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. **Final Appraisal Determination (FAD)** issued to consultees and commentators on 19 April 2012

2. **Final Appeal panel decision** issued on 7 September 2013

3. **Manufacturer additional evidence submission** from GlaxoSmithKline in response to the final appeal panel decision

    - Post appeal submission with revised PAS
    - Post appeal submission appendix without PAS

4. **Evidence Review Group (ERG) response to the additional evidence** prepared by Warwick Evidence

    - The ERG response to the GSK post appeal information
    - The ERG's further response post-appeal regarding discontinuation rates
    - The ERG non PAS and PAS ICERs assuming a 11.66% discontinuation rate

5. **Decision Support Unit Project Specification form**

6. **DSU Report** prepared by the Decision Support Unit

7. **UK BILAG registry information** from GlaxoSmithKline

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 CLINICAL EXCELLENCE

Final appraisal determination

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

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 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.

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 (SPC), adverse reactions with belimumab include bronchitis, viral gastroenteritis, cystitis, pharyngitis, nasopharyngitis, leucopenia, 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 SPC.

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 SPC 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

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of belimumab and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 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.

3.2 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

3.3 The main evidence for the clinical effectiveness of belimumab was from two 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 (NSAIDs), antimalarials, corticosteroids or other immunosuppressants (azathioprine, methotrexate, and mycophenolate mofetil) either alone or in combination. Although

each of the BLISS trials were three-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.

3.4 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.

3.5 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.

3.6 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).

3.7 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 ($p = 0.02$).

3.8 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.

3.9 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 the BLISS-52, BLISS-76 or pooled analyses.

3.10 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.

3.11 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.

3.12 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 one 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 three (0.4%) in the standard care group, five (0.7%) in the 1 mg/kg group and six (0.9%) in the 10 mg/kg belimumab group. Four deaths were infection-related; one in the standard care group, one in the 1 mg/kg belimumab group and two in the 10 mg/kg belimumab group. Infection may have contributed to the deaths of two further patients (one in the 1 mg/kg belimumab group and one in the

10 mg/kg belimumab group). There were two suicides, both in patients receiving belimumab (one in the 1 mg/kg group and one in the 10 mg/kg group), and one 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.

3.13 The manufacturer explained that many 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

3.14 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.

3.15 The health states in the model were informed by data from the BLISS trials, observational cohort data (the Johns Hopkins cohort, see 3.17), 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 patient demonstrating a SELENA-SLEDAI score decrease of 4), 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.

3.16 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.

3.17 Prediction models based on data from the Johns Hopkins cohort were used to predict change in adjusted mean SLEDAI (AMS) score (which is used as a proxy for SELENA-SLEDAI score), average steroid 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.

3.18 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.

3.19 Steroid 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.

3.20 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 £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.

3.21 The model showed lower disease activity for patients on belimumab than in patients on standard care only, which led to decreased steroid 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.

3.22 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, reduced cumulative monthly steroid 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 two 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.

3.23 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.

3.24 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.

3.25 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.

3.26 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.

3.27 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.

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

3.28 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 steroid 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. An annual

discontinuation rate of approximately 13% was also observed in this trial.

3.29 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 QALY 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 QALY gained of 0.747.

3.30 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 up to a duration of 6 years with the newly available long-term data for belimumab from the phase II extension study (see section 3.28). 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.

3.31 According to the manufacturer it was appropriate to use NICE's clarification to section 5.6 of the Guide to methods of technology appraisals on the discounting of health benefits in special circumstances for a number of reasons. These were because of 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 steroids, 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. Further, 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.

Evidence Review Group comments on the original submission

3.32 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.

3.33 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.

3.34 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 scores changes.

3.35 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 of £65,530 per QALY gained.

3.36 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.

3.37 The ERG stated that the model assumed that patients whose disease had not responded to belimumab by week 24 (one third of patients) experienced the average SELENA-SLEDAI score seen with standard care (which includes approximately equal proportions of patients whose disease had responded and patients whose disease had not responded in the pooled target population). The ERG considered that this assumption 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.

3.38 The ERG noted that the adjusted mean SLEDAI score contributed to the likelihood of a 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 ten, with the target population, who all had scores of greater than ten at baseline.

3.39 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.

3.40 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.

3.41 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; rapid review of technology appraisal guidance 198]), 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.

3.42 The ERG completed an exploratory analysis that used the estimates from the single 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 single estimates. 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

3.43 The ERG commented on the new evidence provided by the manufacturer about the long-term steroid sparing effect of belimumab. The ERG noted that the basis of the calculations was not clear and the ERG questioned whether the average baseline steroid use was calculated for the same patients in whom steroid use was estimated at 6 years. The ERG stated that the manufacturer proposed that the steroid 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.

3.44 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 six revert to scores expected for patients receiving standard care, the AMS 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.

3.45 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.

3.46 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 steroid 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.

3.47 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.

3.48 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.

3.49 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.

3.50 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from 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. Further, 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 are currently treated with rituximab, frequently through individual funding requests. 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 steroids 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 the group of people for whom belimumab was indicated. The Committee therefore concluded that both rituximab and standard care were relevant comparators, as specified in the final scope and in the manufacturer's decision problem. The Committee was also aware that cyclophosphamide was also included as a comparator in the scope, 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. Further, it heard from clinical specialists that cyclophosphamide is used infrequently because of side effects.

4.4 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 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 in the SPC belimumab is indicated as an add-on treatment in patients with a high degree of disease activity despite standard therapies 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 inducing remission, but rather for maintenance therapy. In addition the Committee noted that the data supporting longer term use of belimumab used a continuous schedule of administration over 6 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 no efficacy data that reflects this use of belimumab is available.

4.5 The Committee discussed the population in the manufacturer's decision problem. It noted that the manufacturer focused on a target population who were 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. 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 antibody test), would be used for demonstrating evidence of serological disease activity and would detect changes in disease activity. The Committee concluded that though 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

4.6 The Committee discussed the manufacturer's submission of clinical evidence, noting that most of the evidence in the manufacturer's submission was from the two BLISS trials (BLISS-52 and BLISS-76) that compared belimumab against standard care. The Committee considered the composite end point of the 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 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 outcome in the trials.

4.7 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. Further, the Committee understood from the clinical specialists that clinical practice varies between countries, for example in the USA higher doses of steroids 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.

4.8 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. Further, 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.

4.9 The Committee discussed baseline standard care in the two 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.

4.10 The Committee discussed the results of the BLISS trials and noted that although in the individual trials the difference between the two arms for the primary outcome (the SRI) was statistically significant, the difference between the two arms for the components of the SRI were not statistically significant in BLISS-76, with the exception of the SELENA-SLEDAI outcome. The Committee also discussed the evidence of steroid sparing, noting that a statistically significant reduction in steroid use was observed in the pooled analysis. The Committee noted the absolute reduction in use was about 1 mg per day in the 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 two arms for the 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. Further, 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, nature of standard care and effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus (see sections 4.7, 4.8 and 4.9).

4.11 The Committee discussed the long-term data provided by the manufacturer from 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 steroid 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 reductions in steroid dose, noting that these showed an absolute reduction in steroid dose at 6 years of 5 mg a day. 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. 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 ERG that the reduction in steroid use modelled in the economic analyses showed an absolute change in steroid 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 steroids associated with belimumab treatment. However, the Committee understood the importance of reductions in steroid dose for patients and recognised the positive indications of these findings.

4.12 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 of rituximab compared with placebo from the EXPLORER trial and considered whether any indirect analysis 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 steroid 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 three outcomes for which an indirect comparison could be completed (that is, BILAG, SLEDAI and SF-36 scores), but data were only available in the public domain for the SF-36. The ERG also highlighted the differences in the trial populations, which it considered meant that the results of an indirect comparison were not meaningful. The Committee concluded that there are no reliable data to show the relative efficacy of belimumab compared with rituximab.

Cost effectiveness

4.13 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, steroid 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 steroid 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.

4.14 The Committee discussed the effects that the expected annual discontinuation rates for belimumab after the first 24 weeks, assumed in the original and revised models, had on the cost effectiveness of belimumab. The Committee noted that in the original model the manufacturer had assumed an 8% annual discontinuation rate after 24 weeks, based on data from the BLISS trials. In the manufacturer's additional evidence provided after consultation, longer term data were provided from the phase II extension study, which showed an annual discontinuation rate of 13%. The Committee noted the manufacturer's analysis in their original submission, which showed that a low discontinuation rate, such as 2%, increases the ICER to £85,900 per QALY gained, and

a higher discontinuation rate of 14% improves it to £54,500 per QALY gained. The Committee 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. It also noted that the reasons for discontinuation in the phase II extension study were not described. However, 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.

4.15 The Committee again discussed the expected duration of use of belimumab in clinical practice, noting that 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 was unlikely to reflect how belimumab would be used in clinical practice (see section 4.4). However, it was aware that the SPC 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 data for longer term use of belimumab were for a continuous schedule of administration in patients whose disease responded to treatment and the manufacturer's original and revised economic models used continuous treatment for potentially lifelong and 6 year durations of treatment, respectively. The Committee was therefore unable to make recommendations taking into account intermittent treatment or alternative administration schedules because there was neither efficacy data that reflected this use of belimumab nor any evidence of the cost effectiveness of such an approach.

4.16 The Committee discussed the revised analyses presented by the manufacturer, 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 clear that it was likely that in clinical practice belimumab would not be used continuously over a lifetime. 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 until 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 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 considered the continuation rules applied in the economic model, noting that the SPC 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 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 SPC. 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 and heard from the clinical specialists that they would prefer the lower continuation rule of an improvement of 4 points in the SELENA-SLEDAI score, and would be uneasy using the higher continuation rule of 6 points unless it reduced the base-case ICER to an acceptable level. The Committee discussed the additional analyses provided by the ERG, noting that the ICERs were only modestly sensitive to the application of different continuation rules, but on their own did not reduce the ICERs in the Committee's preferred base-case analyses to a level considered to be cost effective. The Committee noted that the ICERs provided by the ERG without the patient access scheme for belimumab assuming lifetime treatment were £61,200 and £53,700 per QALY gained for the scenarios with 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 (see section 3.48). 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. On balance, it was persuaded that the application of continuation rules was appropriate, but concluded that it was not appropriate to consider using the more restrictive rule of a SELENA-SLEDAI score improvement of 6 or more as the base-case analysis for decision making.

4.18 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. 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 for systemic lupus erythematosus, those patients whose disease responded to rituximab and who needed retreatment with rituximab at a later stage had shown a good response to retreatment. The Committee again noted that the only longer term data submitted by the manufacturer in relation to the benefit of belimumab was the open label phase II extension study which had been reported in a conference abstract (Petri et al. 2011). 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.

4.19 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 concluded that the manufacturer's approach may have overestimated the treatment effect of belimumab.

4.20 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 while 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 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.

4.21 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 they 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.

4.22 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 two 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. Further, the Committee noted comments from consultation that pharmacy preparation time had not been included in the economic analyses. The Committee concluded that administration costs had been underestimated, and agreed that a value of £154 should be used as in previous appraisals of intravenous treatments of rheumatoid arthritis.

4.23 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 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.

4.24 The Committee noted that in the additional analyses provided by the manufacturer a discount rate of 1.5% for health benefits had been proposed. 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 appraisals). 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 belimumab as it was currently modelled reflected a scenario where it was assumed there was continued treatment with continued benefit. This differed from the scenario that had led to the clarification of the methods guide, where there was limited duration of treatment with curative intent. Therefore the Committee concluded that belimumab did not meet the criteria for differential discounting of health benefits.

4.25 The Committee considered the cost effectiveness of belimumab in comparison with standard care. It discussed the ERG's additional analyses that included an annual discontinuation rate of 13% after week 24, an administration cost of £154 and benefits and costs discounted at 3.5%. It accepted the application of the continuation rule of SELENA-SLEDAI score of greater than or equal to 4 at 24 weeks (see section 4.17), but considered that this may overestimate the proportion of patients stopping treatment if

clinicians did not stop treatment in people who were improving, but had not reached an improvement of 4 points. The Committee recognised that a scenario reflecting lifetime continuous treatment may not accurately capture how belimumab would be used in clinical practice. However, it did not consider that the proposed 6 year maximum treatment duration was sufficiently evidence-based to use as a basis for decision making. Alternative scenarios including intermittent treatment or 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 without the patient access scheme was £61,200 per QALY gained, provided by the 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 noted that the ICER with the patient access scheme applied remained above the threshold range usually considered as an acceptable use of NHS resources. The Committee discussed the sensitivity analyses completed by the manufacturer as well as the exploratory analyses from the ERG. The Committee considered that the revised base-case ICER with the patient access scheme presented in the additional ERG analyses was at the lower end of the likely values for the ICER given the uncertainties associated with treatment effect, estimation of the benefits over time, the linking of short-term trial outcomes to long-term data with differing study populations, validity of the modelled gains in survival, and administration costs (see sections 4.18, 4.19, 4.13, 4.20 and 4.22). The Committee concluded that, compared with standard care, belimumab could not be considered a cost-effective use of NHS resources 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.

4.26 The Committee explored the cost-effectiveness argument for belimumab compared with rituximab. The Committee discussed the dosing of rituximab. It 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 two doses followed by a waiting period, rather than four 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. Further, the Committee noted that the costs of administration and pharmacy preparation for the treatments had not been included in the analyses, and including these would increase the costs for both drugs, but more so for belimumab because it is given every 4 weeks. It heard from the manufacturer that they considered it appropriate to compare the drug costs for both treatments as they had been used in clinical trials. Further, 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 was not persuaded that the comparison of costs provided by the manufacturer accurately reflected the costs of providing rituximab and belimumab in UK clinical practice.

4.27 The Committee considered the cost effectiveness of belimumab compared with rituximab. In the absence of any formal economic modelling, the Committee considered the comparison of costs of rituximab and belimumab. The Committee had previously discussed the clinical effectiveness of rituximab in comparison with belimumab (see section 4.12) and concluded that no reliable data

were available to demonstrate the relative efficacy of belimumab in comparison with rituximab. The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. For these reasons, the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources 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, compared with rituximab.

4.28 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 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. Further, there were no statistically significant differences at week 52 for FACIT-fatigue scores in the target population in people receiving belimumab compared with people receiving standard care. The Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life from belimumab had not been adequately captured. The Committee

concluded that the issues identified around innovation did not change its conclusions about the cost effectiveness of belimumab.

4.29 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
Key conclusion		
Belimumab is not recommended, within its licensed indication, as add-on therapy in adult 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. The Committee concluded that compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the most plausible ICER without the patient access scheme was £61,200 per QALY gained, provided by the 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 noted that the ICER with the patient access scheme applied remained above the threshold range usually considered as an acceptable use of NHS resources. There are no reliable data to show the relative efficacy of belimumab compared with rituximab. For the comparison of belimumab with rituximab the Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. Consequently, the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources, compared with rituximab.		1.1 4.10 4.25 4.12 4.27
Current practice		
Clinical need of patients, including the availability of alternative treatments	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 specifically for this disease.	4.2

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The treatment might be steroid sparing and may reduce the side effects of other drugs, especially corticosteroids. Few drugs are licensed for treating systemic lupus erythematosus. Belimumab was developed to target the underlying pathology of this disease.	4.2, 4.10 4.28
What is the position of the treatment in the pathway of care for the condition?	Between 10 and15% of systemic lupus erythematosus patients have high disease activity despite standard therapy. A proportion of these are currently treated with rituximab, frequently through individual funding requests. Belimumab would be used in a similar way to rituximab.	4.3
Adverse reactions	Adverse reactions were not a key factor in this appraisal.	
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	Most of the evidence in the manufacturer's submission was from the two BLISS trials (BLISS-52 and BLISS-76) that compared belimumab against standard care. There are no reliable data to show the relative efficacy of belimumab compared with rituximab.	4.6 4.12
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.	4.7
Uncertainties generated by the evidence	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, nature of standard of care and effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus.	4.10

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The manufacturer focused on a target population who were a subgroup of the marketing authorisation population and 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. The Committee concluded that though specifying a SELENA-SLEDAI score of greater than or equal to 10 may be considered arbitrary, the specified target population is clinically relevant.	4.5
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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 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.	4.10
Evidence for cost effectiveness		
Availability and nature of evidence	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.	4.13
Uncertainties around and plausibility of assumptions and inputs in the economic model	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.	4.13
	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.	4.14
	The Committee understood that continuous treatment over many years was unlikely to reflect how belimumab would be used in clinical practice. However, the SPC for belimumab describes	4.4 4.15 4.16

	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 for the choice of 6 years could not be considered sufficiently robust for use as the basis for decision making.	
	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.	4.18
	Although gains in survival from reduced organ damage were plausible, there was considerable uncertainty around the validity of the modelled gains in survival.	4.20
	Deriving cost data from different sources may have led to some inconsistencies in the estimates and the manufacturer may have underestimated some of the benefits associated with delaying certain types of organ damage.	4.23

Incorporation of health-related quality-of-life benefits and utility values 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?	The Committee noted that in the additional analyses provided by the manufacturer a discount rate of 1.5% for health benefits had been proposed. The Committee considered that belimumab as it was currently modelled reflected a scenario where there was continued treatment with continued benefit. This differed from the scenario that had led to the clarification of the methods guide, where there was limited duration of treatment with curative intent. Therefore the Committee concluded that belimumab did not meet the criteria for differential discounting of health benefits. 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. The Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life had not been adequately captured, noting in particular that FACIT-fatigue scores were not significantly better at week 52 in the target population in people receiving belimumab compared with people receiving standard care.	4.24 4.28 4.28
Are there specific groups of people for whom the technology is particularly cost effective?	The manufacturer focused on a target population, who were 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. The ICERs for the target population were lower than those for the marketing authorisation population.	4.5
What are the key drivers of cost effectiveness?	The model was driven by changes in the SELENA-SLEDAI score based on data from the Johns Hopkins cohort. Cost effectiveness was not particularly driven by other factors, such as steroid use.	4.13

Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered that the most plausible ICER without the patient access scheme was £61,200 per QALY gained, provided by the ERG. 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. The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. For these reasons, the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources 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, compared with rituximab.	4.25 4.27
Additional factors taken into account		
Patient access schemes (PPRS)	A patient access scheme which 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 an acceptable use of NHS resources.	4.25
End-of-life considerations	End-of-life considerations were not discussed.	
Equalities considerations and social value judgements	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 other groups.	4.29

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 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). [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 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 retreatment, and considered that these studies would be of value.

7 Related NICE guidance

There is no related guidance for this technology.

8 Review of guidance

8.1 The guidance on this technology will be considered for review in August 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Clark

Chair, Appraisal Committee

April 2012

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 Peter Clark (Chair)

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

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

Professor Usha Chakravarthy

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

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

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

Gillian Ells

Prescribing Advisor, NHS 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 Hutton

Professor of Health Economics, University of York

Professor Peter Jones

Emeritus Professor of Statistics, Keele University

Dr Steven Julious

Senior Lecturer in Medical Statistics, University of Sheffield

Rachel Lewis

Advanced Nurse Practitioner, Manchester Business School

Professor Femi Oyebode

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

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Cliff Snelling

Lay member

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray D Smith

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

Paddy Storrie

Lay Member

Charles Waddicor

Chief Executive, NHS Berkshire

C 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.

Dr Helen Starkie and Richard Diaz

Technical Lead(s)

Zoe Garrett

Technical Adviser

Kate Moore

Project Manager

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 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

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

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor 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 were also 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

D 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 were also invited to comment on the ACD.

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

E 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

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 18 July 2012 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus.

2. The Appeal Panel consisted of –
   Non-executive Directors: Prof Patrick Morrison (Chair), Ms Jenny Griffiths
   Industry Representative: Dr Mercia Page
   Lay Representative: Mr Peter Sanders
   NHS Member: Prof Robin Ferner

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The Panel considered appeals submitted by –
   GlaxoSmithKline ("the Company")
   Lupus UK
   Primary Care Rheumatology Society

5. The Company was represented by:
   Professor Patrick Valance
   Professor Paul-Peter Tak
   Mr Jason Foo
   Ms Toni Maslen
   Dr Adela Williams (legal representative)

6. Lupus UK was represented by:
   Ms Jane Dunnage

Professor David Isenberg

Professor Ian Bruce

7. The Primary Care Rheumatology Society was represented by:

Dr John Dickson

Dr Alastair Dickson

Dr Peter Lanyon

8. Professor Bruce declared that he had received research grants from GlaxoSmithKline and others. No other participant declared a conflict of interest.

9. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel:

Professor Peter Clark

Professor Jonathan Michaels

Mr Meindert Boysen

Ms Helen Knight

Ms Zoe Garrett

10. All the above declared no conflicts of interest

11. The Institute's legal adviser — Ms Eleanor Tunnicliffe of DAC Beachcroft LLP — was also present

12. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal. A limited part of the hearing was held in private (with all appellants' representatives present) at the request of the Company, as the Company wished to discuss information that was commercially sensitive.

13. There are three grounds under which an appeal can be lodged:

- The Institute has failed to act fairly
- The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted

- The Institute has exceeded its powers

14. On behalf of the Chair of the Appeal Committee Sir Michael Rawlins in preliminary correspondence had confirmed that:

    - The Company had potentially valid grounds of appeal as follows: Grounds 1, 2, and 3.
    - Lupus UK had potentially valid grounds of appeal as follows: Ground 2
    - The Primary Care Rheumatology Society had potentially valid grounds of appeal as follows: Grounds 2 and 3.

15. 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'.

16. The appraisal that is the subject of the current appeal provided advice to the NHS on the use of belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus.

17. Before the Appeal Panel inquired into the detailed complaints the following made preliminary statements:

    Professor Valance, for GlaxoSmithKline, stated that belimumab was a medicine with the potential to offer very significant benefits. It was innovative because it was the first drug to target B-lymphocyte stimulator, and therefore to deplete autoreactive B-cells preferentially. That was very different from drugs that depleted all B-cells. There were good clinical trial data showing that belimumab worked, and complementary safety data. It was the only drug shown to be effective in systemic lupus erythematosus. The Company could not understand how the Appraisal Committee had

arrived at the conclusion that they did. He was totally aligned with the need to ensure that NHS used cost-effective treatments. However, the Company could not understand how the cost-effectiveness of belimumab had been judged by comparison with rituximab, which was unlicensed and lacked trial evidence.

18. Professor Isenberg, for Lupus UK, described how lupus was an uncommon condition. He had cared for 650 patients over 30 years. The first 600 patients had an average age of onset of 29 years and an average survival of 15 years after diagnosis. Of them, 10–15% did not respond to standard treatments, or developed adverse effects to them.

Ms Dunnage, for Lupus UK, stated that there were only two drugs licensed for the treatment of systemic lupus erythematosus. The evidence assessed by the Appraisal Committee regarding belimumab was very uncertain, and that the Institute's failure to recommend belimumab would deprive patients of a medicine shown to have an effect on systemic lupus erythematosus. It would be better if the Institute authorized its use under strict controls so that more information could be acquired.

19. Dr Lanyon, for the Primary Care Rheumatology Society, introduced the Society's appeal. He noted that equity was a major strand in considering systemic lupus erythematosus. The Institute's guidance in rheumatoid arthritis had led to substantial improvements in care, independent of drug therapy. Severe systemic lupus erythematosus was rare and complex. Belimumab represented the first new drug for systemic lupus erythematosus for 50 years. Patients wanted safe and effective treatment.

Dr A Dickson, for the Primary Care Rheumatology Society, expressed concerns about the use of case series, the

sufficiency of sensitivity analyses, and other matters.

20. Professor Clark, on behalf of the Institute, emphasized that the Appraisal Committee understood that systemic lupus erythematosus was a debilitating, multi-system disorder that principally affected young women, that waxes and wanes, and that leads to significant morbidity and mortality. The Committee also knew that treatments were limited. It was important to recognize that, in a single technology appraisal such as this one, the burden of proving that a medicine was cost-effective rested on the Company, and not on the Appraisal Committee. Belimumab was clearly effective, but the Appraisal Committee judged it not to be cost-effective: the most plausible incremental cost-effectiveness ratio was too high; and there was a great deal of uncertainty around the incremental cost-effectiveness ratio, as described at length in the Appraisal Consultation Document and Final Appraisal Determination. The Appraisal Committee recognized that there remains unmet need. They had applied the rules in the Methods Guide, but still were unable to recommend the use of belimumab to the NHS, because the Committee had a duty to represent the interests of all NHS patients.

Appeal Ground 1: The Institute has failed to act fairly

Appeal Point Ground 1

GlaxoSmithKline

1.1 The innovative nature of belimumab has not been appropriately taken into account in this appraisal

21. Professor Tak, for the Company, argued that the Appraisal Committee had failed to take innovation into account. Fatigue, which is difficult to capture in outcome measures, showed a clinically significant improvement at first. Because subjects become acclimatized to their current state, changes are more difficult to show at 12 months.

The medication itself was innovative, as it was directed against a novel target, B-lymphocyte stimulator, that acted to increase autoantibody responses such as occurred in systemic lupus erythematosus. Belimumab really improved the quality of life and reduced disease activity when no other treatment did. Since a significant minority of patients failed to respond to standard treatments, belimumab fulfilled an unmet need.

Ms Maslen, for the Company, noted that for innovative products such as belimumab, the Institute should consider incremental cost-effectiveness ratios over £20,000 per quality-adjusted life-year.

22. Professor Clark, for the Appraisal Committee, told the Appeal Panel that the Committee did indeed recognize the innovative nature of belimumab, as had been clearly stated in the Company's submission, and also that innovation was important. As explained in sections 4.2 and 4.28 of the Final Appraisal Determination, the Appraisal Committee understood that belimumab interacted with a novel target and was the first medicine in its class. The Appraisal Committee had formally and fully discussed the several innovative features of belimumab. He took them in turn.

Flares

Flares were not explicitly allowed for in the Johns Hopkins cohort that formed the basis of the Company's economic model, but were indirectly captured. In retrospect, section 4.28 of the Final Appraisal Determination should state that effects on flare were 'not fully incorporated,' rather than 'not incorporated.'

Fatigue

The Evidence Review Group had reviewed the data on fatigue.

It only improved at one time-point, and was anyway reflected in EQ-5D scores, which were included in the model, and in SF-36 scores.

Delay in organ damage

The postulated reduction in organ damage was incorporated in the model, and was a major reason why the model showed benefit, as described in section 4.20 of the Final Appraisal Determination. The Appraisal Committee was conscious that the BLISS clinical trials whose results formed the basis for the Company's submission excluded patients with damage to the kidneys or lungs.

Steroid sparing

Steroid sparing was clearly important, and the reduction in corticosteroid dose in the BLISS trials, which were masked, underestimated the likely reduction in practice. The six-year Petri continuation cohort described in section 4.11 of the Final Appraisal Determination gave a more realistic picture. The model assumptions about organ damage relied on information about the reduction in corticosteroid dosage.

Novel mode of action

The Committee was mindful of belimumab's mode of action.

Taking all these factors into account, the Appraisal Committee came to the view that the incremental cost-effectiveness ratio captured all of them other than some aspects of the effect on disease flares. Its deliberations were consistent with the Institute's Methods Guide, at paragraph 6.2.2.3, and the Appraisal Committee took into account that the incremental cost-effectiveness ratio without allowing for the Patient Access Scheme (PAS) was around £61,000 per quality-adjusted life

year.

23. Professor Tak put before the Appeal Panel a copy of a graph of mean change in fatigue scores in patients with high disease activity treated with belimumab or placebo over 52 weeks, that showed significant difference between the two groups at eight and 12 weeks (although not at three other times). He accepted that the data had been one of four such graphs included in the Company's submission, had been restricted to a subset of patients specified after the trial had been completed, and had shown no significant difference in the area-under-the-curve, an integrated measure of the result.

Professor Valance stated that modelling was difficult, and underestimated corticosteroid reduction—the Company's latest estimate was a reduction in practice twice as large as assumed in the model.

24. The Appeal Panel considered the arguments advanced by the Company and the response of the Appraisal Committee. They noted that the Appraisal Committee was clearly aware of the several innovative aspects of belimumab and had considered them carefully, and in a manner consistent with the Institute's Methods Guide. They had understood the need to consider which benefits of innovation were captured in the incremental cost-effectiveness ratio and which were not, had considered them, and had found that the likely benefits to patients of the innovation were insufficient to bring the incremental cost-effectiveness ratio within the acceptable range.

25. The Appeal Panel concluded that the Appraisal Committee had not acted unfairly.

26. The Appeal Panel therefore dismissed this appeal point.

Appeal Point Ground 1

GlaxoSmithKline

1.2 The Committee's decision to reject GlaxoSmithKline's proposal that

discontinuation of treatment with belimumab after week 24 should be considered if there was no improvement in a patient's SELENA-SLEDAI score of 6 points or more is not explained

27. Ms Maslen, for the Company, stated that the Appraisal Committee had failed to explain clearly why it had dismissed the proposed continuation rule, which was that patients should only continue treatment after six months if they improved by at least 6 points on the SELENA-SLEDAI score. The Appraisal Committee had been willing to accept the principle that SELENA-SLEDAI score determine whether treatment continue, since it had based its original discussions on an alternative continuation rule, namely that the SELENA-SLEDAI score improve by at least 4 points after six months of treatment.

