10$  at baseline and the results for this subgroup appear to be consistent with the broader population. These initial analyses have only just been conducted and more detailed analysis is ongoing but will not be available in time for the next Appraisal Committee Meeting in October. However the reason we would like to bring these early data to the Appraisal Committee’s attention is because we feel it adds to the body of evidence on the longer term safety and effectiveness of belimumab. These are the first data to evaluate the accrual of damage in patients treated with belimumab. One of the areas of uncertainty raised by the Committee concerned the longer term effectiveness of belimumab so we hope that these data, in addition to the published 7-year data from the phase 2 extension study (Ginzler et al, *J Rheumatol.* 2014; 41(2):300-309) provide some reassurance towards this concern. Also, collecting real-life data via the UK BILAG registry would allow validation of these observations specifically for UK patients as detailed in our recent proposal to NICE to support the UK registry alongside a positive recommendation of access with further research.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Managed Access Agreement

### [Appraisal name]

<b>Date of Agreement</b>	<b>[Insert date]</b>
<b>NICE Agreement Manager</b>	<b>[Insert details of name of manager of this Agreement for NICE]</b>
<b>NHS England Agreement Manager</b>	<b>[Insert details of name of manager of this Agreement for NHS England]</b>
<b>[Company] Agreement Manager</b>	<b>[Insert details of name of manager of this Agreement for the company]</b>
<b>[Other] Agreement Manager</b>	<b>[Insert details of name of manager of this Agreement for (other e.g. research organisation)]</b>

## **1 Purpose of agreement**

- 1.1 To inform consideration of a recommendation with research (Section 6.4 Research recommendations, Guide to the methods of technology appraisal 2013) for [appraisal name].
- 1.2 The purpose of the agreement is to describe the arrangements and responsibilities for further research/data collection for [appraisal name], in the event that NICE issues a recommendation with research as specified in the NICE technology appraisal guidance (TA X).

## 2 Background

2.1 Background to appraisal.

2.2 When the evidence of clinical effectiveness or impact of a technology on other health outcomes is either absent, weak or uncertain, NICE's ['Guide to the methods of technology appraisal'](#) (section 6.4) states that the Appraisal Committee may recommend that the technology is used only in the context of research or while the technology is recommended as an option, research is also conducted.

2.3 Before issuing such recommendations, the Committee considers the following factors:

- the need for and potential value of additional evidence
- what certainty could be gained by reconsidering the decision in the light of research findings
- whether the research is feasible
- irrecoverable costs
- the likely net benefits for all NHS patients of use only in a research setting during the time that the recommended research is being conducted.

Recommendations on the use of technologies only in the context of research do not include consideration of funding. For further details of how an Appraisal Committee reaches its decision when recommending a technology as an option with research, see section 6.4 of ['Guide to the methods of technology appraisal'](#).

## 3 Commencement and period of agreement

3.1 This agreement shall take effect on... [publication of NICE final guidance] and will run until the publication of the review of TA



[appraisal number]. The NICE review of the guidance [TA X] is expected to start... [date].

## **4 Research/data collection**

4.1 If a recommendation with research is considered an appropriate option, the proposed patient population and data to be collected is as follows:

4.2.1 List specifics

## **5 Ownership of the Data**

5.1 Specify who owns the data being collected.

## **6 Data Analysis**

6.1 Specify details and timeframe of data analysis.

## **7 Timelines**

7.1 Upon publication of NICE guidance, data will be collected for... [specify timeframe].

7.2 A review of NICE guidance will be planned to start... [specify timeframe].

## **8 Funding**

8.1 Specify details of funding.

## **9 Publication**

9.1 Specify details/authorship of publications arising from this data collection/research.

**Signed by** **NICE**  
**[Insert name of Authorised Signatory] [for and on behalf of] [ ]**

**Signed by** **NHS England**  
**[Insert name of Authorised Signatory] [for and on behalf of] [ ]**

**Signed by** **Company**  
**[Insert details of name of manager of this Agreement for the company]**

**Signed by** **[Other e.g. research organisation]**  
**[Insert name of Authorised Signatory] [for and on behalf of] [ ]**