28. Professor Clark responded on behalf of the Appraisal Committee that a series of selections had been required in the Company's original submission: from the two BLISS trial cohorts, the Company had selected a subset of patients for the Marketing Authorization submission; and for the Institute submission, they had selected from the Marketing Authorization subset a smaller group, the target population. They had subsequently constructed a continuation rule and also a stopping rule, limiting treatment to successively smaller subsets of patients all of which had been specified after the trial had been completed.

The Appraisal Committee had considered the amended continuation rule in great detail. The SELENA-SLEDAI score, which was not routinely used in clinical practice, included both patient symptoms and laboratory measures. Clinical experts had told the Appraisal Committee that they would be reluctant to cease treatment if a patient had shown an improvement of 4 points on the SELENA-SLEDAI score, since that had been

judged a clinically significant improvement by, among others, the United States Food & Drug Administration. The Appraisal Committee was therefore worried that the amended continuation rule would be difficult to apply in practice; and the six-year continuation study had suggested that belimumab leads to continual improvement over time, so that even the 4 point continuation rule might be difficult to implement.

There were also concerns that stopping treatment at six months would lead to disease flares, as happened with hydroxychloroquine.

29. Professor Valance replied that, if it was true that improvement continued over six years, then belimumab was in fact more effective than the Appraisal Committee had allowed; and the revised continuation rule improved the cost-effectiveness.

Professor Tak noted that, by analogy with rheumatoid arthritis, introduction of good systems of assessment and of treatment success would improve care in systemic lupus erythematosus. Moving from 4 to 6 points would enhance the clinical benefit of belimumab.

Dr Williams, for the Company, stated that the appeal was on grounds of fairness. It was not for the Appraisal Committee to take into account the policing of the rule, given that it did not consider policing the 4 point rule to be a difficulty. It was not fair that, having accepted a continuation rule based on 4 points, it should reject a continuation rule based on 6 points.

Professor Isenberg and Dr A Dickson echoed Professor Tak's views on the desirability of improved standards for the care of systemic lupus erythematosus, mandated by the Institute.

Professor Clark referred to the Institute's Methods Guide

section 5.10.12 with regard to continuation rules, and noted that the Appraisal Committee had considered the robustness and plausibility of the endpoint, which in this case was based on a *post hoc* rule in a population defined *post hoc*; the appropriateness of the time at which the response was measured, which at six months was short even using the 4 point rule (clinicians would prefer to make a decision at 12 months); the incorporation of the rule into clinical practice, which was possible but would require introduction of the SELENA-SLEDAI score; the ability of the rule to select those in whom the technology is particularly cost-effective, about which there was uncertainty; and issues with respect to withdrawal, about which the Appraisal Committee had significant concerns regarding rebound and regarding data from other studies.

Mr Boysen, for the Appraisal Committee, considered that the difficulty was that section 4.17 of the Final Appraisal Determination might not have explained clearly enough the reasoning of the Committee.

30. The Appeal Panel understood from Professor Clark that the Appraisal Committee had in fact considered in detail whether a continuation rule based an improvement of at least 6 points in SELENA-SLEDAI score was appropriate, but agreed that the reasoning was not sufficiently well explained in the Final Appraisal Determination, in particular why a 4 point rule was acceptable but a 6 point rule was not, for the appellant to engage fairly with the range of issues considered.

31. The Appeal Panel therefore upheld this appeal point.

Appeal Ground 2: The Institute has formulated guidance that cannot be reasonably justified in the light of the evidence submitted

Appeal Point Ground 2

Lupus UK

2.1 [The institute is premature in issuing its decision.] It should ensure that it has all relevant data necessary before it makes a final decision and ... by making a decision at this point it will leave some lupus patients who have the most difficult manifestations of the illness paying a very heavy physical price, without effective treatment.

32. Professor Bruce, for Lupus UK, explained that the estimates of benefit from belimumab were very uncertain. There were two large clinical trials, but the model was based on data from the Johns Hopkins cohort. In systemic lupus erythematosus many adverse effects were the result of uncontrolled disease activity, and so treatments that controlled the disease were likely to yield long-term survival benefits. There was uncertainty regarding the utility of rituximab (a comparator in this appraisal); and regarding the effect of stopping or tapering treatment or using it intermittently. While it was true that the BLISS cohorts did not include the full range of adverse effects from systemic lupus erythematosus, the trials followed the standard research practice of separating lupus nephritis from other manifestations of the disease.

Lupus UK was keen that belimumab be used in a cohort of patients in the United Kingdom in the context of a systemic lupus erythematosus Biologics Register, such as had been successfully used for audit and research in other rheumatic diseases. The negative decision of the Appraisal Committee made that impossible. He noted that a high proportion of patients with systemic lupus erythematosus in the United Kingdom were from ethnic minority backgrounds.

In summary, the degree of uncertainty made the decision unreasonable.

Professor Clark explained that the manufacturer has submitted an economic model based on the Johns Hopkins cohort, and the
Evidence Review Group agreed that this was reasonable.

The Appraisal Committee had considered intermittent use of belimumab, as clinical experts suggested that the drug would be used in a similar way to other biologics; but the Company had wanted usage to conform to the *Summary of Product Characteristics*, that is, continuous use.

The exclusion of patients with kidney or lung damage from the belimumab trials had increased the uncertainty around the estimates of cost-effectiveness.

The Appraisal Committee must use the evidence provided to it when making assessment, but must also provide a timely decision. There is inevitable uncertainty. In this instance, the Company had not provided a sensitivity analysis of the extrapolated benefits.

When an incremental cost-effectiveness ratio exceeds £30,000 per quality-adjusted life year the Appraisal Committee has to advance increasingly strong reasons for accepting a technology. The Company were open about uncertainties, and the Evidence Review Group added further uncertainties. If the Appraisal Committee had delayed making a decision until all the uncertainties had been resolved, then the decision would have been greatly delayed.

All the more plausible incremental cost-effectiveness ratios were outside the acceptable range.

Professor Bruce offered the Registry he had described, suggesting it would allow a path through the uncertainty by contributing to evidence collection—a form of research.

Professor Clark told the Appeal Panel that this suggestion had not previously been put to the Appraisal Committee, who were aware of the Biologics Registry for patients with rheumatoid arthritis, and of the French Registry data for systemic lupus erythematosus.

The Panel asked Professor Clark whether the Committee had been comfortable dealing with the level of uncertainty present in this appraisal. Professor Clark replied that the Committee had been.

33. The Appeal Panel considered whether the Appraisal Committee had been unreasonable in making a decision on the basis of the evidence before it, given the uncertainties. The Panel were persuaded that the Appraisal Committee had taken proper account of the uncertainties and had sufficient information on which to base a recommendation. The suggestion to set up a Registry to collect data that would reduce the uncertainty was interesting, but had not been made to the Appraisal Committee.

34. The Appeal Panel therefore rejected this appeal point.

Appeal Point Ground 2

Lupus UK

2.2 LUPUS UK also consider that the comments which the Final Appraisal Determination has made on rituximab have caused considerable confusion and increased the uncertainty about treatment of lupus patients. A direct comparison with this drug cannot be made as is frequently referred to, because the measured outcomes are different from the BLISS trials.

35. Professor Isenberg, for Lupus UK, stated that rituximab had been widely used in treating systemic lupus erythematosus,

but the EXPLORER trial that had examined its use in non-renal systemic lupus erythematosus had shown no difference from placebo in the primary end-point. In the absence of further efficacy data, rituximab and belimumab could not be compared. The Final Appraisal Determination implied that rituximab was effective, but this had not been demonstrated.

36. Professor Clark replied that rituximab was included as a comparator because it is used in routine practice in the NHS. The Company had identified it as a relevant comparator in its comments on the Scope. As explained in section 4.12 of the Final Appraisal Determination, there was no trial directly comparing belimumab with rituximab. All those involved agreed that an indirect comparison of efficacy was not possible, because of the differences between EXPLORER and BLISS. This left the French Registry data, which the Appraisal Committee had considered. The Company in its submission had made what it considered to be a conservative assumption that the efficacy of belimumab was equal to that of rituximab. Given the assumption of equal efficacy, the comparison reduced to a discussion of the relative costs, about which the Committee had considerable concerns. These related to the dosing schedule for rituximab, to the pharmacy costs, and to the differences in the characteristics of patients treated in the EXPLORER and BLISS trials. The appraisal was a single technology appraisal of belimumab, not of rituximab or any other product: the onus was on the Company to demonstrate that belimumab was cost-effective. The guidance on the use of belimumab made no recommendation regarding the use of rituximab.

Ms Dunnage, for Lupus UK, emphasized that rituximab was not the same drug as belimumab. The Final Appraisal Determination was being read by Primary Care Trusts as

saying that rituximab should not be funded as 'it had not reached its end-point in trials,' while at the same time failing to recommend belimumab, which had reached its end-points. She supported Professor Bruce's suggestion of a registry.

Professor Clark reiterated that rituximab was in fact used in the NHS, and therefore was a reasonable comparator. Professor Isenberg had advised the Appraisal Committee that 'rituximab has been a salvation'. In any event, the Final Appraisal Determination dealt very largely with a comparison between belimumab and standard care, and the comparison with rituximab occupied only a small part, proportionate to the discussion of that comparison. The Company had not included rituximab in any model of the cost-effectiveness of belimumab.

Professor Bruce expressed the view that the Final Appraisal Determination was perverse, because it suggested the use of rituximab, which was used off-label, and whose efficacy had not been shown, while denying the use of the licensed product belimumab, whose efficacy was demonstrated in randomized controlled trials.

37. The Appeal Panel considered the possibility that the Final Appraisal Determination be read as an endorsement of the use of rituximab. It accepted that the Appraisal Committee was correct in characterizing a Single Technology Appraisal as an assessment of the cost-effectiveness of a single technology, and not in any way as an assessment of or guidance on comparators. The Panel did not accept that the Final Appraisal Determination supported the use of rituximab. The recommendations related only to belimumab.

38. The Appeal Panel therefore rejected this appeal point.

39. The Appeal Panel asks the Institute Board to consider the inclusion of a standard introductory paragraph reiterating the

nature and purpose of the Single Technology Appraisal in each piece of guidance produced under the Single Technology Appraisal process.

Appeal Point Ground 2

GlaxoSmithKline

2.1 The Committee's findings in relation to the clinical and cost-effectiveness of belimumab compared with rituximab are unreasonable in the context of the available evidence and the licence status of rituximab

40. The Panel heard from Dr Williams on behalf of the Company. Dr Williams explained that the Company thought it was appropriate to have rituximab as a comparator in this appraisal, since it was used in the NHS. Rituximab was used off-label. No robust data existed to demonstrate that it was clinically effective. Therefore, it was not reasonable to require the Company to provide a robust comparison of the relative clinical effectiveness of belimumab and rituximab. Nor was it reasonable to assume that lower doses of rituximab would be used. In summary it was not reasonable to refuse to recommend belimumab because it did not demonstrate cost-effectiveness in comparison with rituximab.

The Appeal Panel heard from Professor Clark for the Committee. Professor Clark explained there were no head-to-head trials of rituximab against belimumab. Within the Single Technology Appraisal process there was no facility for the Committee to itself produce such comparison. The Committee acknowledged that any indirect comparison between the two technologies using the BLISS and EXPLORER data was difficult. Professor Clark noted that the EXPLORER trial of rituximab compared to placebo did not demonstrate efficacy but the bar in that trial was set high compared to the bar in the BLISS trials.

Professor Clark went on to outline the steps the Committee considered the Company could have taken in order to obtain better data about the relative efficacy of belimumab compared to rituximab. The Company could have extracted relevant patient level data from the EXPLORER trial, or could have used the French Registry data.

The Company had suggested that the Committee adopt an assumption of equal effectiveness. Working on that assumption, the issue between rituximab and belimumab was one of cost. [redacted].

The Committee was not able to assess relative clinical effectiveness in the way that it would have liked but the Committee's approach was not unreasonable.

41. The Appeal Panel noted the legal advice it had received in respect of the Company's Ground 3 appeal points. The advice touches on the issue of how a lack of data about a comparator should be dealt with (see paragraph 7).

The Appeal Panel accepted that as a general rule it is for manufacturers to establish that their technology is a cost effective use of NHS resources. However, the Panel recognised the difficulties faced by the Company in doing so in this appraisal, given the limited data on the use of rituximab.

The Panel noted the comments from Professor Clark that the Company could have done more to explore the relative cost-effectiveness of belimumab, in particular by extracting patient level data from the EXPLORER trial or using the French

Registry data. The Panel noted the statement in the Final Appraisal Determination that the Expert Review Group considered that the results of any indirect comparison between EXPLORER and BLISS would not be meaningful and the Committee's conclusion that *"there are no reliable data to show the relative efficacy of belimumab compared with rituximab"* [FAD 4.12]. In these circumstances the Panel did not consider it reasonable to require the Company to demonstrate relative clinical and cost-effectiveness when compared with rituximab.

The next question the Panel considered was whether the Committee had, in fact, required the Company to demonstrate cost-effectiveness in comparison with rituximab. Professor Clark stated at the hearing (in relation to GSK Ground 3.1) that had belimumab been cost-effective against standard care the Committee would have recommended its use regardless of the lack of an outcome in belimumab's favour in its comparison with rituximab. The Panel considered that this approach would have answered the Company's complaint but were unable to find evidence from the Final Appraisal Determination or from supporting documents that the Appraisal Committee had in fact adopted it.

The Panel understood from the hearing that the Committee had dealt with the paucity of data on rituximab by adopting an assumption (proposed by the Company) that belimumab and rituximab were equally efficacious. The Committee had then gone on to assess the costs relating to each technology. However, this is not clear from the Final Appraisal Determination which reiterates in its concluding paragraph on relative cost-effectiveness with rituximab that *"no reliable data were available to demonstrate the relative efficacy of belimumab compared with rituximab"* [4.27]. In that paragraph

the Committee reached a conclusion on cost-effectiveness compared with rituximab: *"The Committee concluded that there was no sound case presented to it on the cost-effectiveness of belimumab compared with rituximab. For these reasons, the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources… compared with rituximab."* (Panel's emphasis).

It therefore appeared from the Final Appraisal Determination and supporting documentation that the shortage of data relating to rituximab has led the Committee to conclude that the use of belimumab would not be a cost-effective use of NHS resources. As the Committee has concluded elsewhere in the Final Appraisal Determination that *"no reliable data were available to demonstrate the relative efficacy of belimumab compared with rituximab"* [4.27] and in the Panel's view the Company was not in a position to remedy the shortage, the Panel determined that the conclusions in the Final Appraisal Determination regarding the comparison of rituximab and belimumab were not reasonable in light of the evidence submitted.

The Panel understood that the exploration of the costs associated with rituximab was in part necessary [redacted]. While the Panel appreciated the desire to reduce to a minimum the amount of commercial-in-confidence information that had to be removed from the public version of the NICE Guidance, the priority must be that the Final Appraisal Determination is adequately reasoned. As the Final Appraisal Determination stands, it appears that the Committee has reached a conclusion on the cost-effectiveness of belimumab compared with rituximab based solely on an assessment of costs. If the

costs of rituximab needed to be explored in order to understand the value of the manufacturer's patient access scheme, this should have been stated explicitly and dealt with separately.

Furthermore, if there was a point on which the Committee was unable to reach a conclusion due to a lack of data, this should have been distinguished from a situation where there was a limited amount of data that were unpersuasive.

42. The Appeal Panel therefore upheld this appeal point.

Appeal Point Ground 2

GlaxoSmithKline

2.2 The Committee's conclusion that the choice of a maximum treatment duration of 6 years could not be considered sufficiently robust for decision making is unreasonable

43. Professor Tak described how in clinical practice 50% of patients treated for rheumatoid arthritis with tumour necrosis factor-alpha inhibitors are able to discontinue treatment within 2–5 years. Early treatment that controlled the disease showed continued benefits. In the revised base case for belimumab submitted by the Company, 6 years was consistent with the likely manner in which it would be used.

44. Professor Clark explained to the Panel that the clinical experts said belimumab would be used in the way rituximab was currently used: the dose would be reduced if the patient's disease went into remission, and increased if the disease relapsed. The experts said that some patients would be treated for less than six years, and some for longer. By contrast, the clinical trial data came from the Petri continuation study, in which the majority of patients treated for two years continued treatment at six years. That cohort showed sustained benefits in the long term. The Appraisal Committee

were therefore concerned that stopping treatment at six years would reduce the benefit of treatment, and were uncertain about withdrawal effects.

The Appraisal Committee were not provided with evidence for intermittent treatment and therefore made no recommendation about such use.

Professor Valance informed the Appeal Panel that the six year study was a safety cohort, in whom adherence was encouraged.

Professor Tak stated that very few patients with rheumatoid arthritis were treated with biologics for more than five years.

Ms Garrett, for the Institute, stated that all the Institute assessments of drugs for rheumatoid arthritis were based on an open duration of treatment with natural discontinuation.

45. The Appeal Panel listened to the arguments for and against the adoption of a stopping rule for treatment after six years, and understood the position taken by the Committee. As the evidence from the single continuation cohort appeared to show sustained use of belimumab at 6 years, it was reasonable to conclude that it was inappropriate to assume that treatment would cease at six years.

46. The Appeal Panel therefore rejected this appeal point.

Appeal Point Ground 2

GlaxoSmithKline

2.3 The Appraisal Committee's conclusion that there is uncertainty about whether the treatment effect of belimumab is maintained over time does not reflect the available evidence and is therefore unreasonable

47. Professor Tak stated that there were no data to suggest that the effect of treatment waned over time. Since a long-term

randomized controlled trial was very unlikely to gain ethics committee approval, no such data were likely to be forthcoming.

48. Professor Clark drew the Appeal Panel's attention to sections 4.18 and 4.25 of the Final Appraisal Determination. The model of cost-effectiveness assumed that the effect of belimumab was maintained over time. The data to support this were limited. The only long-term data submitted by the Company came from a conference abstract describing the Petri Phase II study, not the randomized trials.

49. The Appeal Panel considered whether it was reasonable for the Committee to conclude that there is uncertainty about whether the treatment effect of belimumab is maintained over time. Given the limited data available about long-term treatment effect, the Panel concluded that the Committee's view could be reasonably justified in light of the evidence submitted.

50. The Appeal Panel therefore rejected this appeal point.

Appeal Point Ground 2

The Primary Care Rheumatology Society

2.1. We consider that one of the main flaws to the guidance is the prominence given in the decision making process, to a comparison of rituximab with belimumab

51. Dr Peter Lanyon, for the Primary Care Rheumatology Society, stated that there were no reliable data comparing belimumab with rituximab, and therefore no reasonable way in which the incremental cost-effectiveness ratios for belimumab and rituximab could be compared.

The funding of rituximab depended on local discussion with Commissioners, and in the presence of a licensed product for systemic lupus erythematosus, it would be increasingly difficult to persuade Commissioners to fund rituximab; but the Final

Appraisal Determination did not support the use of belimumab.

52. Professor Clark for the Committee explained that the Company, the Evidence Review Group, and the Appraisal Committee agreed that rituximab was used in the NHS to treat patients with systemic lupus erythematosus, and was therefore an appropriate comparator. There was good evidence regarding the principal comparison between belimumab and standard care, and that was modelled by the Company. The comparison between belimumab and rituximab was made on the assumption of equal efficacy put forward by the Company, so that only the relative costs were in fact compared.

Rituximab was used in the NHS to treat systemic lupus erythematosus as a matter of fact, so it was a valid comparator. Its status as a licensed product used off-label was not relevant.

The Appraisal Committee was aware that rituximab was not shown to be effective in the EXPLORER trial, and had discussed that issue. In rejecting belimumab, the Appraisal Committee had stated that there was no reliable comparison between belimumab and rituximab, while there was a more robust comparison with standard care. The rejection of belimumab was based on that, [redacted]. The decision to use rituximab as a comparator was rational.

Dr A Dickson suggested that a meta-analysis of results of trials involving rituximab might be helpful, although Professor Clark explained that this was not for the Institute to undertake in the course of a Single Technology Appraisal. Ms Maslen pointed

out that no such analysis was possible, because the two randomized trials of rituximab were in mutually exclusive populations.

53. The Panel was unpersuaded that the time given in the Final Appraisal Determination to discussing the comparison of belimumab with rituximab was not justified in light of the evidence submitted. Rituximab was named as a comparator in the scope so needed to be considered. Most of the discussion in the Final Appraisal Determination centred on the comparison with standard care.

54. The Appeal Panel therefore rejected the appeal on this ground.

Appeal Ground 3: The Institute has exceeded its powers

Appeal Point Ground 3

GlaxoSmithKline

3.1 [originally ground 1.3]

The Appraisal Committee's finding that belimumab has not been shown to represent a cost-effective use of NHS resources compared with rituximab, acts to protect continued use of a product which is not authorised for the condition under consideration, contrary to the medicines licensing regime and the European Court decision in Case C-185/10 European Commission v. Republic of Poland ("the Poland case")

55. Following the reallocation of this ground from ground 1 to ground 3 at the initial scrutiny stage, the Company submitted further legal arguments directed towards ground 3 ("GlaxoSmithKline legal submissions"). It divided these arguments into four strands, each of which is dealt with below.

56. The Panel received advice from its legal advisors in advance of the hearing in respect of the GlaxoSmithKline legal submissions. This advice was circulated to the appellants in advance of the hearing. .

57. **(i) The conclusion that belimumab should not be recommended unless GlaxoSmithKline is able to robustly**

demonstrate its cost-effectiveness compared with "off-label" rituximab, despite the lack of any RCT data indicating that rituximab is effective in this indication, undermines the protection to public health provided by the medicines licensing regime (GlaxoSmithKline legal submissions para 17-21).

The Panel considered that this point could be broken down into two parts: (a) a complaint about the way in which the Company had been required to demonstrate the cost-effectiveness of belimumab against rituximab and (b) an argument that the Final Appraisal Determination was unlawful because through it NICE supports or prefers off-label use by clinicians.

(a) Demonstrating comparative clinical and cost effectiveness

The Company referred to its written submissions on this point. The Panel heard from the Committee that in a single technology appraisal (STA) the onus was on the manufacturer to demonstrate the cost-effectiveness of their technology. The Committee considered that the Company could have used data from the clinical trials or from the French Registry, or both, to compare the clinical effectiveness of belimumab and rituximab; or alternatively could have concluded that no comparison was possible. However, the Company did not do this, but asked the Committee to adopt an assumption of equal efficacy of the two technologies. The Committee went on to explain that if belimumab had been found to be cost-effective against standard care, then the Committee would have recommended its use irrespective of cost-effectiveness when compared with rituximab.

58. The Panel concluded that the fact that the comparator technology was being prescribed off-label did not add anything to the argument that the Company had unreasonably been

required to demonstrate relative cost-effectiveness and clinical effectiveness against rituximab in a situation where it was not possible to do so due to a paucity of evidence about the comparator (rather than about the Company's own technology). It may well be the case that there will often be less evidence in respect of an off-label use, but that is a question of fact rather than a matter of law. This argument (i.e. without the European Law and licensing dimension) was made by the Company under their ground 2.1, which had been allowed by the Panel.

So far as the European Law aspects of this argument are concerned, these are dealt with below in relation to the Company's arguments on the *Poland* case.

59. ***(b) Supporting or preferring off-label use***

The Company referred to its written submissions, which it reiterated at the hearing.

60. The Panel heard from the Committee that the Final Appraisal Determination did not endorse or support the use of the off-label comparator. Rather it made recommendations about belimumab as it had been tasked to do by the scope. NICE guidance was not a ban on the use of belimumab within the NHS as all NICE guidance was stated to be subject to clinical judgment. It was unclear what would happen to rituximab use if the Final Appraisal Determination were to become NICE Guidance. Finally, it was not NICE's job to regulate use of unlicensed products. The existence of the licence for a comparator could not be a consideration, nor was it, when deciding upon the recommendations to be made in respect of belimumab.

61. The Panel was unpersuaded that the Final Appraisal Determination "preferred" or "supported" the use of the off-label comparator. The Final Appraisal Determination provided

guidance on the use of belimumab alone. It did not provide guidance on the off-label comparator and could not do so, given the terms of the scope. Furthermore, having concluded that belimumab was not a cost-effective use of NHS resources on the usual approach (as set out in the Methods Guide) it would have been inappropriate for the Committee to make a different recommendation simply in an attempt to reduce off-label use of the comparator. It was not NICE's role to police compliance with the marketing authorisations or the Directive which set up the marketing authorisation system.

62. **(ii) [The Final Appraisal Determination] is inconsistent with guidance issued by the MHRA in April 2009, entitled "Off-label or unlicensed use of medicines: prescribers' responsibilities"**

The Company referred to its written submissions. The Panel heard from the Committee that in the Committee's view nothing in the MHRA Guidance or GMC Guidance conflicted with the Final Appraisal Determination. If clinicians wished their patients to access belimumab they could prescribe it and pursue an individual funding request. The Final Appraisal Determination did not advocate off-label use of rituximab.

Peter Lanyon and Professor Isenberg explained that in practice it would be difficult to access belimumab if it was not recommended by NICE.

63. The Panel concluded that, for the reasons outlined above, the Final Appraisal Determination did not advocate off-label use of rituximab. The recommendations in the Final Appraisal Determination were not inconsistent with the MHRA and GMC Guidance.

64. **(iii) [The Final Appraisal Determination] is inconsistent with the decision of the European Court in Case C-185/10 *European Commission v. Republic of Poland.***

65. Dr Adela Williams representing the Company referred to the GlaxoSmithKline legal submissions. In response to the legal advice provided to the Panel by DAC Beachcroft LLP Dr Williams argued that NICE's role was not outside the scope of the Directive.

So far as the Court of Appeal permission decision that was referred to in the DAC Beachcroft advice was concerned, Dr Williams considered that Jacob LJ's words could not be taken at face value as it was manifestly incorrect that European licensing has nothing to do with NICE. For example, NICE only appraises products that are licensed for use within the proposed indication (i.e. for the use to be considered by the appraisal).

66. Dr Williams argued that the *Poland* case was clear that although member states had the power to organise their own health systems, this had to be undertaken in accordance with the Directive 2001/83 (the Licensing Directive).

Dr Williams acknowledged that the facts in the *Poland* case were different from those in this appraisal. In *Poland* the drugs were completely unlicensed, whereas in this appraisal NICE was considering off-label use of a licensed comparator medicine. Furthermore, in the *Poland* case the imported drugs had the same active ingredients as licensed products. The only reason for the import was because the unlicensed drugs were cheaper.

Regarding off-label use, the rationale behind the licensing regime was to protect public health. Safety concerns were relevant to off-label use as well as unlicensed use.

Extrapolating from the *Poland* case it was wrong to recommend off-label use of a product over a licensed

alternative or to encourage or support such off-label use.

The Panel's legal advisor asked what the Company considered the possible outcomes to be in this appraisal if its argument on the application of the European Directive were accepted. In particular, did the argument that NICE could not prefer off-label use mean that wherever a technology was compared against off-label use, the technology appraised would have to be recommended?

67. Dr Williams explained that the Company's position was that the following options were open to NICE in this appraisal:

(1) to recommend belimumab; or

(2) conclude that belimumab was not cost-effective against standard care and that no conclusion could be reached on the comparison with the off-label comparator leading to a "no result" appraisal.

For the Committee, Professor Clark noted that much of standard care is unlicensed too. The Final Appraisal Determination did not endorse use of rituximab. Increased off-label use of rituximab was not an inevitable consequence of the Committee's recommendations. It was not the Committee's role to regulate the use of unlicensed products. The Committee's assessment of efficacy and cost effectiveness is based on scientific evidence not licensing status.

The situation in the appraisal was not analogous to that in the *Poland* case as belimumab and rituximab were very different technologies, albeit they shared benefits in this patient group.

The Committee's decision was not based solely on price, as explained in the Final Appraisal Determination.

68. The Panel considered the arguments. It concluded that the *Poland* case was not analogous to this appraisal because:

(1) NICE had not preferred or supported the off-label use of rituximab, for the reasons outlined above in relation to strand (i) of GlaxoSmithKline's legal arguments above; and

(2) in the *Poland* case the Polish government relied on the argument that Article 5(1) applied rather than Article 4(3).

The Panel accepted the position stated in DAC Beachcroft's advice [para 28] that Article 4(3) does not permit decisions regarding inclusion in a national health scheme to supplant or remove the need for a marketing authorisation. However, that article does mean that the decision of member states on which products will be available (including available to a greater or lesser degree) under their national health systems is not dictated by the fact that a product is licensed. There is no obligation under the Directive to provide a licensed product at all or to any particular degree. The Company's argument, taken to its logical conclusion, has the effect that no product appraised by NICE for use within its licence could be "not recommended" for use in the NHS if compared to an unlicensed or off-label comparator. Such a result would be contrary to Article 4(3).

While the words of the Court of Appeal on Article 4(3) and NICE's role in the permission decision in the *Servier* case appeared clear to the Panel, the Panel found that it does not need to rely on this judgement (which it noted was not binding on the UK courts) to reach this conclusion.

69. Considering the relationship between NICE appraisals and a product receiving a licence, NICE appraises technologies referred to it by the Department of Health. While products appraised by NICE are normally appraised for use within their

licensed indication, so far as NICE is concerned this is a consequence of the referrals that the Department of Health has chosen to make to it.

70. The Panel noted the advice received by it from DAC Beachcroft LLP that Article 4(3) can only be relied upon if the Transparency Directive has been complied with. The Panel concluded that, in accordance with the judgement of the High Court in *R ota Bristol-Myers Squibb Pharmaceuticals Limited vs National Institute for Health and Clinical Excellence* ([2009] EWHC 2722 (Admin), paragraphs 42 to 44 inclusive) that NICE technology appraisals do comply with the requirements of the Directive. In that case the judge concluded that that as the UK Government had notified the Commission that medicinal products may not be available on the NHS where the forecast aggregate costs to the NHS is unjustified, NICE Technology Appraisals did comply with the requirements of the Transparency Directive.

71. **(iv) [The Final Appraisal Determination] substantially deprives patients of any right of recourse under the Consumer Protection Act 1987**

72. The Company referred to its legal submissions.

73. The Panel did not accept that if the Final Appraisal Determination were to become NICE guidance then off-label use of rituximab would increase, given that no recommendation of use of rituximab has been made. Furthermore, the Final Appraisal Determination notes that *"… in a study that compared rituximab with placebo … no statistically significant differences were reported in major or partial clinical responses"*. [Final Appraisal Determination 3.13].

Moreover, the Panel was unpersuaded that the nature of the

remedy available to patients suffering harm as a result of treatment with a comparator was relevant to a question of whether NICE has exceeded its powers.

74. The Appeal Panel therefore rejected the appeal on GlaxoSmithKline Ground 3.1 (strands (i) to (iv) inclusive).

Appeal Point Ground 3

Primary Care Rheumatology Society

3.1. The NICE guidance, which indicates that there is no advantage of "licensed" belimumab compared to "unlicensed" rituximab, will potentially lead doctors into a situation which conflicts with advice issued by the General Medical Council (2008) and the MHRA (2009)

75. This point was considered by the Panel alongside GlaxoSmithKline Ground 3.1(ii).

76. For the reasons outlined above in relation to GlaxoSmithKline Ground 3.1(ii) the Appeal Panel rejected this ground of appeal.

Appeal Point Ground 3

Primary Care Rheumatology Society

3.2 The NICE guidance, which indicates that there is no advantage of "licensed" belimumab compared to "unlicensed" rituximab, will potentially lead to severe adverse unintended consequences for lupus patients… Not only will they not be able to access treatment with belimumab, but it is likely that they will now find it much more difficult to access the comparator drug rituximab.

77. Dr John Dickson from the Primary Care Rheumatology Society explained that if the Final Appraisal Determination became NICE guidance it would be very difficult for patients to access belimumab. Dr Alistair Dickson highlighted that the disease affected women in their reproductive years and any extension of life would make a significant difference to families with young children. The Panel noted the concern raised in the

Society's written submission that if the Final Appraisal Determination becomes guidance, this will potentially lead to reduced patient access to rituximab.

78. Professor Clark on behalf of the Committee explained that while a positive recommendation in the Final Appraisal Determination would lead to a legal obligation to fund use of belimumab, it would still be possible to obtain funding for both belimumab and rituximab through individual funding requests.

79. The Panel considered the arguments and concluded that the Committee had carried out the task given to it by the scope – the appraisal of belimumab with rituximab as one of the comparators – and had not acted beyond its powers in doing so.

80. The Appeal Panel rejected this ground of appeal.

Conclusion and effect of the Appeal Panel's decision

81. The Appeal Panel therefore upholds the appeal on GlaxoSmithKline ground 1.2 and GlaxoSmithKline ground 2.1. The appeal is dismissed on all other grounds.

82. The appraisal is remitted to the Appraisal Committee who must now take all reasonable steps to address the issues on which the appeal has been allowed.

83. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and the Institute's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.

GlaxoSmithKline's (GSK) Post-Appeal Submission for the Single Technology Appraisal (STA) of Belimumab in the Treatment of Active Autoantibody-Positive Systemic Lupus Erythematosus (SLE)
26th October 2012

Background

The Final Appraisal Determination (FAD)[1] for belimumab in the treatment of SLE states that it is not recommended for use, however this guidance is subject to the outcome of an appeal process. The appeal hearing for belimumab was held on the 18th July 2012. The outcome from this hearing was that the Appeal Panel upheld two of GSK's appeal points and referred them back to the Appraisal Committee for further consideration. These specific points were related to the inclusion of a more stringent treatment continuation rule in the health economic model and the Committee's conclusions regarding the comparison with rituximab. Having considered these two appeal points and in order to maximise the opportunity for a subgroup of SLE patients with serious disease and limited treatment options to access belimumab, GSK is submitting some additional cost-effectiveness analyses for the Appraisal Committee to consider at their Appraisal Committee meeting on 27th November 2012. These new analyses include a revised Patient Access Scheme (PAS) and some updated assumptions in the health economic model related to the annual discontinuation rate and drug administration cost, which the Evidence Review Group considered the most plausible values. All other assumptions used in the model are identical to those discussed in our original submission (dated April 2011).

Full details of the analysis methodology and cost-effectiveness results are presented in Appendix 1 of this document, however the rationale for these additional analyses and a summary of the main results are presented below.

Revised Health Economic Analysis

Base case

The revised base case for the health economic model comprised:

- A subgroup of the licensed population (UK Target Population) of SLE patients with serious disease activity (low complement and anti-dsDNA and a SELENA-SLEDAI (SS) score of ≥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 ≥4 point reduction in SS (base case continuation rule).
- Up to lifetime use of belimumab with an annual natural discontinuation rate of 13%.

The aim is to target belimumab to those patients with uncontrolled disease despite standard of care and allow continued use after six months only if a clinically relevant response is observed, consistent with the SmPC for belimumab.

Key Scenario Analyses

1) Annual discontinuation rate

An assumption of up to lifetime use of belimumab is used for the base case economic analysis. However this assumption will lead to a very conservative assessment of cost-effectiveness for the following reasons:

- NICE stated in Section 4.4 of the FAD that the Committee "...*heard from the clinical specialists that continuous use of belimumab for a long time would be very unlikely. The clinical specialists explained that one of the aims of treatment with belimumab would be to work towards coming off the treatment*." Having consulted with lupus specialists after the release of the Appraisal Consultation Document (ACD) in September 2011, the advice GSK received was that other

immunosuppressants used to treat lupus are frequently prescribed for three to five years for patients with active disease with the aim of maintaining suppression of disease activity, and once achieved, the doses of the immunosuppressants are tapered and eventually stopped.

- The specialists also informed GSK that it is mainly patients with significant renal disease (severe active lupus nephritis) or CNS lupus whom are likely to require very long durations of treatment i.e. beyond 5 or 6 years and these patients are outside the current licensed indication for belimumab.

- The annual discontinuation rate used in the health economic model for responders to belimumab determines the overall distribution of treatment durations. The base case value uses an annual rate of 13% which represents the average annual withdrawal rate seen in the Phase II open-label extension study (LBSL-99) over six years of follow-up. The ERG agreed that this was a more plausible value than the 8% annual rate used in our original submission, estimated from the shorter-term BLISS trials. However we believe that using an annual value of 13% in the model is also likely to overestimate the number of patients that we would expect to see in clinical practice receiving prolonged treatment durations. Using a 13% annual rate in the model there are still 26% of "responders" receiving belimumab after 10 years, 13% after 15 years and 7% after 20 years (Appendix Table A1.2). Hence we believe the estimate of cost-effectiveness obtained from this base case is conservative.

In our response to the ACD, and consistent with the discussions we had with lupus specialists, we provided NICE with a revised base case cost-effectiveness analysis where a maximum treatment duration with belimumab of 6 years was assumed; an alternative scenario analysis which assumed up to 10 years use of belimumab was also presented. However, the Appraisal Committee favoured the original base case analysis, which assumed up to lifetime use of belimumab, over these revised analyses with maximum durations. The main reasons discussed in the FAD were that in the Phase II extension study 50% of the patients enrolled were still demonstrating a benefit from belimumab after six years of follow-up and the Committee was concerned that stopping treatment at six years could reduce the benefit seen with added uncertainty around any withdrawal effects that may be experienced. In addition, at the appeal hearing, where our proposed maximum duration of six years was discussed, related to one of our appeal points, it was stated by NICE that it would be inappropriate for NICE guidance to stipulate a maximum treatment duration when the SmPC for belimumab did not. However, one of the reasons that so many patients continued on belimumab for six years in the Phase II extension study was because it was designed as a ten-year study to monitor long-term safety as well as efficacy. In real-life clinical practice the approach would be different as more emphasis would be placed on taking patients off belimumab as early as possible once sustained disease control was achieved.

In consideration of the above points we have provided a key additional scenario analysis which involves an alternative approach using a variable time-dependent annual withdrawal rate. For this analysis a withdrawal rate of 13% was used for Years 1 to 5 and then the rate is increased to 30% from Year 6 onwards. This leads to 37% of responders being retained on belimumab after 6 years, 9% after 10 years, <2% after 15 years and <1% after 20 years (Appendix Table A1.2). We believe this more closely represents the likely distribution of treatment durations as prescribed in clinical practice for the patients in our target population, than that for the base case, and may in fact still be an overestimate.

Treatment continuation criterion at week 24

In recognition of limited NHS resources, as an alternative to 4-point treatment continuation criterion used in the base case, a more stringent treatment continuation criterion (SS reduction ≥6 points) was considered as it enabled continuous treatment with belimumab to be targeted to those patients showing the most significant early response, and improves the cost-effectiveness. Inclusion of this

more stringent continuation rule was not supported by the Committee in the FAD (Section 4.17) and GSK felt the reason for rejecting this rule was not clear when cost-effectiveness was improved and when the Committee had accepted the inclusion of the base case continuation rule. This was raised as an appeal point by GSK which the Appeal Panel upheld. The Committee at the appeal hearing explained that their main reasons for rejecting this rule were that they felt it may be difficult to implement in practice and that the level of cost effectiveness achieved when incorporating it in their preferred base case was not sufficient to support a positive recommendation.

GSK believe this more stringent rule is relevant for consideration in this appraisal, particularly in the context of the updated PAS. Although using the base case continuation rule is preferable, if the level of cost-effectiveness is only considered to be of an acceptable level when the more stringent rule is used in the management of patients, then acceptance of this rule will at least enable a subgroup of our target patients to gain access to and continue treatment with belimumab. The alternative is that with a negative recommendation no patients would be likely to be able to access belimumab. Therefore scenarios using this more stringent rule are provided when considering both our base case annual discontinuation rate of 13% per annum and when using the variable annual discontinuation rate.

Other relevant scenario analyses included in our original submission and our response to the ACD have been updated with our revised PAS and are provided in Table A1.16 of the Appendix for completeness.

Summary of Cost-effectiveness Results

All ICERs presented incorporate the revised PAS.

Base case Analysis

The incremental costs for belimumab treated patients compared to SoC alone are [redacted], with 0.9 added life years, or 0.7 added QALYs, discounted at 3.5%, resulting in a base case ICER of [redacted] per QALY gained (Appendix Table A1.12).

Scenario Analyses

Variable annual discontinuation rate

This Scenario analysis using an annual discontinuation rate (Scenario 1) provides an ICER of [redacted] per QALY gained. We consider this ICER is more reflective of the true cost-effectiveness of belimumab in clinical practice for our target population because of the more probable distribution of treatment durations assumed in the model.

More stringent treatment continuation criterion

When the more stringent 6-point continuation criterion is incorporated into the model with the constant 13% discontinuation rate used in the base case (Scenario 2), the ICER is [redacted] per QALY gained - a reduction of just over £4000 per QALY from the base case ICER. When this rule is included with the variable discontinuation rate assumption (Scenario 3) the ICER is [redacted] per QALY gained, which is just over £3000 per QALY lower than the ICER incorporating the base case continuation rule. These ICERs, both of which are [redacted] per QALY, demonstrate why we believe consideration of this more stringent rule is relevant of further consideration in this appraisal.

Table 1. Summary of Scenario Results with Revised PAS - Target population

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised Base Case	Time horizon = lifetime; up to lifetime belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; annual discontinuation rate of 13%; adjusted natural history model; monthly infusion hospital admission cost of £154	[redacted]	0.87	0.663	[redacted]
Scenario 1: Variable discontinuation rate.	As revised base case with the ≥4-point treatment continuation criterion but using a 13% discontinuation rate up to Year 5 and a 30% discontinuation rate from Year 6 onwards	[redacted]	0.79	0.596	[redacted]
Scenario 2: More stringent treatment continuation criterion	As revised base case but with treatment continuation criterion of SS score of ≥6 at week 24	[redacted]	0.79	0.595	[redacted]
Scenario 3: Variable discontinuation rate with more stringent treatment continuation criterion	As revised base case but incorporating the more stringent treatment continuation criterion and using a 13% discontinuation rate up to Year 5 and a 30% discontinuation rate from Year 6 onwards	[redacted]	0.69	0.513	[redacted]

Summary of cost-effectiveness vs. standard of care (SoC)

With these estimates of cost effectiveness which incorporate the revised PAS we believe belimumab represents a cost-effective use of NHS resources. The NICE Guide to the methods of technology appraisal[2] states that with ICERs above the £20,000 per QALY threshold the Committee should also consider the level of innovation inherent in the technology and whether there are any additional aspects of value which have not been fully accounted for in the estimates of cost-effectiveness. As ICERs rise above £30,000 per QALY the arguments in support of a technology need to be increasingly strong. We believe these factors are relevant to this appraisal. Belimumab is an innovative medicine for a 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 treatments have failed. In the Phase 2 extension study belimumab demonstrated steroid sparing benefits and is likely to show even greater benefits when prescribed in clinical practice. This is supported by real-life data[3] from the US which is to be presented at the American College of Rheumatology (ACR) annual meeting in November. In addition, the ERG agreed that belimumab's positive effect on flares may not have been fully accounted for in the estimates of cost-effectiveness. These additional aspects of value should be considered by the Committee when assessing the level of cost-effectiveness estimated for belimumab.

Whilst we accept there remains uncertainty in the cost-effectiveness estimates much of this is inevitable given the nature of the condition where many of the health outcomes occur over a long period of time and cannot be confirmed in the time frame of a clinical trial programme. However we believe the six year data available for the Phase 2 extension study (albeit in an open label study) gives confidence that the benefits demonstrated in the randomised trials are likely to be maintained and in some aspects e.g. the steroid sparing effect could even be greater than estimated in the original trial data.

Comparison with Rituximab

In addition to the comparison of belimumab with standard of care, it is also important to consider rituximab in this appraisal. Both NICE, lupus specialists and GSK agree that rituximab, although

unlicensed for SLE, is used in the SLE patients in our proposed target population in the absence of efficacious, licensed treatments and hence should be considered a valid comparator. There are no head to head clinical trials comparing belimumab with rituximab in SLE and throughout this appraisal we have provided a clear justification of why, based on currently available data, indirect comparisons of efficacy were inappropriate; this was also supported by the Evidence Review Group (ERG). However, in the two rituximab Randomised Controlled Trials (RCTs) in SLE efficacy with rituximab was not established, whereas belimumab has demonstrated clinically relevant benefits for patients in two Phase 3 RCTs. Hence we believe that we are taking a conservative approach by assuming belimumab is at least as effective as rituximab in SLE.

As previously stated in our original submission in April 2011, the 52 week EXPLORER trial[4] used a dose of rituximab of 1000mg by infusion at days 1, 15, 168, 182, which, based on 10mg/ml solution with a vial price of 50ml=£873.15,[5] gives an annual price of £6985.20. In addition, administration costs amount to approximately £1386 (4 X £346.50 per 5.5hr infusion) giving a total annual cost of rituximab to the NHS of £8385.20 per annum.

The cost effectiveness of belimumab is determined both by the drug acquisition cost and the monthly hospital infusion administration costs. [redacted] With this in mind our revised PAS has been devised to provide a rebate towards the annual administration costs for IV belimumab without introducing an additional administration burden to the NHS to account for these costs. The annual cost of belimumab with our revised PAS is [redacted] (i.e. [redacted] drug costs + £2002 admin costs). [redacted] for administering rituximab in our target subgroup of patients.

Therefore in the context of the clinical trial data, and with our revised PAS, belimumab can be considered an efficient use of resources when compared with rituximab use and would [redacted]

Alternative Use of Rituximab.

At the Appraisal Committee meetings for belimumab the clinical experts stated that in clinical practice rituximab may be used in a different way to the dosing schedule used in the EXPLORER clinical trial. We do not have any clear evidence available on the extent of this use or the associated costs. In addition there is no clinical trial evidence to support this alternative use and thus the effectiveness of rituximab when used in this way is highly uncertain. Although there is limited published real-life data on rituximab from the French AutoImmunity and Rituximab Registry[6], the difficulties in identifying a sub-population of the patients which corresponds to our target population, and the higher doses of steroids being taken by many of the small group of patients, does not enable a comparison to be made.

Therefore in the context of off-label use we are not able to draw any conclusions as to the relative efficacy or cost effectiveness of the products, particularly as we can only consider the use of belimumab for chronic use according to its license and established evidence of efficacy and safety. Indeed the Appeal Panel in consideration of our Appeal Point 2.1[7] concluded that the Committee should distinguish between situations where they were unable to reach a conclusion due to a lack of data, from those where there was a limited amount of data that were unpersuasive.

Conclusion

In summary, we would ask the Appraisal Committee to reconsider the guidance outlined in the current FAD taking into account the revised assessment of cost-effectiveness including the updated PAS, the innovative nature of the technology, the severity of the disease with significant unmet medical need and the aspects of value that have not been fully incorporated in the cost effectiveness estimates. In this context we believe belimumab should be considered an efficient use of NHS resources and hence justify a positive recommendation.

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Appendix 1

Cost-effectiveness Analyses for the Updated Base Case Incorporating the Revised PAS

Provided below are the results from the health economic analysis for our proposed target SLE population (high disease activity subgroup) with our updated base case which incorporates updated values for two assumptions in the economic model and our revised PAS. Consistent with the base case in our original submission and with the SmPC this new base case includes a treatment continuation criterion (SS score decrease of ≥4 points) at week 24 i.e. after six months of treatment.

Methodology

The methodology for the analysis of SELENA-SLEDAI scores from the two Phase 2 BLISS studies, and the disease activity, steroid dose and natural history mortality and organ damage models, based on the Johns Hopkins longitudinal database, is identical to that presented in our original submission in April 2011.

The key assumptions described for the base case in our original submission still apply with two exceptions where we have used values for annual withdrawal rate and for the hospital infusion administration cost which the Evidence Review Group (ERG) preferred to the values used in our original base case. In our original submission an annual withdrawal rate of 8% was used for belimumab patients for the duration of the model lifetime horizon however this was based on only 18 months of follow-up data from the BLISS studies. Long-term data (up to six years) from the open-label Phase II extension study was made available after our original submission. Over the six-year study period the average annual withdrawal rate was observed to be 13%. This higher withdrawal rate was discussed in our response (dated October 2011) to points raised in the Appraisal Consultation Document. The ERG agreed that this withdrawal rate was valid to use in the health economic model for the belimumab "responders" (i.e. those patients who satisfied the treatment continuation criterion at week 24) and that the value of 8% used in our base case was likely to be an underestimate. Also, in our original submission we used a monthly hospital infusion administration cost of £126 and this was calculated based on two hours of specialist nurse time using 2010 hourly rates obtained from the Personal Social Services Research Unit (PSSRU). However the ERG preferred to use an infusion administration cost of £154 in order to be consistent with an earlier appraisal (completed August 2010) of tociluzimab in rheumatoid arthritis (TA198).

Detailed below is the analysis conducted for the UK target population incorporating the above two updated values and our revised PAS.

Data Analysis

A summary of the key assumptions used in the model for our revised base case are presented in Table A1.1. These are identical to those provided with our original submission except for the two assumptions discussed above.

Table A1.1. Summary of Key Assumptions included in the Health Economic Model

Assumptions	Justification/explanation
The economic evaluation estimates costs and health benefits over the full lifetime of each individual (lifetime time horizon)	This time horizon is necessary for the main health outcomes and resource use to be fully explored in this chronic disease.
A yearly cycle length is used without including a half-cycle correction	SLE is a long-term chronic disease. The changes in overall disease activity and the accumulation of organ damage are believed to be adequately captured with a yearly cycle over a lifetime horizon. However, if long-term data on the incidence and severity of flares had been available (see discussion later in this section), a shorter cycle length may have been more appropriate to capture the pattern of flares over time.
An NHS and PSS perspective was used. Health effects were measured in QALYs. A discount rate of 3.5% was applied for both health effects and costs for the base case.	Consistent with the NICE reference case
Patients who withdraw from belimumab due to natural discontinuation or patients on belimumab who do not satisfy the treatment continuation criterion at week 24 remain in the belimumab arm of the model but continue to receive SoC treatments after this time-point and assume the average SoC level of disease activity for the remainder of the model horizon.	This reflects how patients would currently be managed in clinical practice. Withdrawing patients from belimumab due to inadequate response to the drug is consistent with the SmPC for belimumab. If patients do not demonstrate a sufficient level of response after six months of treatment with belimumab they would not continue on this drug and would be managed with other standard of care medications.
The difference between the SELENA-SLEDAI and SLEDAI instruments has no influence on the estimated efficacy and cost-effectiveness.	Both instruments contain the same items and weights with only a very slight change to definitions.
No impact of a difference between the pre and post 1996 version of SLICC.	There were only minor changes to the number of items included.
Adjusting the constant in natural disease model (JH).	There is a significant difference in baseline SS score between BLISS patients and JH cohort. To account for this the constant in the regression predicting disease activity over time was increased.
The absolute effect of belimumab on disease activity (SS score) remains constant after 1 year.	This assumption is supported by the Phase 2 study LBSL99 data where the benefit of belimumab was maintained over 6 years of follow-up
Disease flares were not directly included in the health economic model however AMS was incorporated and will account for disease flare activity to some degree although it is likely to have underestimated the predicted cost-effectiveness of belimumab.	The JH cohort database did not record data on disease activity flares so these data could not be modelled directly. Disease activity at time of organ damage is reflected in the individual system involvement covariates in the NHD models; these data would complement the AMS score by describing current disease activity and type of activity.
The probability of discontinuation remains constant over time (i.e. after 1st year) for belimumab responders.	Assumption supported by data from Phase 2 LBSL99 continuation study. Annual discontinuation rate has been estimated as 13%.
The SoC treatments used for the JH patients are similar to the SoC treatments used in the BLISS trials.	Assumed that best standard of care has been given both to the JH cohort and the patients in the BLISS trials.
The JH natural history of disease (NHD) model can be applied to the BLISS population even thought the JH population may be less severe on average than the patients in the BLISS trials.	The NHD models are multivariate models that allow adjustment for differences in cohorts at baseline. A specific adjustment for difference in average disease activity was included.
The average exposure to the belimumab was assumed to be 100%.	As this technology is not self-administered, patients are under specialist care and in a considerably poor state of health, it seems reasonable that compliance will be high while the physician perceives that the patient is receiving benefit from continuing this treatment.

Assumptions	Justification/explanation
It is assumed in the base case that vial sharing between patients will not automatically occur.	As the number of patients with moderate to severe SLE is relatively small in UK, vial sharing may not be easy to manage in tertiary care units due to storage requirements. If vial sharing were to occur, its inclusion would only serve to improve cost effectiveness.
Adverse events are not incorporated into the model	There was little difference between treatment groups in both BLISS trials in the incidence of all reported adverse events or all serious events and hence there would not be an important cost differentiation between arms in the health economic model.
The monthly hospital infusion administration costs of £154 is used	This cost was preferred by the ERG to be consistent with an earlier appraisal (completed August 2010) of tociluzimab in rheumatoid arthritis (TA198) which has a similar infusion duration.
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years	

Treatment continuation probabilities with belimumab and annual natural discontinuation

The percentage of patients in the UK target population (high disease activity subgroup) who satisfy the treatment continuation criterion of a decrease of 4 points of more in SELENA-SLEDAI, considered a clinically relevant improvement in disease activity, is 66.8% (Table A1.2). The withdrawal rate from Week 24 onwards in Year 1 and for Year 2 onwards for belimumab "responders" are 7.2% and 13% respectively. The withdrawal rate for the belimumab "non-responders" i.e. those patients who discontinue treatment at week 24 due to insufficient improvement in SS is 37.4%. This withdrawal rate is only relevant when the model is run without including a treatment continuation criterion because with the inclusion of a continuation criterion the non-responders are switched to SoC after week 24. (Table A1.2).

Table A1.2. Summary of natural discontinuation and probability of treatment continuation after 24 weeks for belimumab patients – Target Population

Patients satisfying the treatment continuation rule	66.8%	
Natural discontinuation (Withdrawal)	**Patients who continue belimumab after 24 weeks (responders)**	**Patients who discontinue belimumab after 24 weeks (non-responders)**
Daily hazard	0.00038	0.00128
Year 1	7.2%	37.4%
Subsequent years	13.0%	37.4%

Discontinuation over time for belimumab responders based on an annual withdrawal rate of 13% is shown in Figure A1.1. The steep fall observed for patients on belimumab in the first year is caused by those patients not satisfying the treatment continuation criterion at 24 weeks and hence moving to standard of care (SoC) in the model.

Figure A1.1 Discontinuation from belimumab (includes death) – Target population

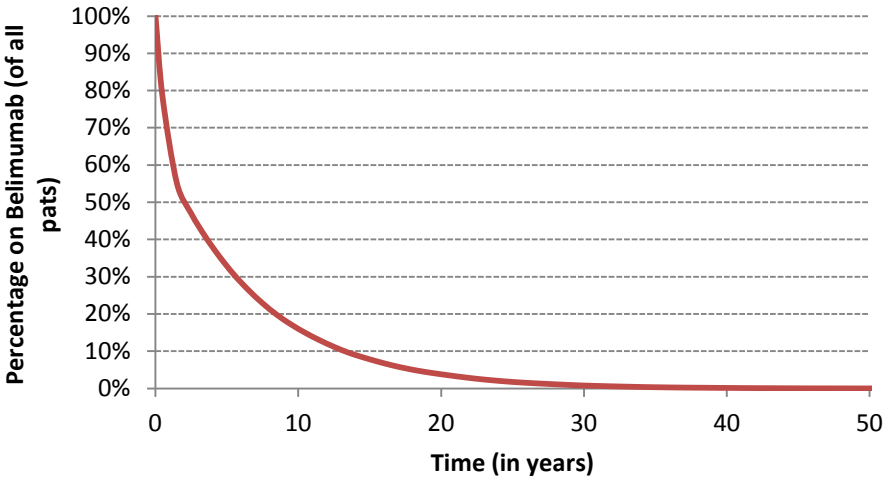


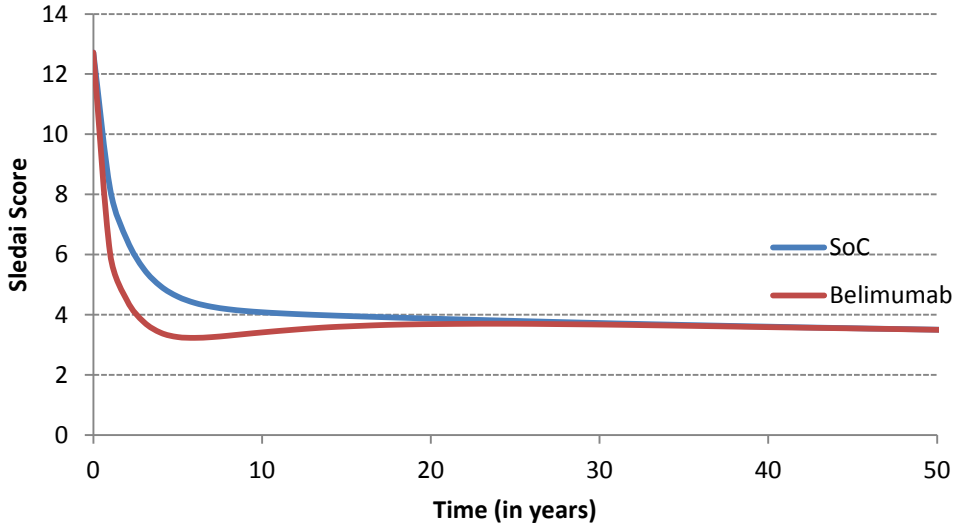
Table A1.3 below presents the estimated percentage of responder patients remaining in the model when different assumptions for annual withdrawal rate are assumed.

Table A1.3: Summary of estimated belimumab responders remaining on the drug over time –Target population

	13% annual withdrawal rate		8% annual withdrawal rate		Variable annual withdrawal rate	
Year	Rate applied to each year	% Pts remaining at end of Year	Rate applied to each year	% Pts remaining at end of Year	Rate applied to each year	% Pts remaining at end of Year
1	7.20%	92.8	4.4%	95.6	7.20%	92.8
2	13.0%	80.7	8.0%	88.0	13.0%	80.7
3	13.0%	70.2	8.0%	80.9	13.0%	70.2
4	13.0%	61.1	8.0%	74.4	13.0%	61.1
5	13.0%	53.2	8.0%	68.5	13.0%	53.2
6	13.0%	46.3	8.0%	63.0	30.0%	37.2
7	13.0%	40.2	8.0%	58.0	30.0%	26.1
8	13.0%	35.0	8.0%	53.3	30.0%	18.2
9	13.0%	30.5	8.0%	49.1	30.0%	12.8
10	13.0%	26.5	8.0%	45.1	30.0%	8.9
11	13.0%	23.1	8.0%	41.5	30.0%	6.3
12	13.0%	20.1	8.0%	38.2	30.0%	4.4
13	13.0%	17.4	8.0%	35.1	30.0%	3.1
14	13.0%	15.2	8.0%	32.3	30.0%	2.1
15	13.0%	13.2	8.0%	29.8	30.0%	1.5
16	13.0%	11.5	8.0%	27.4	30.0%	1.1
17	13.0%	10.0	8.0%	25.2	30.0%	0.7
18	13.0%	8.7	8.0%	23.2	30.0%	0.5
19	13.0%	7.6	8.0%	21.3	30.0%	0.4
20	13.0%	6.6	8.0%	19.6	30.0%	0.3

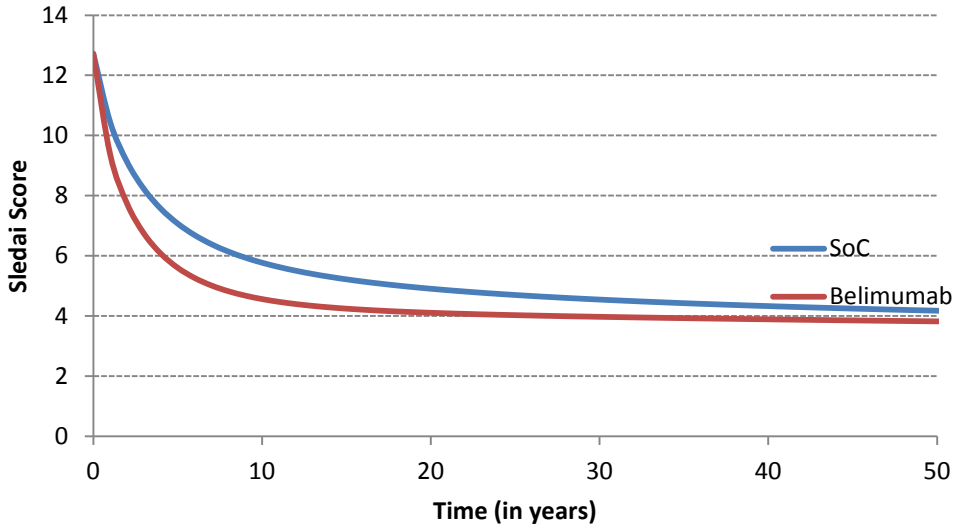
The adjusted (average) SLEDAI score (AMS) over time for those patients who remain alive based on 50,000 simulated patients is shown in Figure A1.2. It is clear from the graph that patients who are treated with belimumab (in addition to SoC) have a larger reduction in SS score than patients who are treated with SoC alone over approximately the first fifteen years.

Figure A1.2. SLEDAI Score over time for 50,000 patients simulated – Target population.



Although the level of disease activity for belimumab patients after discontinuation of the treatment returns to SoC levels, a beneficial effect from belimumab treatment is kept through a decreased average disease activity score over time (Figure A1.3).

Figure A1.3. Adjusted Mean SLEDAI (AMS) over time censored for death - Target population.



The adjusted (average) disease activity score is an important predictor of organ damage in the cardiovascular, renal, pulmonary and peripheral vascular systems (Table A1.4).

The lower disease activity for patients receiving belimumab treatment will lead to a decreased steroid dose over this time period and a decreased risk for organ damage. The average disease activity (AMS) over lifetime, cumulative average prednisone dose and certain types of organ damage, contribute to the mortality risk (Table A1.5).

Table A1.4. Organ damage time to event models and corresponding covariates from Johns Hopkins cohort analysis

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

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

Table A1.5. 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 survival over time is improved for belimumab patients compared with patients on SoC (Figure A1.4) due to the benefits of belimumab on disease activity, steroid dose and certain types of organ damage. The relatively steep decline in survival in the first year for both treatment arms is caused by the relatively high standardised mortality ratio for patients younger than 24 years (Table A1.6).

Figure A1.4. Survival of patients over time – Target population

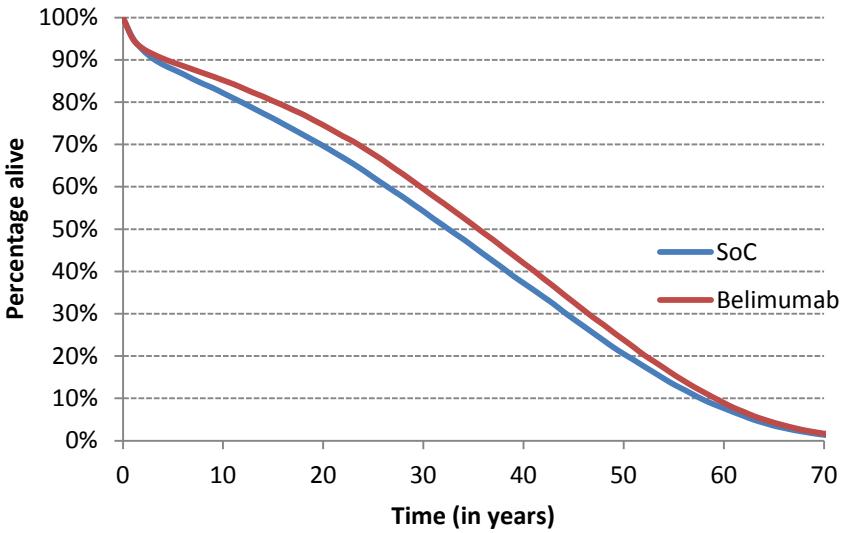


Table A1.6. Standardised Mortality Ratios for SLE patients stratified by age groups according to Bernatsky et al (2006).

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

As belimumab patients have an estimated longer life expectancy, the exposure to the risk of organ damage is increased for belimumab patients, hence, for eight of the organs (diabetes, gastrointestinal, malignancy, musculoskeletal, neuropsychiatric, ocular, premature gonadal failure and skin) the percentage of damage occurrence is similar or higher than for SoC (Table A1.7). However, for the cardiovascular, peripheral vascular, pulmonary and renal systems, fewer patients on belimumab develop damage compared to SoC. This is due mainly to the dependence of damage risk on disease activity which is lower for patients receiving belimumab.

Table A1.7. Organ damage occurrence for SLE patients until death - Target population

	SoC	Belimumab	Difference
Cardiovascular	23.9%	21.8%	-2.1%
Diabetes	17.9%	18.9%	0.9%
Gastrointestinal	22.1%	24.4%	2.3%
Malignancy	32.0%	33.6%	1.7%
Musculoskeletal	48.5%	49.0%	0.4%
Neuropsychiatric	44.7%	45.9%	1.2%
Ocular	35.1%	35.9%	0.8%
Peripheral vascular	21.5%	21.0%	-0.6%
Premature gonadal failure	7.2%	7.2%	-0.1%
Pulmonary	39.9%	37.0%	-2.8%
Renal	24.3%	19.9%	-4.4%
Skin	7.9%	7.8%	0.0%

As belimumab is estimated to reduce the risk of damage to 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. 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 average duration of damage is shown for the cardiovascular, pulmonary and renal organ systems, the average duration of damage for most other organ systems is increased due to the prolonged life-expectancy (Table A1.8).

Table A1.8. Average duration (yrs) of organ damage – Target Population

	SoC	Belimumab	Difference
Cardiovascular	5.60	5.28	-0.32
Diabetes	2.64	2.93	0.29
Gastrointestinal	4.62	5.42	0.81
Malignancy	4.39	4.86	0.48
Musculoskeletal	11.24	11.99	0.75
Neuropsychiatric	11.17	11.87	0.71
Ocular	7.88	8.30	0.42
Peripheral vascular	3.66	3.67	0.01
Premature gonadal failure	1.77	1.85	0.07
Pulmonary	9.87	9.42	-0.45
Renal	5.38	4.52	-0.86
Skin	2.47	2.62	0.14

As discussed above, the occurrence of damage in the organ systems other than cardiovascular, peripheral vascular, pulmonary and renal systems, is higher or similar in the belimumab arm compared with the SoC arm, due mainly to the increased life expectancy with belimumab. Although other organ systems also depend on AMS (Table 1.4), and show that a higher percentage of belimumab patients are shown to develop damage in these systems over time (Table A1.7), for the patients still alive, the risk of developing organ damage is lower with belimumab. This is illustrated in a Kaplan-Meier plot of musculoskeletal damage censoring for death (Figure A1.5).

Figure A1.5 Kaplan-Meier plot of the proportion of patients alive with musculoskeletal damage – Target population

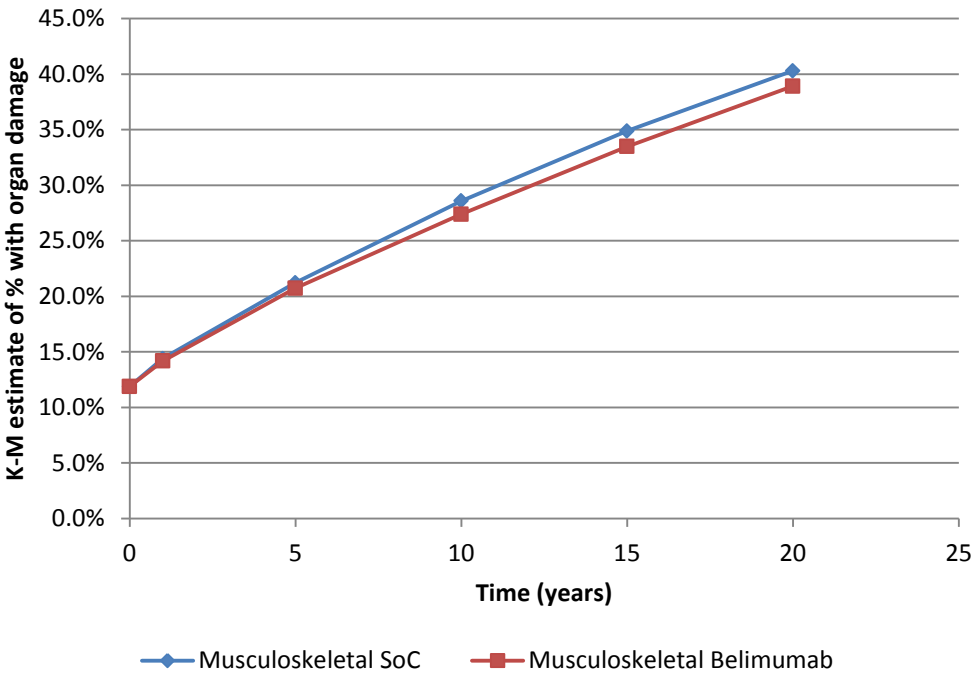


Table A1.9 summarises the main outcome results for the revised base case. As demonstrated previously in Figure A1.4, belimumab patients have an estimated increased life-expectancy. The model predicts that belimumab-treated patients, in the subgroup with high disease activity, live on average 2.3 years longer, have a reduction in average mean SLEDAI score of -0.7, and a similar total SLICC organ damage score at death compared with SoC patients. Treatment with belimumab in this target population provides an estimated additional 0.9 life years and 0.7 QALYs (discounted at 3.5%).

Table A1.9. Summary of health economic outcomes with revised base case – Target population

	SoC	Belimumab	Difference
Age at Death	66.2	68.5	2.3
SLICC at Death	4.1	4.0	-0.1
AMS	5.5	4.77	-0.7
Average monthly steroid cumulative dose	228.1	212.6	-15.4
Life Years (undiscounted)	31.93	34.25	2.31
Life Years (discounted at 3.5%)	17.05	17.93	0.87
QALYs (undiscounted)	17.31	18.78	1.46
QALYs (discounted at 3.5%)	9.81	10.47	0.66

All the cost effectiveness results 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 A1.10 below.

Table A1.10. Unit costs associated with the new technology in the economic model – Target population

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 = [redacted] Year 2 annual cost = [redacted]	The list price vial costs are [redacted] and [redacted] 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
Total Year 1 costs	[redacted]	
Total Subsequent Year costs	[redacted]	

Table A1.11 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 A1.8, 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 with belimumab 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 and although belimumab patients have less disease activity and consequently lower direct resource costs per year, on average, the increased lifetime cost seen with belimumab is due to the estimated increased life expectancy. Overall, the main difference in costs is caused by belimumab acquisition and administration costs, amounting to [redacted] of the total absolute cost difference of [redacted].

Table A1.11. Summary of (discounted) costs over a lifetime model horizon for revised base case - Target population

Discounted	SoC	Belimumab	Difference	Absolute difference	% absolute difference
Disease activity related costs	£27,882	£28,301	£418	£418	[redacted]
Belimumab drug acquisition	£0	[redacted]	[redacted]	[redacted]	[redacted]
Belimumab administration	£0	[redacted]	[redacted]	[redacted]	[redacted]
Organ damage costs					
Cardiovascular	£1,838	£1,666	-£172	£172	[redacted]
Diabetes	£2,493	£2,682	£189	£189	[redacted]
Gastrointestinal	£359	£392	£33	£33	[redacted]
Malignancy	£998	£1,020	£22	£22	[redacted]
Musculoskeletal	£9,758	£10,097	£339	£339	[redacted]
Neuropsychiatric	£6,434	£6,672	£239	£239	[redacted]
Ocular	£392	£391	-£1	£1	[redacted]
Peripheral vascular	£1,380	£1,330	-£50	£50	[redacted]
Premature gonadal failure	£0	£0	£0	£0	[redacted]
Pulmonary	£42,692	£39,559	-£3,133	£3,133	[redacted]
Renal	£11,139	£9,176	-£1,963	£1,963	[redacted]
Skin	£0	£0	£0	£0	[redacted]
Sum of organ damage costs	£77,483	£72,985	-£4,499	-	
Total direct costs	£105,366	[redacted]	[redacted]	[redacted]	100.0%

Table A1.12 summarises the results for the revised base case analysis. Belimumab-treated patients are estimated to live longer, however, due to their increased life expectancy and due to belimumab acquisition and administration costs, the total costs of managing SLE patients with high disease activity are higher than for SoC patients. The incremental costs are [redacted], with 0.9 added life years, or 0.7 added QALYs, discounted at 3.5%, resulting in an ICER of [redacted] per QALY gained.

Table A1.12. Discounted revised base case results – Target population

	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
SoC	£105,366	17.05	9.81	-			
Belimumab	[redacted]	17.93	10.47	[redacted]	0.87	0.66	[redacted]
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 revised base case are almost identical to those documented in our original submission with our base case which included up to lifetime duration of belimumab treatment. The only difference relates to the annual withdrawal rate and the lower and upper bound values used. The original analysis used 95% confidence limits taken from the Kaplan-Meier time to withdrawal analysis of the BLISS trial data, whereas for this sensitivity analysis a 20% lower and higher value was used around the base case value of 13%, resulting in values ranging from 10.4% to 15.6%.

Results of the Univariate Sensitivity Analyses

Tornado diagrams for the ICER, incremental QALYs and incremental costs are presented in Figures A1.6, A1.7 and A1.8 respectively. A description of the 15 variables which had the most impact on the ICER, incremental QALYs and incremental costs are presented in Tables A1.13, A1.14 and A1.15 respectively.

The ICERs yielded from the univariate sensitivity analyses ranged from from [redacted] to [redacted] per QALY gained. The main drivers of cost-effectiveness in our revised base case model are the treatment effect regression to estimate the effect of belimumab on SS score after 52 weeks; the greater the benefit seen with belimumab compared to SoC on reducing SS score, the higher the incremental QALY and hence the lower the ICER.

The effect of the AMS on pulmonary damage is also an important driver of the model results. The greater the reduction in AMS with belimumab, the lower the risk of pulmonary damage and the lower the costs for treating pulmonary-related damage compared with SoC, consequently leading to lower ICERs.

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

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

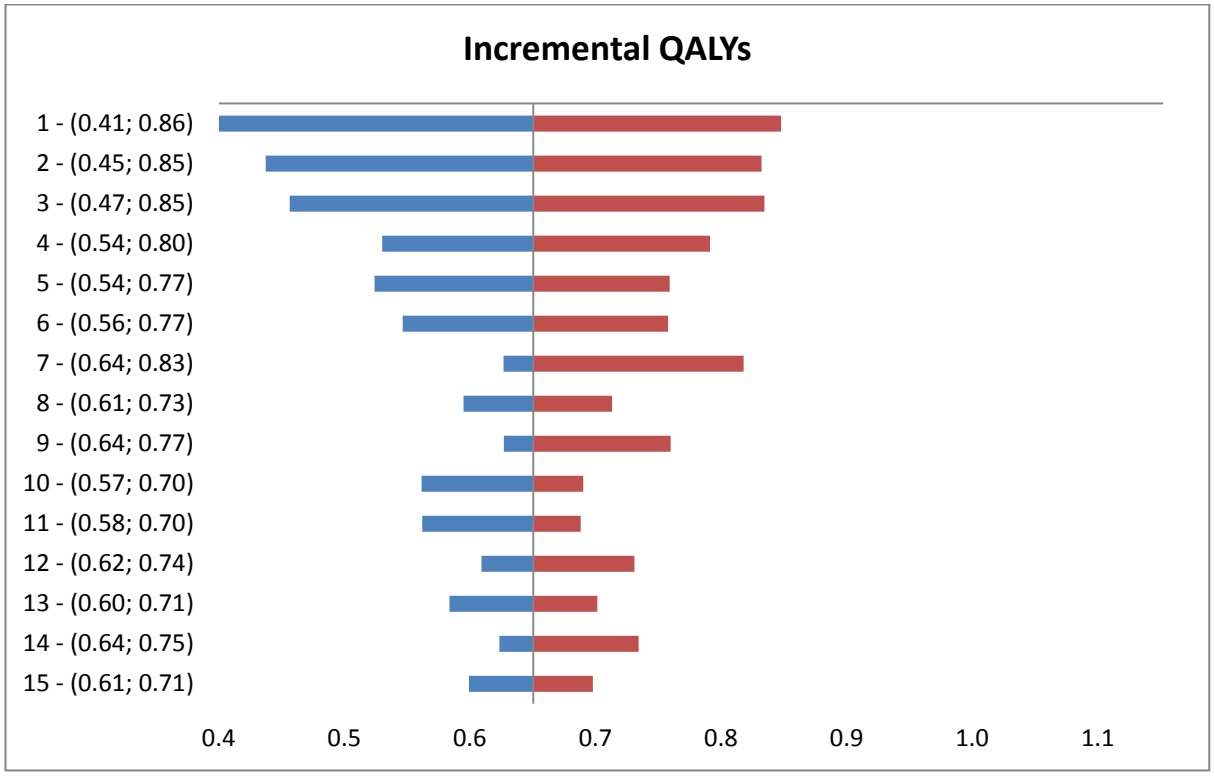
Figure A1.6. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on ICERs Incorporating the PAS – Target population

Note: Table A1.13 below details the variables identified as numbers in this tournado plot.

Table A1.13. Description of key variables with the largest impact on the ICER incorporating the PAS

Variable ID	Variable Name	Base Value	Lower bound	Upper bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
4	Coefficient of Log of age from the "clean utility" regression	0.15	-0.18	-0.10
5	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	Adjusted Mean SLEDAI coefficient at current visit from the natural history mortality model	0.21	0.09	0.33
8	Coefficient of log of age at current visit from the natural history neuropsychiatric model	0.61	0.03	1.23
9	Adjusted Mean SLEDAI coefficient at current visit from the natural history renal model	0.31	0.23	0.39
10	Constant coefficient from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
11	Coefficient of log of age at current visit from the natural history pulmonary model	1.23	0.59	1.92
12	Constant coefficient from the natural history renal model	-8.29	-9.01	-7.56
13	Natural yearly discontinuation rate for belimumab responders	0.870	0.896	0.844
14	Constant coefficient from the natural history pulmonary model	-9.17	-11.78	-6.86
15	Coefficient of log of age at current visit from the natural history diabetes model	2.25	1.16	3.35

Figure A1.7. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental QALYs – Target population



Note: Table A1.14 below details the variables identified as numbers in this tournado plot.

Table A1.14. Description of key variables with the largest Impact on Incremental QALYs

Variable ID	Variable	Base Value	Lower Bound	Upper Bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
4	Coefficient of Log of age from the "clean utility" regression	-0.15	-0.18	-0.10
5	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
6	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	Annual Discontinuation rate for belimumab “responders”	0.870	0.896	0.844
9	Coefficient Log of age at current visit in natural history peripheral vascular model	1.16	0.43	1.89
10	Coefficient constant from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
11	Coefficient 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 renal model	0.32	0.23	0.41
13	Adjusted constant from the natural history of disease activity model.	3.00	2.20	3.93
14	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
15	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history pulmonary model	0.14	0.06	0.22

Figure A1.8. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental costs with PAS – Target population

Note: Table A.15 below details the variables identified as numbers in this tournado plot.

Table A1.15. Description of key variables with the largest impact on Incremental costs

Variable ID	Variable	Base value	Lower Bound	Upper Bound
1	Annual probability of remaining in study for belimumab responders	0.870	0.896	0.844
2	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
3	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
4	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
5	Constant coefficient in the natural history diabetes model	-14.66	-19.14	-10.29
6	Log of age coefficient at current visit in natural history diabetes model	2.25	1.16	3.35
7	Log of age at current visit coefficient in natural history pulmonary model	1.23	0.59	1.92
8	Constant coefficient from the natural history pulmonary model	-9.27	-11.78	-6.86
9	Log of age at current visit coefficient in natural history peripheral vascular model	1.16	0.43	1.89
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 belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
13	Adjusted Mean SLEDAI at current visit coefficient from the renal model	0.32	0.23	0.41
14	Coefficient for all belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
15	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.17	0.02	0.31

Probabilistic Sensitivity Analyses (PSA)

The results for the probabilistic sensitivity analyses are presented in the form of a scatter plot (Figure A1.9) and a cost-effectiveness acceptability curve (Figure A1.10) below.

Figure A1.9. Scatter plot of the PSA with PAS - Target population

Figure A1.10. Acceptability curve of PSA with PAS - Target population

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

Scenario Analyses

Key Scenario Analyses

Detailed below are scenario analyses which we believe are important for consideration by the Appraisal Committee.

1) Annual discontinuation rate

An assumption of up to lifetime use of belimumab is used for the base case economic analysis. However this assumption will lead to a very conservative assessment of cost-effectiveness for the following reasons:

- NICE stated in Section 4.4 of the FAD that the Committee "...*heard from the clinical specialists that continuous use of belimumab for a long time would be very unlikely. The clinical specialists explained that one of the aims of treatment with belimumab would be to work towards coming off the treatment*." Having consulted with lupus specialists after the release of the Appraisal Consultation Document (ACD) in September 2011, the advice GSK received was that other immunosuppressants used to treat lupus are frequently prescribed for three to five years for patients with active disease with the aim of maintaining suppression of disease activity, and once achieved, the doses of the immunosuppressants are tapered and eventually stopped. The specialists also informed GSK that it is mainly patients with significant renal disease (severe active lupus nephritis) or CNS lupus whom are likely to require very long durations of treatment i.e. beyond 5 or 6 years and these patients are outside the current licensed indication for belimumab.

- The annual discontinuation rate used in the health economic model for responders to belimumab determines the overall distribution of treatment durations. The base case value uses an annual rate of 13% which represents the average annual withdrawal rate seen in the Phase II open-label extension study (LBSL-99) over six years of follow-up. The ERG agreed that this was a more plausible value than the 8% annual rate used in our original submission, estimated from the shorter-term BLISS trials. However we believe that using an annual value of 13% in the model is also likely to over-estimate the number of patients that we would expect to see in clinical practice receiving prolonged treatment durations for our target population. Using this annual rate there are still 26% of "responders" receiving belimumab after 10 years, 13% after 15 years and 7% after 20 years. Hence we believe the estimate of cost-effectiveness obtained from this base case is conservative.

In consideration of the above points we have provided a key scenario analysis which involves an alternative approach using a variable time-dependent annual withdrawal rate. For this analysis a withdrawal rate of 13% was used for Years 1 to 5 and then the rate is increased to 30% from Year 6 onwards. This leads to 37% of responders being retained on belimumab after 6 years, 9% after 10 years, <2% after 15 years and <1% after 20 years. We believe this more closely represents the likely distribution of treatment durations as prescribed in clinical practice for the patients in our target population.

2) Treatment continuation criterion at week 24

In recognition of limited NHS resources, as an alternative to the 4-point treatment continuation criterion used in the base case, a more stringent treatment continuation criterion (SS reduction ≥6 points) was considered as it enabled continuous treatment with belimumab to be targeted to those patients showing the most significant early response, and improves the cost-effectiveness further. Inclusion of this more stringent continuation rule was not supported by the Committee in the FAD (Section 4.17) and GSK felt the reason for rejecting this rule was not clear when cost-effectiveness was

improved and when the Committee had accepted the inclusion of the base case continuation rule. This was raised as an appeal point by GSK which the Appeal Panel upheld. The Committee at the appeal hearing explained that their reason for rejecting it was because they felt it would be difficult to implement in practice as the clinical experts had informed the Committee during the Appraisal Committee Meetings that they would be reluctant to cease treatment if a patient had shown an improvement of 4 points, which was judged a clinically significant improvement by the United States Food & Drug Administration and other organisations.

GSK believe this more stringent rule is relevant for consideration in this appraisal, particularly in the context of the revised PAS. Although using the base case continuation rule is preferable, if the level of cost-effectiveness is only considered to be of an acceptable level when the more stringent rule is used in the management of patients, then acceptance of this rule will at least enable a subgroup of our target patients to gain access to and continue treatment with belimumab. The alternative is that with a negative recommendation no patients would be likely to be able to access belimumab. Therefore scenarios using this more stringent rule are provided when considering both our base case annual discontinuation rate of 13% per annum and when using the variable annual discontinuation rate.

Additional Scenario Analyses

1) Maximum treatment duration

In our response to the ACD in October 2011, and consistent with the discussions we had with lupus specialists after publication of the ACD, we provided NICE with a revised base case cost-effectiveness analysis where a maximum treatment duration with belimumab of 6 years was assumed; an alternative scenario analysis which assumed up to 10 years use of belimumab was also presented. The Appraisal Committee favoured the original base case analysis which assumed up to lifetime use of belimumab over these revised analyses with maximum durations due to concerns over potential withdrawal effects and because maximum durations of treatment were not specified in the SmPC. However we believe it is still important to consider these analyses as they allow assessment of cost-effectiveness when patients do not receive belimumab for prolonged durations and may be reflective of how belimumab will be used in clinical practice. These analyses are presented as additional scenarios but incorporating the 13% discontinuation rate and separate results are provided when using the base case treatment continuation criterion and the more stringent criterion.

Exclusion of a treatment continuation criterion

Another scenario analysis presented comprises the exclusion of a treatment continuation criterion at 24 weeks in the health economic model. Lupus specialists believe that inclusion of a continuation criterion will improve the management of patients on belimumab and allows treatment to be targeted to those patients showing clear early benefits. Incorporating a continuation criterion in the model is also consistent with the SmPC which states that discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months. Hence the main purpose of presenting this additional scenario analysis is to highlight the amount of improvement in estimated cost-effectiveness achieved, and hence a more efficient use of NHS resources, when a treatment continuation rule is included in the management of patients in our target population.

Lower annual discontinuation rate

Finally, in response to a specific request from NICE, the model was run using the annual discontinuation rate of 8% observed in the BLISS trials and which was used in our original submission. However this is likely to significantly underestimate the rate of natural discontinuation from belimumab treatment and hence overestimate the distribution of treatment durations likely to be seen in clinical practice, as after

10 years there would still be 45% of belimumab responders receiving treatment, and after 20 years there would be 20% still receiving continuous belimumab, which is very unlikely.

The results of all the scenario analyses are presented in Table A1.16 below.

Table A1.16. Summary of Scenario Results with revised PAS - Target population

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised Base Case	Time horizon = lifetime; up to lifetime belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; annual discontinuation rate of 13%; adjusted natural history model; monthly infusion hospital admission cost of £154	[redacted]	0.87	0.663	[redacted]
Variable discontinuation rate.	As revised base case with the ≥4-point treatment continuation criterion but using a 13% discontinuation rate up to Year 5 and a 30% discontinuation rate from Year 6 onwards	[redacted]	0.79	0.596	[redacted]
More stringent treatment continuation criterion	As revised base case but with treatment continuation criterion of SS score of ≥6 at week 24	[redacted]	0.79	0.595	[redacted]
Variable discontinuation rate with more stringent treatment continuation criterion	As revised base case but incorporating the more stringent treatment continuation criterion and using a 13% discontinuation rate up to Year 5 and a 30% discontinuation rate from Year 6 onwards	[redacted]	0.69	0.513	[redacted]
Maximum 10 year belimumab treatment duration	As revised base case but with maximum belimumab treatment duration of 10 years and treatment continuation criterion defined as SS reduction ≥4 at week 24;	[redacted]	0.82	0.619	[redacted]
Maximum 10 year treatment duration with more stringent continuation criterion	As revised base case but with 10 year maximum belimumab treatment duration; more stringent treatment continuation criterion defined as SS reduction ≥6 at week 24;	[redacted]	0.74	0.556	[redacted]
Maximum 6 years treatment duration	As revised base case but with maximum belimumab treatment duration of 6 years and treatment continuation criterion defined as SS reduction ≥4 at week 24;	[redacted]	0.74	0.557	[redacted]
Maximum 6 year treatment duration with more stringent continuation criterion	As revised base case but with maximum belimumab treatment duration of 6 years and more stringent treatment continuation criterion defined as SS reduction ≥6 at week 24;	[redacted]	0.68	0.503	[redacted]

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised base case assumptions but using an annual discontinuation rate of 8%;	As original base case: including the base case treatment continuation criterion (SS reduction ≥4 at week 24); annual discontinuation rate of 8%; drug administration cost of £154	[redacted]	1.05	0.806	[redacted]
Revised base case with discontinuation rate of 8% and more stringent treatment continuation criterion	As revised base case including the more stringent treatment continuation criterion; annual discontinuation rate of 8%; drug administration cost of £154	[redacted]	0.98	0.714	[redacted]
Revised base case excluding a treatment continuation criterion	As revised base case but no treatment continuation rule at week 24	[redacted]	0.83	0.642	[redacted]

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

Incorporating the more stringent responder rule into our revised base case reduces the ICER by just over £4000 to [redacted] per QALY.

When the variable discontinuation rate is considered to reflect more closely the likely rate of withdrawal in clinical practice, the ICER is [redacted] per QALY gained, just over £4,000 per QALY gained lower than the ICER for the revised base case when the ≥4-point treatment continuation criterion is incorporated. When inclusion of the more stringent treatment continuation criterion is considered the ICER obtained is [redacted] per QALY gained.

Alternatively, when a maximum treatment duration of 10 years for belimumab is considered and incorporating the base case treatment continuation criterion the ICER is [redacted] per QALY gained. When the more stringent treatment continuation criterion is used in the model the ICER yielded is [redacted] per QALY gained.

When 6 years is considered as a maximum treatment duration for belimumab, the ICER was [redacted] per QALY gained and when the more stringent treatment continuation criterion is incorporated the ICER is [redacted] per QALY gained.

Excluding the treatment continuation rule completely from the cost-effectiveness analysis altogether increases the ICER compared with the revised base case by just over £5600 to [redacted] per QALY gained.

Scenario analyses incorporating an annual discontinuation rate of 8%, yielded ICERs of [redacted] per QALY gained and [redacted] per QALY gained for the base case and more stringent treatment continuation criteria respectively.

Discussion

Incorporating the revised PAS resulted in a base case ICER of [redacted] per QALY gained, assuming up to lifetime use of belimumab in the model and a treatment continuation criterion of ≥4-point decrease in SELENA-SLEDAI at week 24. ICERs from the univariate sensitivity 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 with belimumab on reducing SS score, the assumed duration of belimumab treatment and the choice of continuation criterion after six months of treatment.

When the variable discontinuation rate is considered the ICER obtained is which we believe provides a more plausible estimate of cost-effectiveness for belimumab. We believe the base case ICER incorporating our revised PAS over-estimates the cost-effectiveness of belimumab and that the ICER obtained for the scenario using the variable annual discontinuation rate ([redacted] per QALY gained) provides a more plausible estimate as the distribution of treatment durations obtained from this analysis are likely to be more reflective of those seen in clinical practice for our target population. When the more stringent continuation criterion is incorporated into the modelling the cost-effectiveness is further improved.

We believe that these estimates of cost-effectiveness, which incorporate our revised PAS, demonstrate an efficient use of NHS resources, particularly when considering the innovative nature of the technology, the significant unmet need in our target population and aspects of value not fully captured in the QALYs.

Appendix 2
Cost-effectiveness Analyses for the Updated Base Case Excluding the Revised PAS

Data Analysis

Provided below are the results from the health economic analysis for our proposed target SLE population (high disease activity subgroup) with our revised base case which incorporates updated values for two assumptions (treatment withdrawal rate and monthly infusion administration cost) in the economic model. Consistent with the base case in our original submission and with the SmPC this new base case includes a treatment continuation criterion (SS score decrease of ≥4 points) at week 24 i.e. after six months of treatment.

The analyses presented in this appendix do not incorporate the improved PAS however the methodology and assumptions used for these analyses are identical to those described in Appendix 1 of our additional submission dated 26th October 2012 which does incorporate the PAS.

Cost-Effectiveness Results

Yearly drug acquisition costs for belimumab based on the list price for the 120mg and 400mg vials are presented in the Table A2.1 below.

Table A2.1. Unit costs associated with the new technology in the economic model – Target population

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 = £9731 Year 2 annual cost = £9036	The list price vial costs are £121.50 and £405.00 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
Total Year 1 costs	**£11,887**	
Total Subsequent Year costs	**£11,038**	

Table A2.2 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, 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 with belimumab 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 and although belimumab patients have less disease activity and consequently lower direct resource costs per year, on average, the increased lifetime cost seen with belimumab is due to the estimated increased life expectancy. Overall, the main difference in costs is caused by belimumab acquisition and administration costs, amounting to £44,771 (87.2%) of the total absolute cost difference of £51,332.

Table A2.2. Summary of (discounted) costs over a lifetime model horizon for revised base case - Target population

Discounted	SoC	Belimumab	Difference	Absolute difference	% absolute difference
Disease activity related costs	£27,882	£28,301	£418	£418	0.8%
Belimumab drug acquisition	£0	£36,650	£36,650	£36,650	71.4%
Belimumab administration	£0	£8,121	£8,121	£8,121	15.8%
Organ damage costs					0.0%
Cardiovascular	£1,838	£1,666	-£172	£172	0.3%
Diabetes	£2,493	£2,682	£189	£189	0.4%
Gastrointestinal	£359	£392	£33	£33	0.1%
Malignancy	£998	£1,020	£22	£22	0.0%
Musculoskeletal	£9,758	£10,097	£339	£339	0.7%
Neuropsychiatric	£6,434	£6,672	£239	£239	0.5%
Ocular	£392	£391	-£1	£1	0.0%
Peripheral vascular	£1,380	£1,330	-£50	£50	0.1%
Premature gonadal failure	£0	£0	£0	£0	0.0%
Pulmonary	£42,692	£39,559	-£3,133	£3,133	6.1%
Renal	£11,139	£9,176	-£1,963	£1,963	3.8%
Skin	£0	£0	£0	£0	0.0%
Sum of organ damage costs	£77,483	£72,985	-£4,499	-	
Total direct costs	£105,366	£146,056	£40,691	£51,332	100.0%

Table A2.3 summarises the results for the revised base case analysis. Belimumab-treated patients are estimated to live longer, however, due to their increased life expectancy and due to belimumab acquisition and administration costs, the total costs of managing SLE patients with high disease activity are higher than for SoC patients. The incremental costs are £40,691, with 0.9 added life years, or 0.7 added QALYs, discounted at 3.5%, resulting in an ICER of £61,328 per QALY gained.

Table A2.3. Discounted revised base case results – Target population

	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
SoC	£105,366	17.05	9.81	-			
Belimumab	£146,056	17.93	10.47	£40,691	0.87	0.66	£61,328
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity Analyses

Results of the Univariate Sensitivity Analyses

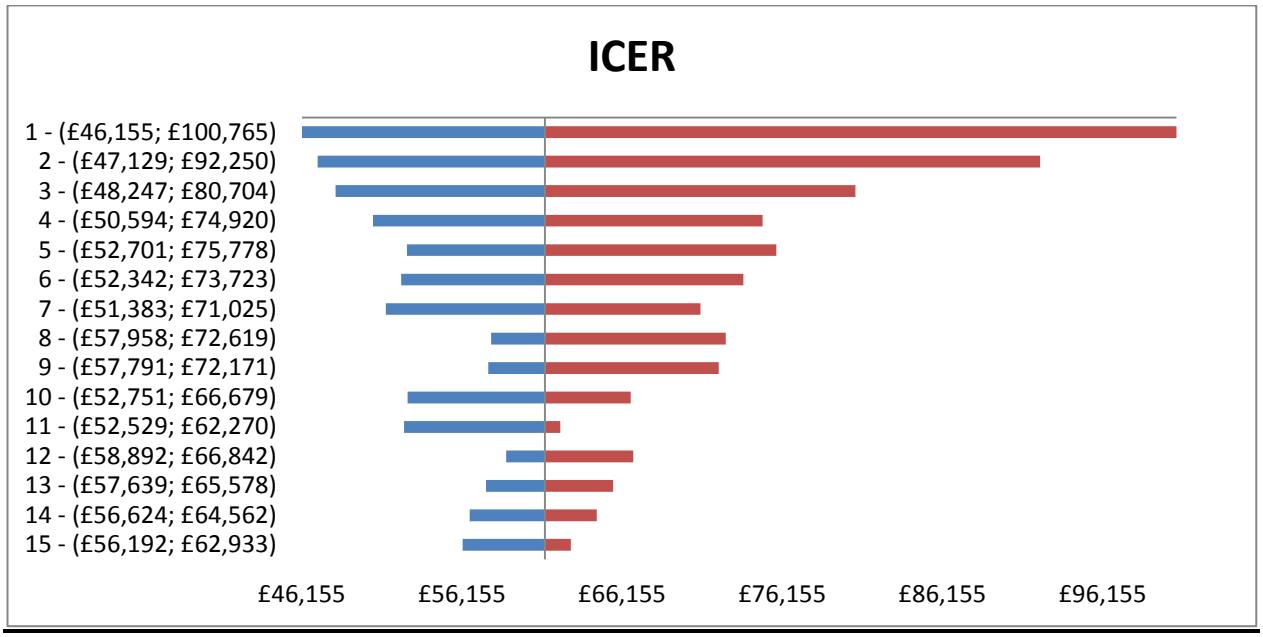
Tornado diagrams for the ICER, incremental QALYs and incremental costs are presented in Figures A2.1, A2.2 and A2.3 respectively. A description of the 15 variables which had the most impact on the ICER, incremental QALYs and incremental costs are presented in Tables A2.4, A2.5 and A2.6 respectively.

The ICERs yielded from the univariate sensitivity analyses ranged from £46,155 to £100,765 per QALY gained. The main drivers of cost-effectiveness in our revised base case model are the treatment effect regression to estimate the effect of belimumab on SS score after 52 weeks; the greater the benefit seen with belimumab compared to SoC on reducing SS score, the higher the incremental QALY and hence the lower the ICER.

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

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

Figure A2.1. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on ICERs – Target population

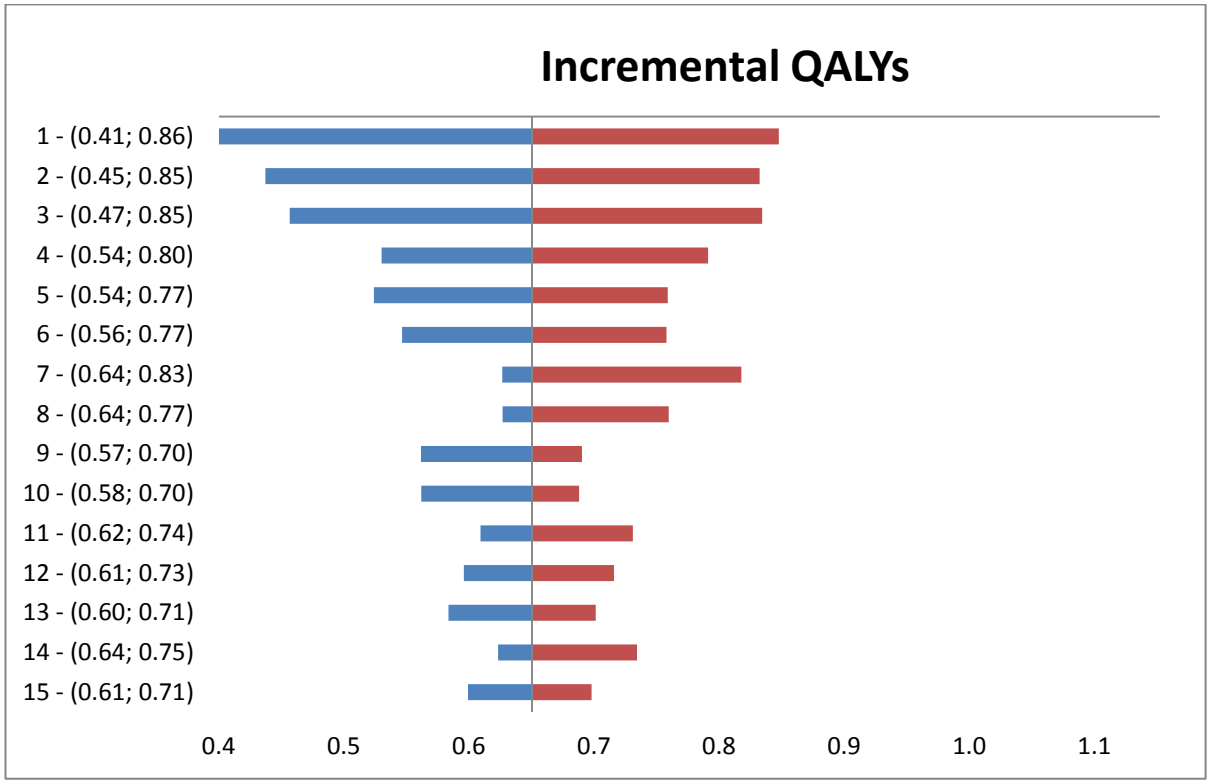


Note: Table A2.4 below details the variables identified as numbers in this tournado plot.

Table A2.4. Description of key variables with the largest impact on the ICER

Variable ID	Variable Name	Base Value	Lower bound	Upper bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI coefficient at current visit from the natural history mortality model	0.21	0.09	0.33
4	Coefficient of Log of age from the "clean utility" regression	0.15	-0.18	-0.10
5	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
6	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
7	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
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	Adjusted Mean SLEDAI coefficient at current visit from the natural history renal model	0.31	0.23	0.39
11	Constant coefficient from the natural history peripheral vascular model	-11.70	-16.47	-6.81
12	Adjusted constant from the natural history of disease activity model.	3.00	2.20	3.93
13	Natural yearly discontinuation rate for belimumab responders	0.870	0.896	0.844
14	Constant coefficient from the natural history renal model	-8.29	-7.56	-9.01
15	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31

Figure A2.2. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental QALYs – Target population

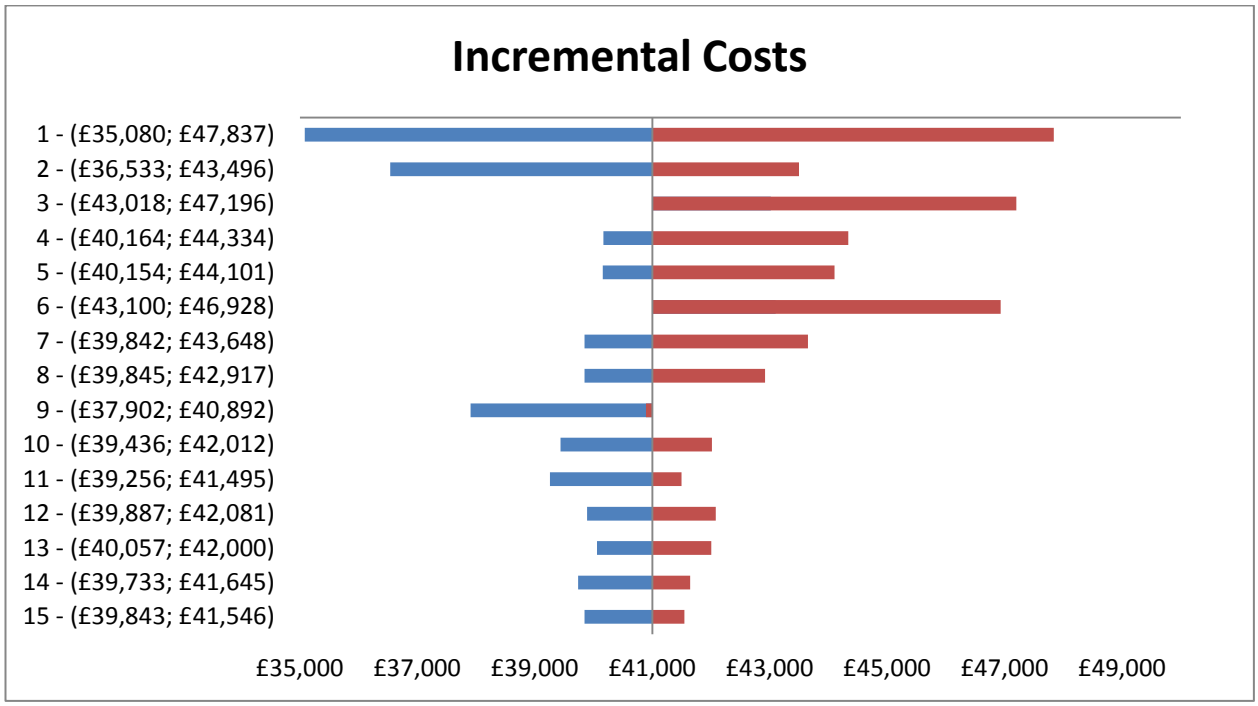


Note: Table A2.5 below details the variables identified as numbers in this tournado plot.

Table A2.5. Description of key variables with the largest Impact on Incremental QALYs

Variable ID	Variable	Base Value	Lower Bound	Upper Bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
4	Coefficient of Log of age from the "clean utility" regression	-0.15	-0.18	-0.10
5	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
6	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 Log of age at current visit in natural history peripheral vascular model	1.16	0.43	1.89
9	Coefficient constant from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
10	Coefficient 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	Natural annual discontinuation rate for belimumab “responders”	0.870	0.896	0.844
13	Adjusted constant from the natural history of disease activity model.	3.00	2.20	3.93
14	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
15	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history pulmonary model	0.14	0.06	0.22

Figure A2.3. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental costs – Target population



Note: Table A2.6 below details the variables identified as numbers in this tournado plot.

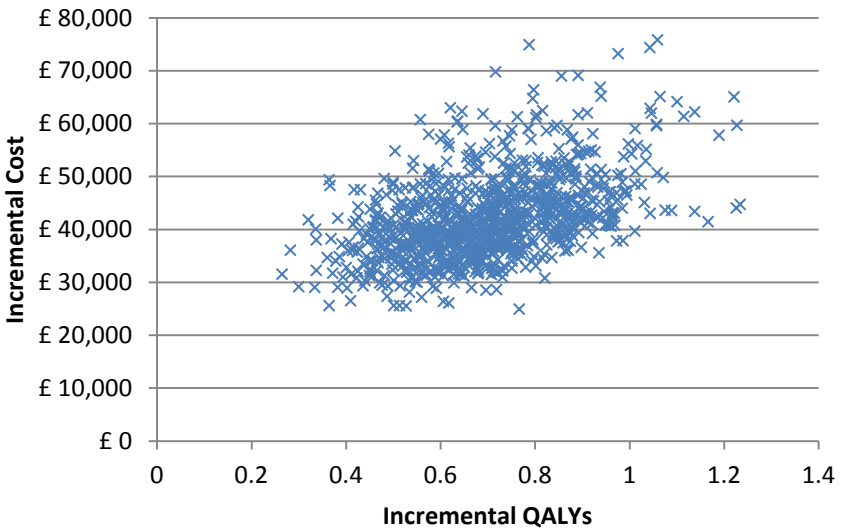
Table A2.6. Description of key variables with the largest impact on Incremental costs

Variable ID	Variable	Base value	Lower Bound	Upper Bound
1	Annual probability of remaining in study for belimumab responders	0.870	0.896	0.844
2	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
3	Log of age at current visit coefficient in natural history pulmonary model	1.23	0.59	1.92
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	Constant coefficient from the natural history pulmonary model	-9.27	-11.78	-6.86
7	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
8	Log of age at current visit coefficient in natural history peripheral vascular model	1.16	0.43	1.89
9	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
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	Adjusted Constant coefficient in the natural history Disease Activity Model	3.0	2.20	3.93
13	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
14	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
15	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25

Probabilistic Sensitivity Analyses (PSA)

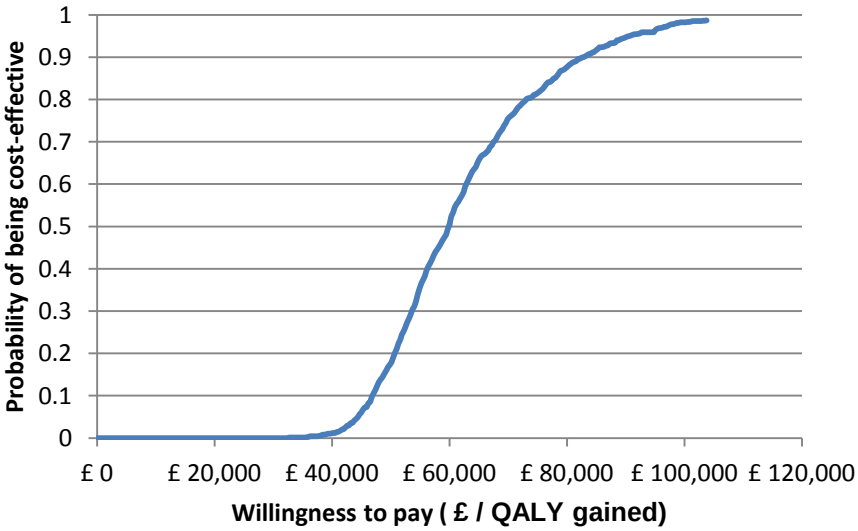
The results for the probabilistic sensitivity analyses are presented in the form of a scatter plot (Figure A2.4) and a cost-effectiveness acceptability curve (Figure A2.5) below.

Figure A2.4. Scatter plot of the PSA - Target population



The mean and median ICERs obtained from the PSA with 1000 iterations were £62,576 per QALY and £59,845 per QALY respectively.

Figure A2.5. Acceptability curve of PSA - Target population



The PSA results show that at a willingness to pay of £30,000 per QALY gained, there is a 0% probability that belimumab is cost-effective compared with SoC. With a willingness to pay of £40,000 per QALY gained and £60,000 per QALY gained, there is a 1.1% and 50.5% probability that belimumab is cost-effective compared with SoC.

Scenario Analyses

The same scenario analyses as detailed in Appendix 1 of the additional GSK submission, dated 26th October 2012, were carried out without inclusion of the PAS and the results are presented in Table A2.7 below.

Table A2.7. Summary of Scenario Results - Target population

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised Base Case	Time horizon = lifetime; up to lifetime belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; annual discontinuation rate of 13%; adjusted natural history model; monthly infusion hospital admission cost of £154	£40,691	0.87	0.663	£61,328
Variable discontinuation rate.	As revised base case with the ≥4-point treatment continuation criterion but using a 13% discontinuation rate up to Year 5 and a 30% discontinuation rate from Year 6 onwards	£31,162	0.79	0.596	£52,299
More stringent treatment continuation criterion	As revised base case but with treatment continuation criterion of SS score of ≥6 at week 24	£32,054	0.79	0.595	£53,855
Variable discontinuation rate with more stringent treatment continuation criterion	As revised base case but incorporating the more stringent treatment continuation criterion and using a 13% discontinuation rate up to Year 5 and a 30% discontinuation rate from Year 6 onwards	£21,612	0.69	0.513	£42,164
Maximum 10 year belimumab treatment duration	As revised base case but with maximum belimumab treatment duration of 10 years and treatment continuation criterion defined as SS reduction ≥4 at week 24;	£33,588	0.82	0.619	£54,256
Maximum 10 year treatment duration with more stringent continuation criterion	As revised base case but with 10 year maximum belimumab treatment duration; more stringent treatment continuation criterion defined as SS reduction ≥6 at week 24;	£26,593	0.74	0.556	£47,849
Maximum 6 years treatment duration	As revised base case but with maximum belimumab treatment duration of 6 years and treatment continuation criterion defined as SS reduction ≥4 at week 24;	£26,364	0.74	0.557	£47,322
Maximum 6 year treatment duration with more stringent continuation criterion	As revised base case but with maximum belimumab treatment duration of 6 years and more stringent treatment continuation criterion defined as SS reduction ≥6 at week 24;	£21,161	0.68	0.503	£42,050

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised base case excluding a treatment continuation criterion	As revised base case but no treatment continuation rule at week 24	£45,845	0.83	0.642	£71,454
Revised base case assumptions but using an annual discontinuation rate of 8%;	As original base case: including the base case treatment continuation criterion (SS reduction ≥4 at week 24); annual discontinuation rate of 8%; drug administration cost of £154	£56,900	1.05	0.806	£70,580
Revised base case with discontinuation rate of 8% and more stringent treatment continuation criterion	As revised base case including the more stringent treatment continuation criterion; annual discontinuation rate of 8%; drug administration cost of £154	£44,313	0.93	0.712	£62,225

The various alternative scenarios investigated resulted in ICERs ranging from £42,050 to £71,454per QALY gained compared with the revised base case ICER of £61,328 per QALY gained.

Incorporating the more stringent responder rule into our revised base case reduces the ICER by just under £7500 to £53,855 per QALY.

When the variable discontinuation rate is considered to reflect more closely the likely rate of withdrawal in clinical practice, the ICER is £52,299 per QALY gained and when inclusion of the more stringent treatment continuation criterion is considered with the variable discontinuation rate the ICER obtained is £42,164 per QALY gained.

When a maximum treatment duration of 10 years for belimumab is considered and incorporating the base case treatment continuation criterion the ICER is £54,256 per QALY gained. When the more stringent treatment continuation criterion is used in the model with a maximum of 10 years treatment the ICER yielded is £47,849 per QALY gained.

When 6 years is considered as a maximum treatment duration for belimumab, the ICER was £47,322 per QALY gained for the base case treatment continuation criterion and £42,050 per QALY gained when the more stringent treatment continuation criterion was included.

Excluding a treatment continuation rule completely from the cost-effectiveness analysis increases the ICER compared with the revised base case by just over £10,000 to £71,454 per QALY gained.

Scenario analyses incorporating an annual discontinuation rate of 8%, yielded ICERs of £70,580 per QALY gained and £62,225 per QALY gained for the base case and more stringent treatment continuation criteria respectively.

Discussion

The revised base case ICER was estimated to be £61,328 per QALY gained, assuming up to lifetime use of belimumab in the model and a treatment continuation criterion of ≥4-point decrease in SELENA-SLEDAI at week 24. ICERs from the univariate sensitivity analyses ranged from £46,155 to £100,765 per QALY gained. Variables and assumptions which had the greatest impact on the ICER comprised the

degree of benefit with belimumab on reducing SS score, the effect of the AMS on mortality, the constant and effect of log age in the utility regression, the assumed duration of belimumab treatment and the choice of continuation criterion after six months of treatment.

We believe the base case ICER which assumes a constant 13% withdrawal rate over-estimates the cost-effectiveness of belimumab and that the ICER obtained for the scenario using the variable annual discontinuation rate provides a more plausible estimate (£52,299 per QALY gained) as the distribution of treatment durations obtained from this analysis are likely to be more reflective of those seen in clinical practice for our target population. When the more stringent continuation criterion is incorporated into the modelling the cost-effectiveness is further improved.

Appendix 2
Cost-effectiveness Analyses for the Updated Base Case Excluding the Revised PAS

Data Analysis

Provided below are the results from the health economic analysis for our proposed target SLE population (high disease activity subgroup) with our revised base case which incorporates updated values for two assumptions (treatment withdrawal rate and monthly infusion administration cost) in the economic model. Consistent with the base case in our original submission and with the SmPC this new base case includes a treatment continuation criterion (SS score decrease of ≥4 points) at week 24 i.e. after six months of treatment.

The analyses presented in this appendix do not incorporate the improved PAS however the methodology and assumptions used for these analyses are identical to those described in Appendix 1 of our additional submission dated 26th October 2012 which does incorporate the PAS.

Cost-Effectiveness Results

Yearly drug acquisition costs for belimumab based on the list price for the 120mg and 400mg vials are presented in the Table A2.1 below.

Table A2.1. Unit costs associated with the new technology in the economic model – Target population

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 = £9731 Year 2 annual cost = £9036	The list price vial costs are £121.50 and £405.00 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
Total Year 1 costs	**£11,887**	
Total Subsequent Year costs	**£11,038**	

Table A2.2 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, 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 with belimumab 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 and although belimumab patients have less disease activity and consequently lower direct resource costs per year, on average, the increased lifetime cost seen with belimumab is due to the estimated increased life expectancy. Overall, the main difference in costs is caused by belimumab acquisition and administration costs, amounting to £44,771 (87.2%) of the total absolute cost difference of £51,332.

Table A2.2. Summary of (discounted) costs over a lifetime model horizon for revised base case - Target population

Discounted	SoC	Belimumab	Difference	Absolute difference	% absolute difference
Disease activity related costs	£27,882	£28,301	£418	£418	0.8%
Belimumab drug acquisition	£0	£36,650	£36,650	£36,650	71.4%
Belimumab administration	£0	£8,121	£8,121	£8,121	15.8%
Organ damage costs					0.0%
Cardiovascular	£1,838	£1,666	-£172	£172	0.3%
Diabetes	£2,493	£2,682	£189	£189	0.4%
Gastrointestinal	£359	£392	£33	£33	0.1%
Malignancy	£998	£1,020	£22	£22	0.0%
Musculoskeletal	£9,758	£10,097	£339	£339	0.7%
Neuropsychiatric	£6,434	£6,672	£239	£239	0.5%
Ocular	£392	£391	-£1	£1	0.0%
Peripheral vascular	£1,380	£1,330	-£50	£50	0.1%
Premature gonadal failure	£0	£0	£0	£0	0.0%
Pulmonary	£42,692	£39,559	-£3,133	£3,133	6.1%
Renal	£11,139	£9,176	-£1,963	£1,963	3.8%
Skin	£0	£0	£0	£0	0.0%
Sum of organ damage costs	£77,483	£72,985	-£4,499	-	
Total direct costs	£105,366	£146,056	£40,691	£51,332	100.0%

Table A2.3 summarises the results for the revised base case analysis. Belimumab-treated patients are estimated to live longer, however, due to their increased life expectancy and due to belimumab acquisition and administration costs, the total costs of managing SLE patients with high disease activity are higher than for SoC patients. The incremental costs are £40,691, with 0.9 added life years, or 0.7 added QALYs, discounted at 3.5%, resulting in an ICER of £61,328 per QALY gained.

Table A2.3. Discounted revised base case results – Target population

	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
SoC	£105,366	17.05	9.81	-			
Belimumab	£146,056	17.93	10.47	£40,691	0.87	0.66	£61,328
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity Analyses

Results of the Univariate Sensitivity Analyses

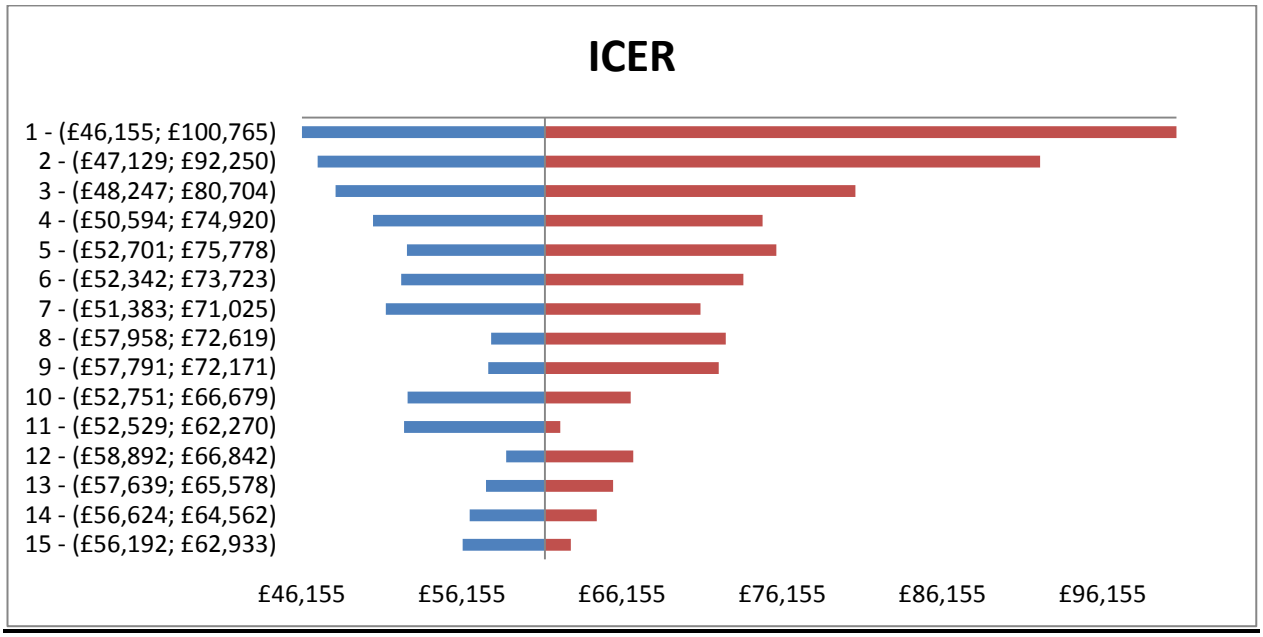
Tornado diagrams for the ICER, incremental QALYs and incremental costs are presented in Figures A2.1, A2.2 and A2.3 respectively. A description of the 15 variables which had the most impact on the ICER, incremental QALYs and incremental costs are presented in Tables A2.4, A2.5 and A2.6 respectively.

The ICERs yielded from the univariate sensitivity analyses ranged from £46,155 to £100,765 per QALY gained. The main drivers of cost-effectiveness in our revised base case model are the treatment effect regression to estimate the effect of belimumab on SS score after 52 weeks; the greater the benefit seen with belimumab compared to SoC on reducing SS score, the higher the incremental QALY and hence the lower the ICER.

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

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

Figure A2.1. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on ICERs – Target population

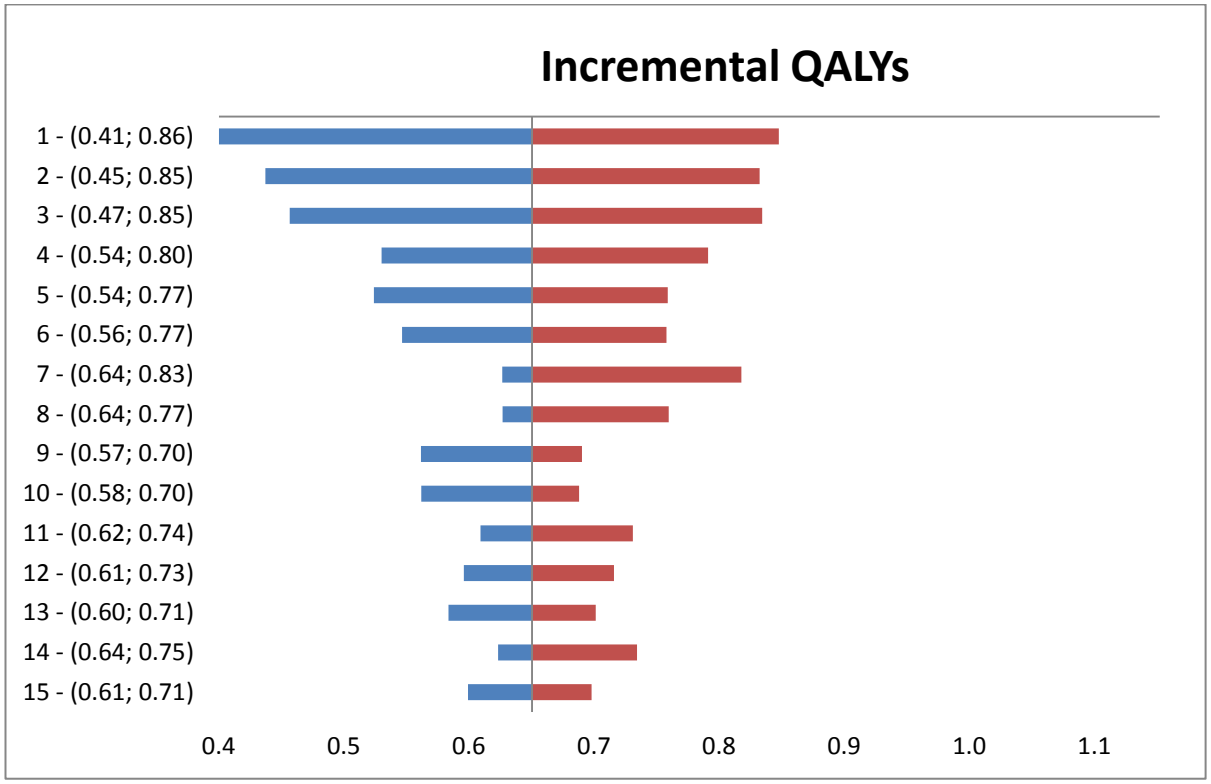


Note: Table A2.4 below details the variables identified as numbers in this tournado plot.

Table A2.4. Description of key variables with the largest impact on the ICER

Variable ID	Variable Name	Base Value	Lower bound	Upper bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI coefficient at current visit from the natural history mortality model	0.21	0.09	0.33
4	Coefficient of Log of age from the "clean utility" regression	0.15	-0.18	-0.10
5	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
6	Coefficient for all SoC patients from the linear regression of change in SLEDAI score at 52 weeks	-0.35	-0.39	-0.31
7	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
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	Adjusted Mean SLEDAI coefficient at current visit from the natural history renal model	0.31	0.23	0.39
11	Constant coefficient from the natural history peripheral vascular model	-11.70	-16.47	-6.81
12	Adjusted constant from the natural history of disease activity model.	3.00	2.20	3.93
13	Natural yearly discontinuation rate for belimumab responders	0.870	0.896	0.844
14	Constant coefficient from the natural history renal model	-8.29	-7.56	-9.01
15	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31

Figure A2.2. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental QALYs – Target population

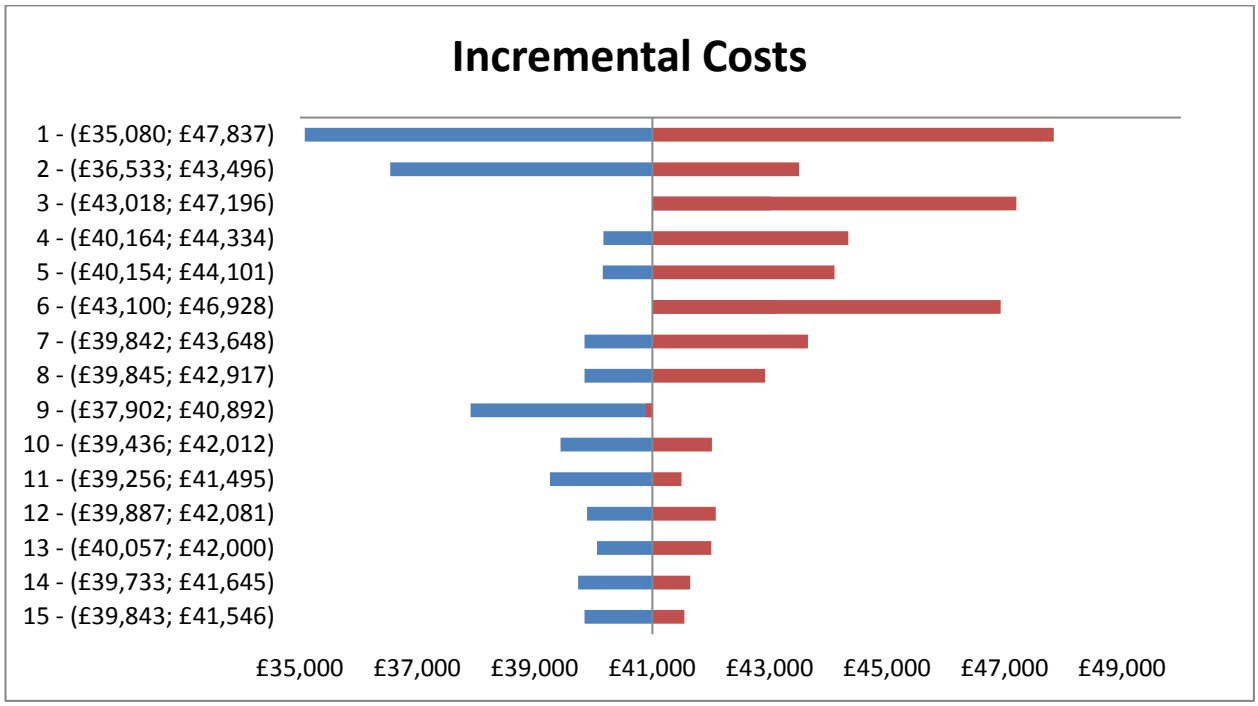


Note: Table A2.5 below details the variables identified as numbers in this tournado plot.

Table A2.5. Description of key variables with the largest Impact on Incremental QALYs

Variable ID	Variable	Base Value	Lower Bound	Upper Bound
1	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
2	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25
3	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
4	Coefficient of Log of age from the "clean utility" regression	-0.15	-0.18	-0.10
5	Constant coefficient in "clean utility" regression	1.30	1.15	1.43
6	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 Log of age at current visit in natural history peripheral vascular model	1.16	0.43	1.89
9	Coefficient constant from the natural history neuropsychiatric model	-7.40	-9.93	-5.12
10	Coefficient 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	Natural annual discontinuation rate for belimumab “responders”	0.870	0.896	0.844
13	Adjusted constant from the natural history of disease activity model.	3.00	2.20	3.93
14	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
15	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history pulmonary model	0.14	0.06	0.22

Figure A2.3. Tornado diagram of univariate sensitivity analysis to demonstrate the impact on incremental costs – Target population



Note: Table A2.6 below details the variables identified as numbers in this tournado plot.

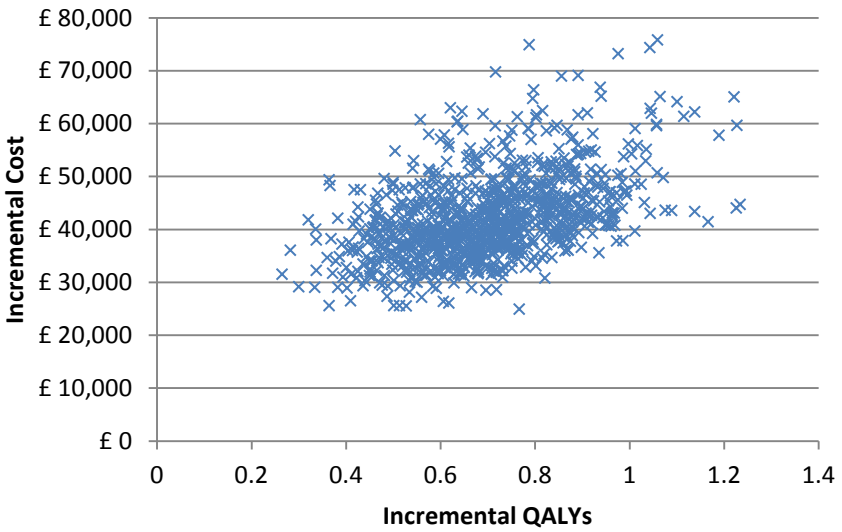
Table A2.6. Description of key variables with the largest impact on Incremental costs

Variable ID	Variable	Base value	Lower Bound	Upper Bound
1	Annual probability of remaining in study for belimumab responders	0.870	0.896	0.844
2	Adjusted Mean SLEDAI at current visit coefficient from the natural history pulmonary model	0.14	0.06	0.22
3	Log of age at current visit coefficient in natural history pulmonary model	1.23	0.59	1.92
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	Constant coefficient from the natural history pulmonary model	-9.27	-11.78	-6.86
7	Constant coefficient in the natural history peripheral vascular model	-11.70	-16.47	-6.81
8	Log of age at current visit coefficient in natural history peripheral vascular model	1.16	0.43	1.89
9	Adjusted Mean SLEDAI at current visit coefficient from the mortality model	0.21	0.09	0.33
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	Adjusted Constant coefficient in the natural history Disease Activity Model	3.0	2.20	3.93
13	Coefficient for Adjusted Mean SLEDAI at current visit from the natural history peripheral vascular model	0.17	0.02	0.31
14	Coefficient for belimumab responders from linear regression of change in SLEDAI score at 52 weeks	-0.28	-0.38	-0.17
15	Coefficient for **all** belimumab patients from linear regression of change in SLEDAI score at 52 weeks	-0.34	-0.44	-0.25

Probabilistic Sensitivity Analyses (PSA)

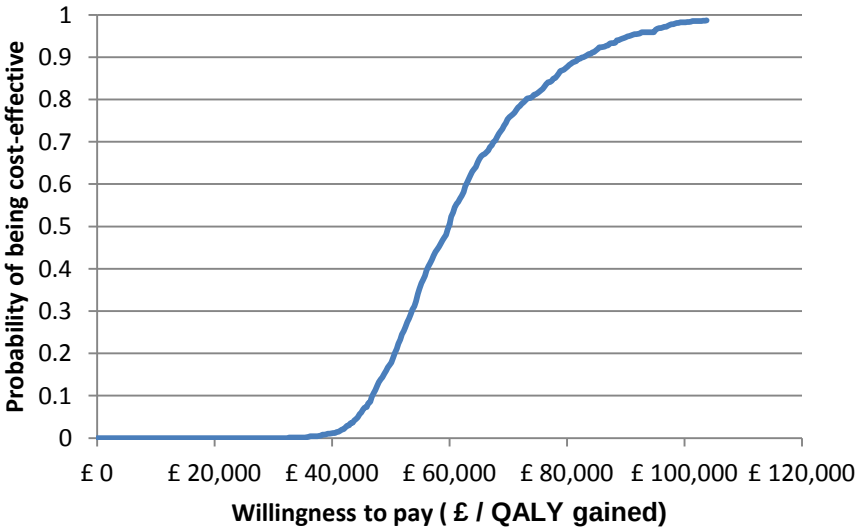
The results for the probabilistic sensitivity analyses are presented in the form of a scatter plot (Figure A2.4) and a cost-effectiveness acceptability curve (Figure A2.5) below.

Figure A2.4. Scatter plot of the PSA - Target population



The mean and median ICERs obtained from the PSA with 1000 iterations were £62,576 per QALY and £59,845 per QALY respectively.

Figure A2.5. Acceptability curve of PSA - Target population



The PSA results show that at a willingness to pay of £30,000 per QALY gained, there is a 0% probability that belimumab is cost-effective compared with SoC. With a willingness to pay of £40,000 per QALY gained and £60,000 per QALY gained, there is a 1.1% and 50.5% probability that belimumab is cost-effective compared with SoC.

Scenario Analyses

The same scenario analyses as detailed in Appendix 1 of the additional GSK submission, dated 26th October 2012, were carried out without inclusion of the PAS and the results are presented in Table A2.7 below.

Table A2.7. Summary of Scenario Results - Target population

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised Base Case	Time horizon = lifetime; up to lifetime belimumab treatment duration; treatment continuation criterion defined as SS reduction ≥4 at week 24; annual discontinuation rate of 13%; adjusted natural history model; monthly infusion hospital admission cost of £154	£40,691	0.87	0.663	£61,328
Variable discontinuation rate.	As revised base case with the ≥4-point treatment continuation criterion but using a 13% discontinuation rate up to Year 5 and a 30% discontinuation rate from Year 6 onwards	£31,162	0.79	0.596	£52,299
More stringent treatment continuation criterion	As revised base case but with treatment continuation criterion of SS score of ≥6 at week 24	£32,054	0.79	0.595	£53,855
Variable discontinuation rate with more stringent treatment continuation criterion	As revised base case but incorporating the more stringent treatment continuation criterion and using a 13% discontinuation rate up to Year 5 and a 30% discontinuation rate from Year 6 onwards	£21,612	0.69	0.513	£42,164
Maximum 10 year belimumab treatment duration	As revised base case but with maximum belimumab treatment duration of 10 years and treatment continuation criterion defined as SS reduction ≥4 at week 24;	£33,588	0.82	0.619	£54,256
Maximum 10 year treatment duration with more stringent continuation criterion	As revised base case but with 10 year maximum belimumab treatment duration; more stringent treatment continuation criterion defined as SS reduction ≥6 at week 24;	£26,593	0.74	0.556	£47,849
Maximum 6 years treatment duration	As revised base case but with maximum belimumab treatment duration of 6 years and treatment continuation criterion defined as SS reduction ≥4 at week 24;	£26,364	0.74	0.557	£47,322
Maximum 6 year treatment duration with more stringent continuation criterion	As revised base case but with maximum belimumab treatment duration of 6 years and more stringent treatment continuation criterion defined as SS reduction ≥6 at week 24;	£21,161	0.68	0.503	£42,050

Description of Scenario	Scenario Details	Incremental Cost Belimumab	Incremental LYs Belimumab	Incremental QALYs Belimumab	Incremental Cost per QALY
Revised base case excluding a treatment continuation criterion	As revised base case but no treatment continuation rule at week 24	£45,845	0.83	0.642	£71,454
Revised base case assumptions but using an annual discontinuation rate of 8%;	As original base case: including the base case treatment continuation criterion (SS reduction ≥4 at week 24); annual discontinuation rate of 8%; drug administration cost of £154	£56,900	1.05	0.806	£70,580
Revised base case with discontinuation rate of 8% and more stringent treatment continuation criterion	As revised base case including the more stringent treatment continuation criterion; annual discontinuation rate of 8%; drug administration cost of £154	£44,313	0.93	0.712	£62,225

The various alternative scenarios investigated resulted in ICERs ranging from £42,050 to £71,454per QALY gained compared with the revised base case ICER of £61,328 per QALY gained.

Incorporating the more stringent responder rule into our revised base case reduces the ICER by just under £7500 to £53,855 per QALY.

When the variable discontinuation rate is considered to reflect more closely the likely rate of withdrawal in clinical practice, the ICER is £52,299 per QALY gained and when inclusion of the more stringent treatment continuation criterion is considered with the variable discontinuation rate the ICER obtained is £42,164 per QALY gained.

When a maximum treatment duration of 10 years for belimumab is considered and incorporating the base case treatment continuation criterion the ICER is £54,256 per QALY gained. When the more stringent treatment continuation criterion is used in the model with a maximum of 10 years treatment the ICER yielded is £47,849 per QALY gained.

When 6 years is considered as a maximum treatment duration for belimumab, the ICER was £47,322 per QALY gained for the base case treatment continuation criterion and £42,050 per QALY gained when the more stringent treatment continuation criterion was included.

Excluding a treatment continuation rule completely from the cost-effectiveness analysis increases the ICER compared with the revised base case by just over £10,000 to £71,454 per QALY gained.

Scenario analyses incorporating an annual discontinuation rate of 8%, yielded ICERs of £70,580 per QALY gained and £62,225 per QALY gained for the base case and more stringent treatment continuation criteria respectively.

Discussion

The revised base case ICER was estimated to be £61,328 per QALY gained, assuming up to lifetime use of belimumab in the model and a treatment continuation criterion of ≥4-point decrease in SELENA-SLEDAI at week 24. ICERs from the univariate sensitivity analyses ranged from £46,155 to £100,765 per QALY gained. Variables and assumptions which had the greatest impact on the ICER comprised the

degree of benefit with belimumab on reducing SS score, the effect of the AMS on mortality, the constant and effect of log age in the utility regression, the assumed duration of belimumab treatment and the choice of continuation criterion after six months of treatment.

We believe the base case ICER which assumes a constant 13% withdrawal rate over-estimates the cost-effectiveness of belimumab and that the ICER obtained for the scenario using the variable annual discontinuation rate provides a more plausible estimate (£52,299 per QALY gained) as the distribution of treatment durations obtained from this analysis are likely to be more reflective of those seen in clinical practice for our target population. When the more stringent continuation criterion is incorporated into the modelling the cost-effectiveness is further improved.

Evidence Review Group Report commissioned by the National Health Service Research & Development Programme on behalf of the National Institute for Health and Clinical Evidence

Title: Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus: response to GSK Post-Appeal Submission

REPORT

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Contributions of authors:
Connock, Sutcliffe, Clarke – critical appraisal of clinical effectiveness. Cummins– critical appraisal of economic modelling. All authors – writing the report.

Evidence Review Group Report in response to GSK Post-Appeal Submission for the Single Technology Appraisal (STA) of Belimumab in the Treatment of Active Autoantibody-Positive Systemic Lupus Erythematosus (SLE)26th October 2012

Introduction and Background

The Final Appraisal Determination (FAD)[1] for belimumab in the treatment of SLE states that it is not recommended for use, however this guidance was subject to the outcome of an appeal process. The appeal hearing for belimumab was held on the 18th July 2012. GSK responded to the Appeal Panel Decision by submitting a Post Appeal Submission with an appendix giving details of the economic model and results and with an additional Excel spreadsheet[2].

The ERG were requested by NICE to supply "a written document outlining whether the revised estimates of cost effectiveness by GSK are accurate and reflect only the changes as stated in their document." The ERG were also informed by NICE that "GSK have confirmed that they will be submitting a revised PAS to be considered by committee at the same time as the two upheld appeal points. The revised PAS will incorporate an [redacted]". And that they "intend to provide revised analyses incorporating the new price and have confirmed they will use the same model previously submitted to NICE".

Below we first summarise and then comment on the submitted documents.

Summary of GSK Post Appeal Documents

GSK submitted a 6 page Post Appeal Submission Word Document,[3] with a 28 page Appendix giving details of the economic model adjustments and results and an Excel spread sheet for the Appraisal Committee to consider at their Appraisal Committee meeting on 27th November 2012. GSK indicated that the Post Appeal Document included the following:

- New analyses include a revised Patient Access Scheme (PAS) and updated assumptions in the health economic model including
- Change in annual discontinuation rate and
- Drug administration cost
- All other assumptions used in the model are identical to those discussed in our original submission (dated April 2011).

Revised base case

The revised base case [3] for the health economic model included:

- A subgroup of the licensed population (UK Target Population) of SLE patients with serious disease activity (low complement and anti-dsDNA and a SELENA-SLEDAI (SS) score of ≥10).
- The comparator was standard care.
- A continuation rule at week 24 based on demonstrating an improvement in disease activity, defined as a ≥4 point reduction in SS (base case continuation rule).
- Up to lifetime use of belimumab with an annual natural discontinuation rate of 13%, which represents the average annual withdrawal rate seen in the Phase II open-label extension study (LBSL-99) over six years of follow-up
- A revised PAS

Scenario Analyses included:

- Scenario 1: using a variable time-dependent annual withdrawal rate. For this analysis a withdrawal rate of 13% was used for Years 1 to 5 and the rate was increased to 30% from Year 6 onwards. This lead to 37% of responders retained on belimumab after 6 years, 9% after 10 years, <2% after 15 years and <1% after 20 years.
- Scenario 2: a treatment continuation criterion of an SS reduction ≥6 points.
- Scenario 3: Scenario 1 and 2 together

Revised results

Summary of Cost-effectiveness Results

- Base case Analysis: The GSK Post appeal submission document reported incremental costs for belimumab treated patients compared to SoC alone of £[redacted], with 0.9 added life years, or 0.7 added QALYs, discounted at 3.5%, resulting in a base case ICER of £[redacted] per QALY gained (Appendix Table A1.12).

Summary of Scenario Analyses

- Scenario 1: using a variable 13% and 30% annual discontinuation rate resulted in an ICER of £[redacted] per QALY.
- Scenario 2: the 6-point continuation criterion with a constant 13% discontinuation rate resulted in an ICER of £[redacted] per QALY
- Scenario 3: Scenario 1 and 2 together resulted in an ICER of £[redacted] per QALY

The post appeal submission also included a discussion of comparison with rituximab

- The post appeal document stated that the 52 week EXPLORER trial used 4 doses of rituximab of 1000mg by infusion which together with administration costs resulted in an annual price to the NHS of £8385.20 per annum. And that the annual cost of belimumab with the [redacted]

Summary of Sensitivity Analyses

In the appendix GSK included sensitivity analyses which showed that ICERS ranged from £[redacted] to £[redacted] per QALY gained, concluding that the main drivers of cost-effectiveness were:

- the treatment effect regression to estimate the effect of belimumab on SS score after 52 weeks
- estimates of the way in which an improvement in AMS due to belimumab would affect pulmonary damage, and reduction in the costs of pulmonary damage
- estimates of the way in which an improvement in AMS due to belimumab would affect mortality
- The constant and effect of log age in the utility regression

Further scenario analyses and PSA results

A number of further scenario analyses were described in the appendix, of which three key ones were:

- As original base case: including the base case treatment continuation criterion (SS reduction ≥4 at week 24); annual discontinuation rate of 8%; drug administration cost of £154 which gave an ICER of [redacted]
- As revised base case including the more stringent treatment continuation criterion; annual discontinuation rate of 8%; drug administration cost of £154 which gave an ICER of [redacted] and
- As revised base case but no treatment continuation rule at week 24 which gave an ICER of [redacted]

The PSA results largely confirmed the deterministic analyses and showed that at a willingness to pay of £30,000 per QALY gained, there was a [redacted] probability that belimumab is cost-effective compared with standard care.

GSK Conclusion

GSK requested the Appraisal Committee to reconsider the guidance outlined in the current FAD taking into account the revised assessment of cost-effectiveness including the updated PAS.

Evidence Review Group Commentary

This response will provide a brief outline indicating whether the combination of changes which include:

- The revised PAS
- The discontinuation rate of 13%
- The IV administration cost of £154
- The dropping of the 6 year discontinuation rule

result in the stated revised cost effectiveness estimate of the manufacturer. We will also note whether the manufacturer has addressed any of the other concerns raised around the model structure and possible bias within its implementation, either within the base case or within sensitivity analyses around the revised analysis.

Methods

We read the revised post appeal document, spreadsheet and appendices and compared these with the original submission and with the revised submission. We undertook a thorough cross check of all model input changes and results. We

- revised the inputs of the GSK post-appeal model to reflect those of original submission submitted in April 2011[3] and re-ran the model confirming that the model corresponded with that of the original submission
- re-ran the revised model

Results

1. Changes to previous base case inputs

   We can confirm that the changes made in the GSK post-appeal submission were as follows

   - An annual discontinuation rate of 13% as per the extension trial.
   - An administration cost of £154 rather than the original £126 as per the ERG report.
   - A PAS, such that the list price of £0.9525 per mg which results in vial costs of £114 for the 120mg vial and £381 for the 400mg vial has been changed to a discount of [redacted]%, resulting in vial costs £[redacted] for the 120mg vial and £[redacted] for the 400 mg vial. This compares to the original PAS discount of [redacted]% which resulted in vial costs of £[redacted] for the 120mg vial and £[redacted] for the 400mg vial.

2. Cross-checks GSK post-appeal model outputs

   The GSK post-appeal model cross-checks with the originally submitted model. The results of the GSK post-appeal revised base case also cross check with those reported in the GSK post-

appeal submission: "*The incremental costs for belimumab treated patients compared to SoC alone are £[redacted] with 0.9 added life years, or 0.7 added QALYs, discounted at 3.5%, resulting in a base case ICER of £[redacted] per QALY gained*".

The results reported in table 1 of the GSK post-appeal submission for scenarios 1 and 3 also cross check with the model. But those of scenario 2 do not, and there appear to be some typos given that the incremental survival and incremental QALYs for scenario 1 and scenario 2 are reported to be the same. The ERG run of the model for scenario 2 results in incremental costs for belimumab treated patients compared to SoC alone of £[redacted], with 0.81 added life years, or 0.61 added QALYs, discounted at 3.5%, resulting in an ICER of £[redacted] per QALY gained.

The ERG have the following additional comments as a results of investigating the revised model in detail:

3. Post year 5 discontinuation rate

   Note that the ERG has not attempted to cross check the model implementation of the post year 5 discontinuation rate. Although the model output has been cross checked it has not been possible to separate discontinuations from deaths. Despite this, the proportion surviving and remaining on treatment is broadly aligned with the initial response rate and 13.0% annual discontinuation rate thereafter.

4. Revised first year discontinuation rate

   Table 6.40 of the original submission [4] outlined a discontinuation rate for responders who achieved a 4-point reduction in SS score in the target population of 4.4% for months 6 to 12 and 8.0% annually thereafter. The GSK post-appeal model[3] has revised the first year discontinuation rate to 7.2% and 13.0% thereafter. This arises by changing the original trial estimate of the 6 month to 18 month rate of remaining on belimumab treatment for the target population of 0.919897 to 0.870820. The 0.870820 and resulting 7.2% 6 month rate are consistent with the assumed 13.0% annual discontinuation rate, as per table A1.2 of the GSK post-appeal submission.

   This is in turn consistent with table 3 of the GSK response to the ACD which gave data on the discontinuations from the Phase II Extension study LBSL99 [4] from the start of the second year through to the end of the sixth year. Whether it might have been more appropriate to apply the original rate of 4.4% for months 6 to 12 is a moot point. In itself this seems unlikely to have a major impact upon results.

5. Sensitivity of the ICER to the time horizon of the model

Note that the anticipated gain in undiscounted survival is 2.31 life years. Given the extrapolation involved, the sensitivity of the ICER to the time horizon of the model can also be presented. (See Figure 1)

[redacted]

6. Pulmonary damage

The GSK post appeal submission points to the costs of pulmonary damage as a significant driver of the ICER as evidenced by the tornado diagrams. The reduction in pulmonary damage saves the belimumab arm ~14% of the cost difference. (Total belimumab cost £[redacted]; SoC cost £[redacted]; diff = £[redacted]; if pulmonary damage cost the same in each arm the difference would be £[redacted] and the ICER would then increase to £[redacted]).

The model used the cost of bosentan for the treatment of pulmonary damage (pulmonary hypertension). However we consider that this is likely to be more expensive than usual current UK treatments of SLE pulmonary damage e.g. Sildenafil whose annual costs is ~£4,500 (half of that used in this current submission). Given that all other inputs are unchanged, a higher estimated cost for pulmonary damage treatment would result in a higher cost for supportive care, estimated greater savings from belimumab treatment and a lower ICER. In addition pulmonary damage is estimated to occur at high frequency. Halving the cost of pulmonary damage would worsen the base case ICER by around £[redacted] per QALY.

There may also be some concerns about the sensitivity analyses within the tornado diagrams. For the pulmonary damage coefficient on log age of the natural history model, the lower and upper bound values of 0.59 and 1.92 both worsen the ICER to £[redacted] per QALY and

£[redacted] per QALY respectively. For information, note that the central estimate and the standard deviation of the central estimate for this coefficient are 1.2316 (0.3358[1]).

This does not imply that the central value of 1.23 is the most beneficial for the ICER, but the model is non-linear in this variable as shown below. The ICER falls reasonably steadily to its lowest point at a coefficient of about 1.50 after which it starts to rise quite steeply. There is no immediately obvious explanation for this, but it should be borne in mind that:

- the model is complex with a number of feed-back loops;
- pulmonary damage affects costs, survival and QALYs; and,
- the patient characteristics are sampled at baseline.

[redacted]

[redacted]

7. Relative costs of rituximab

Although all parties are agreed that since this is an STA, and since there are not currently adequate research data which allow for either a direct or an indirect comparison between belimumab and rituximab, the relative costs of rituximab compared to the proposed costs of belimumab are still mentioned in this post appeal submission

At the original AC meeting, the clinicians expressed the opinion that rituximab use in clinical practice would be unlikely to reach four doses annually. The manufacturer states that the relevant dosage should be that which would be expected should rituximab licensing be based

[1] Based upon taking the standard deviation of the sample of values for this coefficient for the PSA as found in cells OZ11:OZ1010 of the *PSA_Inputs* worksheet.

on the EXPLORER study (i.e. four 1000mg doses per year).[5] However, this is a hypothetical scenario and in the ERG's opinion is less relevant than using current UK clinical practice. Indeed in a recent systematic review Lan et al 2012 [6] found 2RCTs (EXPLORER and LUNAR)[8] and 19 observational studies. Of these EXPLORER used the highest dose regime. In LUNAR the dose was 3000 mg. In the observational studies the dose was commonly 2400 mg (average woman 1.6 m^2, dose 375 mg/m^2, given 4 times). Only one observational study reached the EXPLORER dose (for two of 10 patients, the other eight received 2400 mg or 2000 mg).

[redacted]

8. Continuing concerns of the ERG

Note that the model structure has not been revised to address many of the concerns of the ERG as outlined in the previous ERG report [9] but see quote below from our previous report – since many are still pertinent to the current assessment.

"There are a number of ERG concerns with the modelling of the submission. If these concerns are justified, addressing them appears more likely to worsen the estimate of the cost effectiveness of belimumab than improve it.

i) Assuming that belimumab week 24 non-responders will experience the average SS score within the SoC (standard care) arm seems likely to have over-estimated the average impact upon SS scores of belimumab. Within the belimumab arm week 24 non-responders were found to have a marginally worse SS score than the standard care week 24 non-responders and despite ongoing treatment this continued until week 32. Since the SS scores drive the analysis, any error in their calculation is likely to have a major impact on results.

ii) Not taking into account a patient's history may further exaggerate the impact upon the AMS of belimumab compared to SoC.

iii) The calculation of the cumulative average steroid dose may be subject to a bias similar to that of the calculation of the AMS.

iv) Maintaining the net gain in SS score for a belimumab week 24 responder compared to the parallel patient in the SoC arm, while the belimumab week 24 responder remains on treatment may be optimistic.

v) The analysis of the observational cost data on a six monthly basis in order to relate it to the maximum SS score during that period then doubling it to arrive at the annual relationship appears peculiar given that the observational cost data was collected over a year. It may also lead to bias.

vi) The separate estimation of a cost per organ involved may have double counted costs estimated within the SS score cost function to some degree."

vii) Reported steroid sparing results are still obtained only from a non-peer reviewed abstract (Petri et al., 2011). [5] Although these results are of interest, the study lacks a control group. In addition the SoC arm from the trials shows a similar trajectory of steroid sparing which suggests that the steroid sparing effect found may not be attributable to belimumab treatment.

Summary of ERG analysis

The total GSK CHANGES result in a new ICER of £[redacted]/QALY). This includes the revised PAS, the discontinuation rate of 13%, and IV administration costs of £154. We can confirm that no structural changes have been made to the originally submitted model and that only inputs have been changed. Likewise we can confirm that all the reported ICERs are correct, except for scenario 2 (where an error in the calculations resulted in a value of £[redacted]/QALY rather than the actual value which should be £[redacted]/QALY.) We remain concerned about effects on the ICERs of estimations of pulmonary damage costs, overestimation of rituximab costs and would point out that the GSK submission has not taken account of many of our previous concerns.

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Evidence Review Group Report commissioned by the National Health Service Research & Development Programme on behalf of the National Institute for Health and Clinical Evidence

Title: Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus: further response to GSK Post-Appeal Submission

REPORT Version 2

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Contributions of authors:
Connock, Sutcliffe, Clarke – critical appraisal of clinical effectiveness. Cummins– critical appraisal of economic modelling. All authors – writing the report.

Evidence Review Group Further Report in response to GSK Post-Appeal Submission for the Single Technology Appraisal (STA) of Belimumab in the Treatment of Active Autoantibody-Positive Systemic Lupus Erythematosus (SLE) 26th October 2012

Introduction

In a pre-meeting briefing telephone conference, Warwick Evidence were requested by NICE to supply "the best estimate of likely discontinuation rates' for belimumab, taking into account the Post Appeal submission form Glaxo Smith Kline, previous submissions and recent conference abstracts, presentations and reports of continuation studies of belimumab.

Analysis of previously reported discontinuation rates

Discontinuation rates for belimumab

The GSK response of 21 October 2011 to the ACD Table 3 (page 12) [1] implied the following discontinuation rates from the Phase II Extension study LBSL99.

Table 1: Discontinuation data and equivalent ERG constant rate annual discontinuation estimates based on GSK response of 21 October 2011[1] to the ACD Table 3

	Phase II Extension study LBSL99			Constant annual rate	
Year	N start	Discontinuation	N end	N start	N end
2	339	19.2%	274	339*	294*
3	274	9.5%	248	294*	255*
4	248	10.1%	223	255*	222*
5	223	6.7%	208	222*	192*
6	208	19.7%	*167**	192*	*167**

*These figures estimated by the ERG.

The simple average of the annual discontinuation rates gave the manufacturer an estimate of 13.0%. By coincidence, the total discontinuation proportion of 49.3% (by end of year 6) yields an estimate of 13.2% constant rate annual discontinuation. A least squares fit to the LBSL 99 "observed" proportion retained on belimumab generates an almost identical curve to that derived using the manufacturer's 13% discontinuation model (Figure 1). This reconfirms that, given these annual discontinuation rates, the 13% annual rate applied by the manufacturer was a reasonable constant rate fit to the data as described.

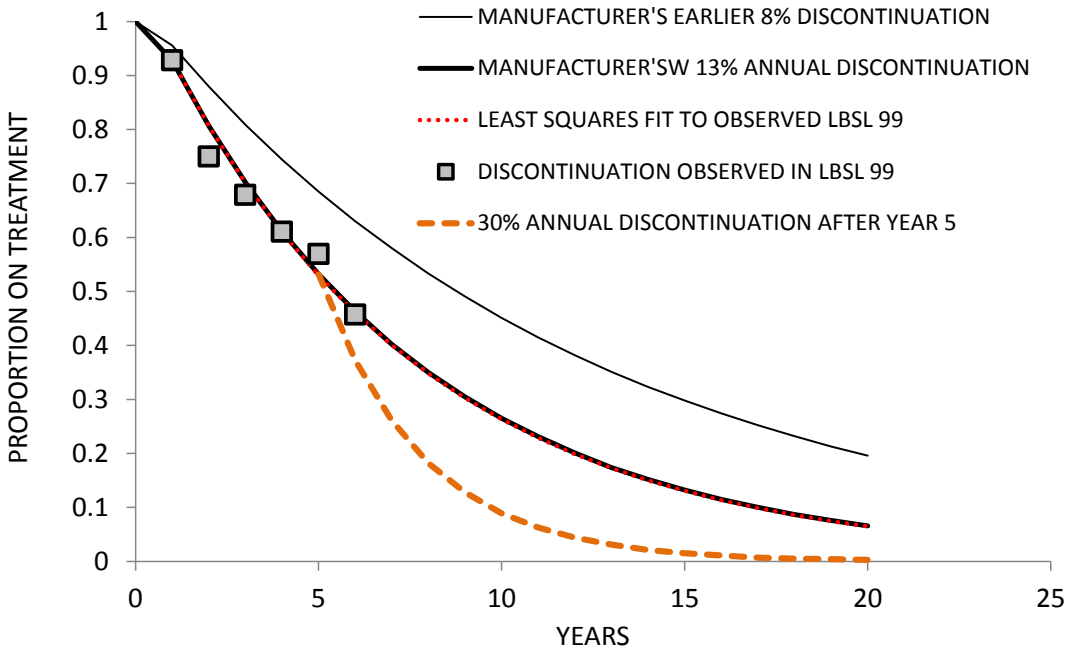

Figure 1 Proportion remaining on Belimumab treatment

The 8%, 13% and 30% curves are taken from data in the manufacturer's Post Appeal Submission Table A1.3[2] *; the observed discontinuation (squares) is derived by applying the annual discontinuation rates for years 2 to 6 from the LBSL 99 study extension starting from manufacturer's year one value of 0.928 for patients on treatment (Table* A1.3 *); the least squares fit used the year one to year 6 observed data (the annual discontinuation rate was 13.07%).*

The recently published abstract and presentation by Merrill (2012)[3 4] provide updated details on the patient cross over and numbers within the LBSL 99 extension trial. At week 56 placebo patients were switched to belimumab 10mg/kg and belimumab patients continued to receive their dose or switched to belimumab 10mg/kg. From week 80 all patients who entered a "*continuation study*" received belimumab 10mg/kg. Note that the 80 week point gives previous placebo patients 24 weeks treatment with belimumab 10mg/kg which corresponds quite nicely with the 24 weeks of the model prior to the assessment of response status. We do not know whether a formal responder analysis and continuation rule was applied within the extension trial, but this 24 week period may give sufficient time to assess the response of those crossing over from placebo and to assess whether to continue or discontinue belimumab.

The ERG sought to use the information provided by Merrill [3 4] to assess the discontinuation rate in the light of the latest information. Merrill gives very similar data to that of the GSK response of 21 October 2011 to the ACD with the exception of what happens from the 6th year onwards (See Table 2 below). Notice that Merrill Abstract provides "patient years" data and that this is numerically 167 for year seven.

Table 2: Discontinuation data: GSK response of 21 October 2011, Merrill abstract and presentation

	GSK response of 21 October 2011[1]			Discontinuation data from Merrill Abstract [3]					Merrill presen-tation[4]
Year	N start	Discontinuation	N end	*Pt years*	Year label ‡	N ‡‡	Discontinuation rate‡‡‡	N end	N end
2	339	19.2%	274	*299*	2	339	19.2%	274	
3	274	9.5%	248	*258*	3	274	9.5%	248	
4	248	10.1%	223	*234*	4	248	10.1%	223	
5	223	6.7%	208	*216*	5	223	6.7%	208	
6	208	19.7%	***167***	*198*	6	208		190	
7	***167***			***167***	7	190		**190¥**	**177¥¥**

Table 2 Notes

1. ‡ Taken from Table in Abstract. [note the N for year 1(not shown) is 336 (i.e. < N for year 2) may correspond with 75% of the 449 patients enrolled, randomised to belimumab 1mg/kg, 4mg/kg or 10mg/kg or placebo].
2. ‡‡ It is unclear if N refers to start of year or end of year; however since the numbers for year labels 1 to 6 correspond to N start in the last submission it is assumed they are N start; in which case 190 is implied to be N start for year 7 in the Table. N end for year 7 is implied in text statement in presentation .
3. ‡‡‡ ERG calculated these percentages from the difference in numbers of patients in each successive year
4. ¥ Stated in abstract as "At end of 7 y, 190 patients remained"
5. ¥¥ Stated as " 177 remained on treatment after 7 years of therapy" and as "177 (39.4%) remain in trial as of the 7 year assessment" 177 is 39.4% of the enrolled patients (449) of the LBSL 99 trial.

Although the table within the abstract[3] gives patient numbers that largely correspond with the patient numbers of the GSK response of 21 October 2011[1] to the ACD there are some evident discrepancies between the Merrill abstract and presentation, and between these and the earlier submission. (see notes to Table 2). The presentation[4] states that 177 patients remained in treatment at the end of 7 years, whereas the abstract text[3] states that 190 patients remained in treatment at the end of 7 years. However the abstract table is consistent with there being 190 patients at the *start* of year 7. The earlier submission[1] provided the number in treatment at the end of year six and start of year 7 as 167. The 167 is incompatible with both the presentation and abstract and requires a high discontinuation rate for year 6 (19.7%). It appears likely that the 167 patients remaining at the end of Year 6 in the GSK response of 21 October 2011 is an error in which patient-years as opposed to actual number of patients was used by mistake. (Figures highlighted in table 2). Warwick Evidence believe these discrepancies are easily resolved if: a] the 167 in the earlier submission is considered an error, b] if patient numbers at the start of year 7 are taken to be is 190, and c] numbers at the end of year seven are 177.

Using these alternative figures we generate discontinuation rates of 8.65% for year six and 6.84% for year 7. The simple average annual discontinuation rate becomes 10.16% and is shown in Figure 2 with the *new* observed proportion discontinuing. A least squares exponential fit provides an annual discontinuation rate of 11.66%. This is similar to the GSK response of 21 October 2011[1] if the 19.7% rate for year six is considered an error, in which case the corrected average discontinuation rate becomes 11.4%.

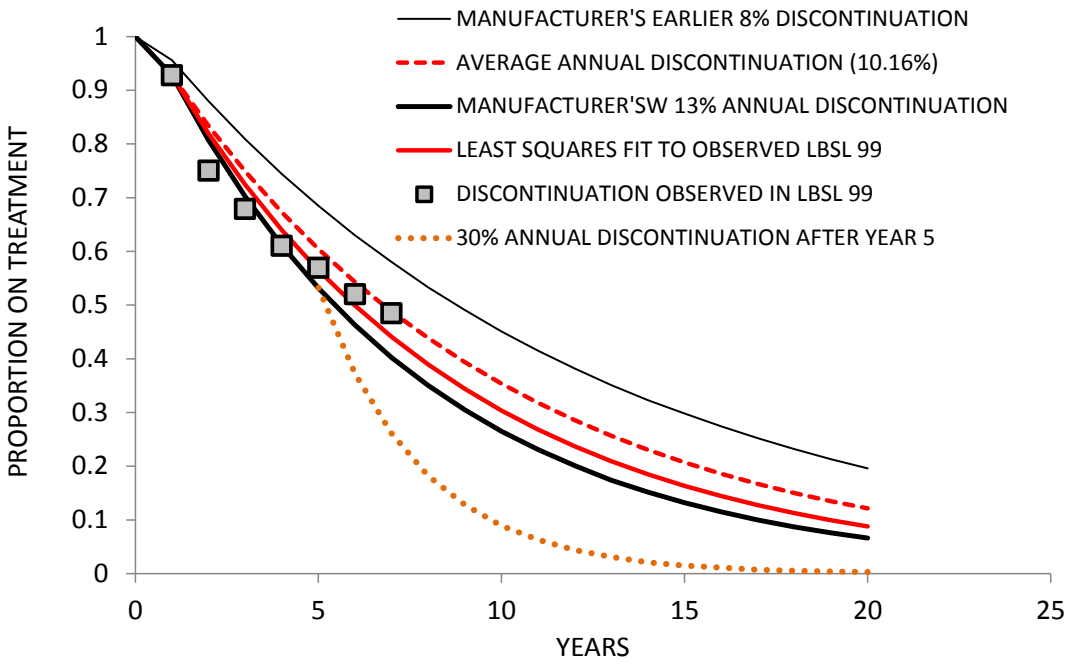

Figure 2 Proportion remaining on Belimumab treatment (ERG correction)

The 8%, 13% and 30% curves are taken from data in the manufacturer's submission Table A1.3[2] *; the observed discontinuation (squares) is derived by applying ERG corrected annual discontinuation rates for years 2 to 7 from the LBSL 99 study extension starting from manufacturer's year one value of 0.928 for patients on treatment (Table* A1.3 *); the least squares fit used the year one to year 7 observed data (the annual discontinuation rate was 11.66%).*

A further alternative explanation is that the 190 patients remaining in treatment at end of year 6 or end of year seven in the Merrill abstract [3] may represent the number remaining of those who entered the "continuation" study (given as 296 in both the Presentation and in the Abstract). If 190 of 296 remain in treatment at end of years six or year seven the constant annual discontinuation rate reduces to 7.8% or 6.6% respectively.

For the following sensitivity analyses the initial six month discontinuation among responders is drawn from the original manufacturer model[2]:

- 4.4% for both the no continuation rule and the SS≥4 continuation rule
- 6.7% for the SS≥6 continuation rule

Table 3: Sensitivity analyses around continuation rules and discontinuation rates: ICERs

	Discontinuation rate									
Continuation rule	5.0%	6.6%	7.0%	7.8%	9.0%	11.0%	11.6%	11.9%	13.2%	15.0%
None	[redacted]									
SS4	[redacted]									
SS6	[redacted]									

Conclusions

There is variable reporting of numbers of patients remaining in treatment at the beginning and end of years 6 and 7 in the different reports of the same data source which are available to us. We surmise that there may have been transcription errors e.g. of patient years at risk rather than patients and also potentially errors in adequately apportioning continuation and discontinuation for the different groups of patients entering the continuation trial from the placebo, 1mg/kg, 4mg/kg and 10mg/kg arms. Given these problems it is difficult to establish a reliable continuation/discontinuation rate. We consider that the value of 13.0% discontinuation given by GSK in their post appeal submission is likely to be high and that the most likely rate is lower than this. In sensitivity analysis we have shown how lower discontinuation rates raise the ICER.

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[3] Joan T. Merrill Sustained Disease Improvement and Safety Profile Over 1745 Patient-Year

Experience (7 years) with Belimumab in Systemic Lupus Erythematosus Patients. Abstract#: 2621 ACR: Wednesday, November 14 Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment, IV: Therapeutics. Category: Systemic Lupus Erythematosus - Clinical Aspects and Treatment.

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Belimumab: Including the revised PAS and excluding the revised PAS

The list price for belimumab was given as £114.30 for 120mg and £381.00 for 400mg. The GSK post appeal submission of the 26 October 2012 included a revised PAS with around a [redacted] discount, resulting in [redacted] for 120mg and [redacted] for 400mg.

Excluding the PAS for the 11.66% discontinuation rate:

- No continuation rule an ICER of £68,986 per QALY
- SS4 continuation rule an ICER of £59,946 per QALY
- SS6 continuation rule an ICER of £52,517 per QALY

Including the PAS for the 11.66% discontinuation rate:

- No continuation rule an ICER of [redacted] per QALY
- SS4 continuation rule an ICER of [redacted] per QALY
- SS6 continuation rule an ICER of [redacted] per QALY

Decision Support Unit Project Specification Form	
Project Number	
Appraisal title	Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus
Synopsis of the technical issue	NICE is currently developing a technology appraisal on belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus. The SPC for belimumab states that the recommended dose regimen is 10 mg/kg on days 0, 14 and 28, and at 4-week intervals thereafter. Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. In the manufacturer submission the belimumab BLISS clinical trials informed the likelihood of response at week 24 and rate of discontinuation thereafter. Patients discontinued treatment after week 24 if they did not have an improvement in SELENA-SLEDAI (SS) score of 4 points or more. Using an SS score of 4 the annual discontinuation rate in those responding to treatment was estimated to be 8% per year. Scenario analyses were presented assuming alternative continuation rules and assuming no continuation rule. These scenario analyses used alternative annual discontinuation rates, again based on the BLISS trial data. Clinical specialists at the Committee meeting considered that a lifetime treatment with belimumab and the durations of treatment predicted in the model were unrealistic. In response to consultation, the manufacturer presented long-term efficacy and safety data for belimumab from an open label, phase II extension study (LBSL99; Petri et al. 2011). An annual discontinuation rate of approximately 13% was observed in this trial. The 13% was subsequently revised by the ERG to be 11.6% based on new availability of 7 year data and what they perceived to be an error in the calculation of the previous 13% figure. In addition, following an appeal, the manufacturer presented a scenario analysis that included a variable annual discontinuation rate of 13% up to year 5 and 30% 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 and that other immunosuppressants for systemic lupus erythematosus, are prescribed only for 2–5 years. The manufacturer stated that belimumab would likely be used in the same way as other immunosuppressants, that is, patients will discontinue belimumab as early as possible once sustained disease control was achieved. The economic model is sensitive to the rate of annual discontinuation assumed, with higher rates of annual discontinuation reducing the estimates of the ICER. The DSU is asked to explore the range of possible rates of annual discontinuation, taking into consideration those that have been used in the analyses submitted for the appraisal, and to explore whether there are alternative evidence sources available that could inform the value used in the economic model.
Question(s) to be answered by DSU	Taking into account the marketing authorisation describing continuous use: • What is the expected discontinuation rate of belimumab in people whose active autoantibody-positive systemic lupus erythematosus has responded to treatment? ○ Would discontinuation rates differ depending whether an SS score improvement of 4 or 6 was required at week 24? If so, how may those discontinuation rates differ? • Is there any further supporting evidence about belimumab treatment discontinuation that has not already been provided to NICE, for example from registries and similar datasets? • In the absence of any further evidence regarding discontinuation rates for belimumab, is there any other evidence for use of immunosuppressants in SLE or other conditions, that can be drawn on to inform estimates of the rate of annual discontinuation for belimumab?

	• What are the estimated ICERs (including appropriate scenario/sensitivity analyses) for belimumab compared with standard care when incorporating any alternative values identified for the discontinuation rate?
How will the DSU address these questions	An elicitation exercise from clinical specialists in SLE, to obtain further information regarding the expected annual discontinuation rate of belimumab in patients whose disease responds to treatment at 24 weeks using either the SS score improvement of 4 or 6 points. Review of the existing evidence sources and estimates of annual rate of discontinuation submitted as part of the appraisal. Identification and review of any supporting research available that could inform estimates of the annual rate belimumab treatment discontinuation. For example, any register data (or similar datasets) where belimumab discontinuation may be calculable, or observational studies involving belimumab or, in lieu of direct belimumab evidence, evidence of discontinuation rates for other immunosuppressants in SLE or related diseases (for SLE such information may be available from SLICC at Central Manchester University Hospitals, part of the SLE International Collaborating Clinics programme which was set up as a research network in 1991, linking 32 investigators from 27 countries worldwide). Conducting further economic analyses, including appropriate scenario/sensitivity analyses, using the manufacturer's model to estimate ICERs for belimumab compared with standard care incorporating any discontinuation rates identified, if different to what has already been considered during the appraisal so far.
How does this relate to the ERG?	Not applicable.
Exact analyses required	1) Collation and summary of elicitation responses from clinical specialists in SLE regarding annual discontinuation rates for belimumab in people whose SLE has

	responded to treatment at 24 weeks with an SS score improvement of 4 or 6. 2) Searches to identify any other available research, registries and similar datasets, with collation and summary of available data sources regarding belimumab treatment discontinuation, or discontinuation of treatment of immunosuppressants that would be used in the way belimumab is expected to be used for SLE. 3) Consideration of 1 and 2 in the context of the submitted rates of annual discontinuation.

BELIMUMAB (BENLYSTA®) FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

ELICITING ESTIMATES OF LONG-TERM TREATMENT DISCONTINUATION RATES

REPORT BY THE DECISION SUPPORT UNIT

10 June 2013

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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 Clinical 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

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1. INTRODUCTION

1.1 BACKGROUND TO THE APPRAISAL

NICE is currently developing a technology appraisal on belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (SLE). The Summary of Product Characteristics (SmPC) for belimumab states that the recommended dose regimen is 10 mg/kg on days 0, 14 and 28, and at 4-week intervals thereafter.[1] Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after the first 6 months of treatment.

In the manufacturer's submission, the belimumab BLISS clinical trials[2] informed the likelihood of response at Week 24 and the rate of discontinuation thereafter. In the manufacturer's model, patients discontinued treatment after Week 24 if they did not have an improvement in SELENA-SLEDAI (SS) score of 4 points or more. Using an SS score of ≥4, the annual discontinuation rate in those responding to treatment was estimated to be 8% per year, based on *post hoc* subgroup estimates from the BLISS trials. Scenario analyses were presented by the manufacturer assuming alternative discontinuation rules and assuming no discontinuation rule. These scenario analyses used alternative annual discontinuation rates, also based on the BLISS trial data.[2] However, clinical specialists at the NICE Appraisal Committee meeting considered that a lifetime treatment with belimumab and the durations of treatment predicted in the model were unrealistic.

In response to consultation, the manufacturer presented long-term efficacy and safety data for belimumab from an open-label, Phase II extension study (LBSL02/99 - Merrill *et al*. 2011; Merrill *et al*. 2012[3;4]). In their response, the manufacturer reported that an annual discontinuation rate of approximately 13% was observed in this study (based on a conference presentation only). This estimate of 13% was subsequently revised by the ERG to be 11.6% based on new availability of 7-year data and what they perceived to be an error in the calculation of the previous 13% estimate. In October 2012, 4-year data from this study were published in full;[4] within this paper, the authors indicated that the overall rate of discontinuation during the first year of belimumab exposure was 16% and the rate decreased during years 2–4 of the long-term continuation study (range 9–14%). The two most common reasons for discontinuation in year 1 (adverse events and patient request) were reported to decrease over time.[4] This study does not however relate specifically to the *post hoc* subgroup reflected within the manufacturer's model.

In addition, following an appeal, the manufacturer presented a scenario analysis that included a variable annual discontinuation rate of 13% up to Year 5 and 30% each year thereafter. 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 and that other immunosuppressants for SLE are prescribed only for between 2 and 5 years. The manufacturer stated that belimumab would likely be used in the same way as other immunosuppressants, that is, patients will discontinue belimumab as early as possible once sustained disease control was achieved. This does not however reflect the licensed indication for belimumab, or the conduct of the trial. It should be noted that the manufacturer has thus changed their assumptions to handling belimumab discontinuation in the model twice since their original submission.

The manufacturer's economic model is sensitive to the rate of annual discontinuation assumed, whereby higher rates of annual discontinuation lead to more favourable estimates of cost-effectiveness for belimumab. The NICE Decision Support Unit (DSU) was asked by NICE to explore the range of possible rates of annual discontinuation, taking into consideration those that have been used in the analyses submitted for the appraisal, and to explore whether there are alternative evidence sources available that could inform the value(s) used in the economic model.

This report presents the methods and findings of additional work undertaken by the DSU to elicit estimates of natural discontinuation rates for SLE patients treated with belimumab, with the intention of reducing, or better expressing, the uncertainty surrounding this quantity.

1.2 QUESTIONS TO BE ADDRESSED BY THE DSU

Taking into account the marketing authorisation describing the continuous use of belimumab, the DSU was asked to address the following questions:

1. What is the expected discontinuation rate of belimumab in people whose active autoantibody-positive systemic lupus erythematosus has responded to treatment?
2. Would discontinuation rates differ depending whether an SS score improvement of 4 or 6 was required at Week 24? If so, how may those discontinuation rates differ?
3. Is there any further supporting evidence about belimumab treatment discontinuation that has not already been provided to NICE, for example from registries and similar datasets?
4. In the absence of any further evidence regarding discontinuation rates for belimumab, is there any other evidence for use of immunosuppressants in SLE or other conditions, that can be drawn on to inform estimates of the rate of annual discontinuation for belimumab?
5. What are the estimated ICERs (including appropriate scenario/sensitivity analyses) for belimumab compared with standard care when incorporating any alternative values identified for the discontinuation rate?

1.3 CONSTRAINTS IMPOSED BY THE MANUFACTURER'S MODEL STRUCTURE

It should be noted that there are two versions of the GSK health economic model:

- "Model 1" - the original version of the model submitted at the beginning of the NICE appraisal process, and;
- "Model 2" a modified version of the model submitted post-appeal.

Model 1 characterises the natural discontinuation parameter as a single probability which is applied from 6-months until the end of the model time horizon. Model 2 is more flexible as it includes the possibility of variable rates for individual years since starting treatment. This represents a different structural assumption between the models - only Model 2 is structurally capable of handling time-dependent discontinuation probabilities.

2. METHODS

2.1 METHODS FOR THE IDENTIFICATION OF EXISTING EMPIRICAL RESEARCH ON LONG-TERM DISCONTINUATION RATES FOR BELIMUMAB

The DSU contacted two Rheumatoid Arthritis (RA) registries to enquire whether they held additional relevant data concerning long-term belimumab discontinuation rates for patients with SLE. These registries were the European SLE International Collaborating Clinics Programme (Manchester contingent – see http://www.cmft.nhs.uk/) and the US National Databank on Rheumatic Diseases (http://www.arthritis-research.org/).

The lead for the UK contingent of the SLICC, Professor Ian Bruce, stated that the registry did not hold relevant data on patient discontinuation for belimumab since the drug had not been approved by NICE. Consequently, uptake has been on an exceptional basis only. He also noted that registry itself is still in the early phases of development. The US registry also informed the DSU that they have not had any patients on belimumab for any substantive period of time. Following advice received from Professor Bruce, Dr Anca Askanase at Bellevue Hospital, New York, was contacted as she has undertaken some work on belimumab use amongst US physicians. However, Dr Askanase's study does not yet contain long-term follow-up data beyond 6 months.

Other published empirical studies relating to belimumab discontinuation were *not* sought as (i) the DSU felt that all relevant published evidence would have been identified during the appraisal process and (ii) initial timescales for the delivery of the report precluded a full systematic search and review process.

Given the absence of other relevant data on belimumab discontinuation, the DSU sought to elicit estimates using expert clinical opinion from UK experts, as detailed below.

2.2 METHODOLOGICAL ISSUES SURROUNDING THE ELICITATION OF DISCONTINUATION RATES

Initially, it had been envisaged that formal face-to-face elicitation would be undertaken, facilitated by expert statisticians within the DSU using the Sheffield Elicitation Framework (SHELF) (http://www.tonyohagan.co.uk/shelf/). There are a number of different ways of designing such exercises within a formal elicitation framework. Whilst planning this elicitation exercise, the DSU considered the Roulette Method[5;6] to be the most applicable to this particular decision problem. Using the Roulette method, the expert provides probabilities of the uncertain quantity of interest (denoted θ – in this case, this quantity relates to the proportion of patients who discontinue belimumab treatment within a particular time interval). The experts' subjective belief that θ lies within particular probability intervals is elicited by specifying intervals as 'bins' and by allocating `gaming chips' to that bin. Thus, the expert distributes n chips amongst m bins, with the proportion of chips allocated to a particular bin representing her subjective belief about the probability of θ. m is fixed within the structure of the exercise, whilst n is chosen by the respondent. This method therefore enables the respondent to construct a graphical representation of their prior beliefs regarding uncertain quantity θ.

It should be noted that in this instance we are not solely interested in eliciting a single distribution for discontinuation rate θ; whilst the original submitted manufacturer's model (Model 1) assumed a fixed discontinuation rate (dependent on initial SS response), the model submitted post-appeal (Model 2) included the facility for this probability to be time-dependent. Therefore, there is uncertainty not only around the value of θ, but also in how other covariates influence this discontinuation rate. The key issues in structuring the elicitation exercise relate to:

(i) The level of detail to which the discontinuation parameter θ is specified (elicitation of a single constant discontinuation parameter or elicitation of multiple discontinuation parameters by cause e.g. lack of efficacy, adverse events, non-compliance, other etc.);
(ii) The nature of the discontinuation parameter(s) defined in (i) over time;
(iii) The conditionality of natural discontinuation specified in (i) and (ii) according to initial response as measured by SELENA-SLEDAI score (SS≥4 or SS≥6);
(iv) The design of more qualitative information collection to explain and justify the quantitative values elicited.

The DSU sought advice on these structural issues surrounding the elicitation exercise from Dr Mohammed Akil, Consultant Rheumatologist, Royal Hallamshire Hospital, Sheffield. Dr Akil advised

that specific causes of discontinuation may be important and that it is reasonable to believe that these may vary over time. The questions asked by NICE (see Section 1.2) also required the elicitation of separate estimates according to initial SS score. As a consequence, this introduces considerable complexity to the elicitation exercise as a number of alternative estimates of discontinuation parameter θ are required.

2.3 PRACTICAL ISSUES SURROUNDING THE ELICITATION OF DISCONTINUATION RATES

Ideally, elicitation exercises should be undertaken in a face-to-face setting whereby the facilitator help the respondent fully express the uncertainty surrounding their beliefs, as well as ensuring that the respondent is fully aware of what they are being asked to do. Furthermore, the use of a graphical interface means that the respondent can immediately see their beliefs expressed as a crudely stated probability distribution for uncertain quantity θ. This has further benefits in ensuring that the respondent's expressed beliefs are stated as they intended.

However, these benefits also carry several costs – in particular, such exercises are time-consuming, requiring an initial training exercise to help respondents think about uncertainty and for them to familiarise themselves with the structure of the exercise, and typically around 1-day of elicitation time per expert (overall time requirements are dependent on the number of estimates of θ to be elicited). Given the need to estimate θ at different timepoints as well as for separate SS subgroups, we concluded that such an exercise would be very unlikely to be feasible in practice across more than 5-6 clinical experts. As an alternative, we also considered the feasibility of undertaking the elicitation exercise via telephone interview individually or within small groups, however this would still have considerable time implications for each participating clinician. The DSU takes the view that it is unlikely that many clinicians would have consented to participate in such an exercise for practical reasons alone.

For reasons of pragmatism, and to allow us to reflect the views of a wider pool of SLE experts, we decided that a survey-based approach would be quicker and more feasible for participants and would produce more generalisable information for the NICE Appraisal Committee.

2.4 SURVEY METHODS

Forty one lupus experts were invited to complete the survey questionnaire. Clinical experts were identified through their membership of either the British Isles Lupus Assessment Group (BILAG, contact details provided by Dr Akil) and/or the St Thomas' Lupus Trust (http://www.lupus.org.uk/contact/find-a-specialist). All experts were expected to have experience treating patients with SLE, but not necessarily to have experience treating SLE patients with

belimumab. Experts were sent an electronic version of the questionnaire via an email from NICE together with a cover letter explaining the anticipated role of the questionnaire in informing the technology appraisal. A reminder email was later sent with the intention of increasing the number of survey respondents.

Within the questionnaire, potential respondents were asked to provide information on the following:

- Personal information (name, role, whether they have treated lupus patients, whether they have treated patients with belimumab)
- The mean proportion of patients expected to discontinue belimumab within a given 12-month time interval
- The upper and lower 95% credible intervals for the discontinuation proportions
- The number of hypothetical patients upon which each discontinuation proportion is based as a further measure of their uncertainty surrounding their beliefs (note – this information was elicited separately to the credibility interval around the mean discontinuation rate)
- Whether the respondent believes the discontinuation probability to be time-dependent.

Separate estimates were requested for patients with an initial SS score ≥4 and initial SS score ≥6. The final survey questionnaire sent to invited participants is presented in Appendix 1. All responses were anonymised within the analysis.

3. SURVEY RESULTS

3.1 RESPONSE RATE

Of the 41 clinicians invited to complete the survey questionnaire, 14 (34.1%) clinicians responded. However, of these only 3 clinicians (7.3%) completed the questionnaire, either in part or in full.

3.2 REASONS FOR NON-COMPLETION

The reasons given for non-completion of the questionnaire are presented in Table 1. The responses provided by the non-completers suggest that the principal reason for non-completion was that belimumab is not approved in the UK, hence they found it difficult, if not impossible, to provide credible estimates of long-term discontinuation rates with any degree of uncertainty.

Table 1: Reasons given for non-completion of the questionnaire

Resp. no.	Reason for non-completion
R1	I never received your original e-mail but did receive a lot of e-mails from colleagues in the BILAG group who had received it. The general consensus appeared to be that due to the very small number of patients with lupus treated with belimumab so far in the UK it was difficult to give meaningful answers to these questions and I think you will have received letters from several people explaining this.
R2	As you will be aware the situation in the UK is that the drug has been restricted quite significantly because while it has a European licence it has got no current NICE guidance to support its use, therefore we have had a very limited experience of using the drug. This is also compounded by the fact that the UK did not have a large number of centres involved in the actual clinical trial programme. The scenarios therefore posed within your questionnaire are therefore too speculative for me to actually put realistic numbers on particularly given the fact that there is likely to be a major decision making process around these figures. My own estimates would be based only on the literature and not from personal experience.
R3	... I could not answer the questionnaire as I have only had one patient on belimumab. I do not have enough experience of this drug to make reasonable estimates. For what it is worth my patient had failed all other medications before and did very well with this drug over first 12 months, and managed to reduce steroids significantly for her from 20mg to 10mg daily.
R4	I am very sorry to say that I am not able to answer your survey with any certainty and indeed this might reasonably be viewed as unanswerable with any degree or range of certainty given the lack of experience which anyone currently has in the UK in the use of this agent, which is likely to cause problems with the validity of any responses.
R5	Many thanks for the questionnaire. I fear that you are going to find it very difficult to get information from this. Most rheumatologists have experience of 1 or 2 patients on belimumab if any. In general SLE patients have flares of severe life threatening disease that can be controlled over several months. However, there are a group of very severe disease who require continuous therapy for years. Sorry I can't help more.
R6	Thank you very much for asking me to participate in this survey. Unfortunately, despite my interest in the field I have so far not used Belimumab and all that I know about this drug comes from published data from clinical trials. I did not participate in these trials and therefore my experience with this drug is nil. Therefore, I think I will not be able to answer the questions raised in your survey. Sorry that I am not able to help on this occasion.
R7	I'm sorry to say that I am unable to answer the survey questionnaire sent to me from NICE regarding the discontinuation of belimumab in the different scenarios posed. I have not used belimumab nor was I involved in the clinical trials and I do not assess my SLE patients using the SELENA-SLEDAI. In any case the change of 4 or 6 is rather arbitrary. Therefore, I am sorry that I am unable to answer the questionnaire sent out by NICE regarding Belimumab.
R8	I received your request to complete the survey questionnaire in relation to the use of Benlysta but I am sorry to have to tell you that I really feel unable to answer it. I would like to explain why. In the past, as new drugs ranging from cyclosporine in the early 1980s to mycophenolate in the late 1990s and, in the last decade to rituximab, have become available, treating a modest number of patients enabled you to get a feel for the period of time necessary to treat, the response rate, the relapse rate etc. I have treated precisely one patient with Benlysta and I simply have no idea how the patients that I might prescribe it for and who, incidentally, are likely to have more than just the skin and joint involvement which Benlysta is approved for, will respond. How could I possibly be expected to know this?? I am also rather flummoxed by your division into SELENA/SLEDAI responses of more than 4 or more than 6. Could I with any degree of accuracy distinguish a patient with a response of 5 SELENA/SLEDAI points compared to one who has a 7 point response? I very seriously doubt it. I think your questions might have made some more sense if you attempted to distinguish patients say of 4 point SELENA/SLEDAI response and one with more than 10. With apologies, I just don't find this questionnaire credible. Finally, I am used to using the BILAG

	system for assessment not the SLEDAI system but this is a relatively minor point.
R9	I see a lot of lupus patients, but I have no experience yet of using Belimumab as other consultants in our dept currently manage these patients
R10	I have not been able to prescribe belimumab so can't help with your expert survey
R11	As you might know the current UK wide experience with belimumab in SLE is very small. We only have one patient in our unit who has been just started on belimumab and I doubt that other lupus units in the UK will have enough numbers to address the points raised in your questionnaire. I have great difficulty in predicting likely discontinuation rates during the period 6 months to 18 months based on imaginary number of patients. I am no statistician but have to raise my concern whether this is a scientifically acceptable way of assessing a drug which has the potential to benefit patients with SLE? I can only assume that approval by the FDA is commensurate with the view that belimumab has something to offer some but not all lupus patients. Can NICE not consider looking at the possibility of allowing the use of belimumab on named patient basis for a defined period of time (18 months) according to a strict protocol and hopefully that will address the issues of efficacy and short term safety in real-life situation. It will also address the issue of drop-outs over the period. Any drug no matter how cheap or expensive will only establish itself in clinical practice when it proves its therapeutic worthiness and no responsible clinician will continue to use a drug that has no therapeutic benefits or is unsafe irrespective of its cost or molecular sophistication. Thanks again for giving us the opportunity to engage with NICE.

3.3 ELICITED ESTIMATES OF DISCONTINUATION

Table 2 presents elicited estimates of discontinuation rates for patients receiving belimumab.

Table 2: Elicited estimates of belimumab discontinuation

Respondent no.	R12	R13	R14
Background information			
Experience in treating lupus patients?	Yes	Yes	Yes
Experience in using belimumab?	Yes	No	Yes
Believed nature of dropout rate over time	Increasing	Increasing	Increasing
Initial response SELENA-SLEDAI 4 (mean proportion, lower CrI, upper CrI), number of patients			
p(discontinue) 6-18 months	**~25%** (NR,NR), 6	**8%** (2%,15%), 50	**15%** (10%,20%), 100
p(discontinue) 18-30 months	**~25%** (NR,NR), 6	**12%** (5%,20%), 25	**20%** (15%,25%), 100
p(discontinue) 30-42 months	**75%** (NR,NR), 6	**15%** (7%,35%), 25	**25%** (20%,30%),50
p(discontinue) 42-54 months	**100%** (NR,NR), NR	**17%** (8%,40%), 20	**30%** (25%,35%), 50
p(discontinue) 54-66 months	**100%** (NR,NR), NR	**20%** (8%,40%), 20	**50%** (45%,55%), 30
p(discontinue) annual >66 months	**100%** (NR,NR), NR	**20%** (10%,45%), 15	**55%** (50%,60%), 50
Initial response SELENA-SLEDAI 6 (mean proportion, lower CrI, upper CrI), number of patients			
p(discontinue) 6-18 months	**~25%** (NR,NR), 6	**8%** (2%,15%), 50	**10%** (5%,15%), 80
p(discontinue) 18-30 months	**~50%** (NR,NR), 6	**12%** (5%,20%), 25	**15%** (10%,20%), 80
p(discontinue) 30-42 months	**75%** (NR,NR), 6	**15%** (7%,35%), 25	**25%** (15%,25%), 20
p(discontinue) 42-54 months	**90%** (NR,NR), NR	**17%** (8%,40%), 20	**25%** (20%,30%), 30
p(discontinue) 54-66 months	**100%** (NR,NR), NR	**20%** (8%,40%), 20	**40%** (35%,45%), 30
p(discontinue) annual >66 months	**100%** (NR,NR), NR	**20%** (10%,45%), 15	**50%** (45%,55%), 30

CrI – credible interval; p(discontinue) – probability of discontinuation

All three participating respondents had experience of treating lupus patients, although only two of these (R12 and R14) had experience in treating patients with belimumab. Two of the three participating respondents (R12 and R14) believed that initial SS response would lead to different long-term discontinuation probabilities; the third respondent (R13) believed that these probabilities of discontinuation would be independent of initial response.

All three participating respondents believed that discontinuation rates would increase over time. Respondent R13 cited disease flares (relapses) and patient tolerability/inconvenience as the main reasons for discontinuation; this respondent also noted that there will be a smaller subgroup with an excellent response in whom all features of disease have gone and there will be patient and physician pressure to discontinue belimumab. Respondent R14 stated that nearly all therapies used in SLE patients are associated with an increased drop-out rate over time. The respondent cited the increased risk of sepsis associated with prolonged immunosuppression, patient preference, pregnancy planning and loss of clinical effect as the main reasons for discontinuation.

The elicited estimates presented in Table 2 indicate a substantial degree of discordance between the three participating respondents. For patients with an initial response of ≥4 SS points, estimates of discontinuation within year 1 range from 8% to 25% with the degree of discordance increasing with each additional 12-month interval. It is also noteworthy that the credible intervals provided by Respondents R13 are particularly wide although these do overlap with the credible intervals from Respondent R14 up to 42 months. One respondent (R12) did not complete these fields of the questionnaire. Overall, this indicates that amongst the responders who completed the questionnaire, there are no strong prior beliefs independent of published data which can help resolve the problem. Whilst based on very few experts' responses, these results indicate considerable uncertainty surrounding their beliefs about the true discontinuation rates. However, given the low completion rate for the questionnaire, limited confidence can be placed on the relative credibility of these estimates over and above those already available in the literature.

4. DISCUSSION

The purpose of this short study was to elicit estimates of natural discontinuation rates for SLE patients treated with belimumab in order to reduce, or better express, the uncertainty surrounding this parameter. Whilst a formal elicitation exercise was originally planned as the means of deriving these subjective judgements, we did not believe this would be feasible for practical reasons. Instead we developed a survey questionnaire to elicit the same type of information. Unfortunately, the completion rate for the questionnaire was very low (3 respondents, 7.3% of the invited sample) and no further model analysis was undertaken by the DSU. Given the reasons for non-completion presented in Table 1, it is reasonable to speculate that those individuals who did not complete the questionnaire would have also refused to consent to participate in the elicitation exercise. The DSU do not believe that the results of this survey have more credibility than other estimates available within the published literature.

In light of the very limited evidence provided by the survey, there appear to be three possible alternative evidence-based options for estimating the long-term discontinuation rate for belimumab:

1. **Draw on evidence of long-term dropouts from other immunosuppressants used to treat SLE or other autoimmune diseases**. The DSU would caution against this type of approach – as noted by within the manufacturer's submission, there has been little therapeutic innovation in treatments for SLE, with no evidence leading to the development of new licensed treatments for several decades. Interpolating discontinuation rates from evidence for other immunosuppressants in SLE, or even across other autoimmune disorders, may not reflect the actual expected rates for belimumab, would inevitably be subject to considerable uncertainty and may conflict with the licensed indication for belimumab.

2. **Use the BLISS trials to inform discontinuation rates.**[2] This was the approach initially adopted by the manufacturer. The most significant problem with this approach is that the BLISS trials were short in duration and the incentives for patients continuing/discontinuing treatment within the clinical trial protocols may not fully reflect expected NHS practice. If the causes of belimumab discontinuation are time-dependent, as suggested by the long-term extension study and the clinical experts who completed the questionnaire, the use of these trials to inform long-term discontinuation is likely to fail to capture such effects.
3. **Use the long-term open-label study to inform discontinuation rates (LBSL02/99[3]).** This evidence was presented by the manufacturer in response to the consultation. Whilst this study provides much longer follow-up than the BLISS trials, these patients may not correspond well with the target population from the BLISS trials, or the 24-week response criteria adopted by the manufacturer. In addition, the design of this study, which focusses on safety, indicates that there may be other incentives to keep patients on treatment which may somewhat bias observed estimates of belimumab discontinuation.

5. REFERENCES

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APPENDIX 1

Survey questionnaire on the long-term use of belimumab (Benlysta®) for systemic lupus erythematosus (SLE)

NICE Decision Support Unit

Please complete this questionnaire electronically and return to [redacted]

1. BACKGROUND

The National Institute for Health and Clinical Excellence (NICE) makes recommendations to the NHS about the use of new and existing health technologies. NICE has recently undertaken an appraisal of belimumab for the treatment of systemic lupus erythematosus (SLE). This technology appraisal has been subject to a number uncertainties relating to the available short-term randomised trial evidence and the absence of longer-term studies. One particular area of uncertainty concerns the rate at which patients with SLE discontinue treatment with belimumab over time. This discontinuation rate has the potential to substantially influence the expected cost-effectiveness of belimumab. The NICE Decision Support Unit (DSU) has been asked to undertake further work with the intention of better characterising the nature and value of expected belimumab discontinuation rates using opinion from clinical experts. You have been sent this survey questionnaire because you have been identified as an expert in the treatment of patients with SLE. In this questionnaire we would like you to express your subjective beliefs about the expected discontinuation rates for patients with SLE receiving belimumab.

2. EXISTING EVIDENCE ON LONG-TERM DISCONTINUATION RATES FOR BELIMUMAB

In April 2011, GlaxoSmithKline (GSK) submitted evidence relating to the clinical effectiveness and cost-effectiveness of belimumab to NICE. This submission included a summary of available clinical trials and a cost-effectiveness model. The main clinical evidence within the submission was taken from the BLISS trials.[1] The BLISS trials were randomised, double-blind, placebo-controlled,

multicentre trials comparing belimumab 1mg/kg and 10 mg/kg plus standard therapy with placebo plus standard therapy in patients with active SLE.[1] Within the GSK cost-effectiveness model, the BLISS trials were used to inform the likelihood of response at Week 24 and the rate of discontinuation thereafter. The model assumes that patients discontinue belimumab after Week 24 if they do not have an improvement in SELENA-SLEDAI score of 4 points or more. Within the patient subgroup that had an improvement in SELENA-SLEDAI score of 4 points or more, the subsequent annual belimumab discontinuation rate was estimated to be 8% each year, based on unpublished BLISS subgroup data. Clinical specialists at the NICE Appraisal Committee meeting considered that lifetime treatment with belimumab and the durations of treatment predicted in the model were unrealistic. Later in the appraisal process, GSK presented long-term efficacy and safety data for belimumab from an open-label, Phase II extension study (Study LBSL99).[2] This extension study suggests an annual discontinuation rate of around 12-13%, however there remain questions regarding the representativeness of the population recruited into this study.

There is no other empirical evidence relating to the long-term discontinuation rates for belimumab treatment in patients with SLE.

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PLEASE READ THE GUIDANCE IN THE NEXT SECTION BEFORE COMPLETING THE QUESTIONNAIRE

3. GUIDANCE ON COMPLETING THIS QUESTIONNAIRE

When answering each question, please carefully consider the following:

(i) Reasons for discontinuation

We are interested only in the continuous use of belimumab (Benlysta®) **in line with its marketing authorisation** – please **do not** include discontinuation due to treatment response or stabilisation in your responses.

When completing the questionnaire, please consider the following reasons for discontinuation:

1. **Loss of efficacy** – patients who discontinue treatment due to a lack of response to belimumab.
2. **Adverse events** – patients who discontinue treatment due to the incidence of side effects, complications or inability to tolerate treatment.
3. **Other patient-related causes for discontinuation** – patients who discontinue treatment for other non-clinical reasons, for example patient choice or migration.

(ii) Type of information requested

The majority of the questions in this questionnaire are presented in the same format. The information we would like to request concern:

(a) **The expected mean discontinuation rate** – Your subjective belief about the mean percentage of patients that would discontinue belimumab treatment within a particular time period.

(b) **The 95% credible interval** – This is the interval within which you are 95% certain that the true mean discontinuation rate lies. The width of the credible interval will give us some idea about how uncertain you are about your stated discontinuation rate. The wider the interval, the more uncertain you are. Suppose your mean estimate is 20% for a given 12 month period - a credible interval of 5% to 35% implies more uncertainty than a credible interval of 18% to 22%. Note that this credible interval does not need to be symmetrical but must include the mean.

(c) **The number of imaginary patients that reflects your uncertainty** – This is another measure of your uncertainty. A smaller sample size (for example *n*=10 patients) would imply more uncertainty around your expressed belief, whilst a larger sample size (for example *n*=1,000 patients), would imply that you are more certain about your expressed belief.

PLEASE COMPLETE ALL QUESTIONS HIGHLIGHTED IN YELLOW

4. PERSONAL INFORMATION

Please note: Your personal information will be held as strictly confidential by NICE and the DSU and will not be shared with any other party.

(i) Your name

PLEASE STATE

(ii) Your institution

PLEASE STATE

(iii) Your professional role

PLEASE STATE

(iv) Have you had experience treating lupus patients?

PLEASE MARK (X) **YES** **NO**

(v) Have you had experience treating lupus patients with belimumab?

PLEASE MARK (X) **YES** **NO**

5. SURVEY QUESTIONNAIRE

QUESTION 1 – BELIMUMAB DISCONTINUATION BETWEEN 6 MONTHS AND 18 MONTHS

Imagine that you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment. We would like you to consider the likely discontinuation rates during the period 6 months to 18 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 1

Discontinuations between 6 and 18 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 2 – LONGER-TERM DISCONTINUATION RATES

Do you believe that the discontinuation rate between 6 months and 18 months would be the same for each subsequent 12 month treatment period? Or alternatively, would the rate increase or decrease? Please also provide a reason for your answer.

Response 2

	PLEASE MARK (X)	**PLEASE PROVIDE A REASON FOR YOUR ANSWER**
(i) Same dropout rate over time		
(ii) Dropout rate increases over time		
(iii) Dropout rate decreases over time		

IF YOU BELIEVE THAT THE DISCONTINUATION RATE IS CONSTANT DURING EACH 12-MONTH INTERVAL, THE QUESTIONNAIRE IS COMPLETE. IF YOU BELIEVE THAT THE RATE DIFFERS FROM YEAR TO YEAR, PLEASE PROCEED TO QUESTION 3.

QUESTION 3 - BELIMUMAB DISCONTINUATION BETWEEN 18 MONTHS AND 30 MONTHS

Imagine that you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 18 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 18 months. We would like you to consider the likely discontinuation rates for the period 18 months to 30 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 3

Discontinuations between 18 and 30 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 4 - BELIMUMAB DISCONTINUATION BETWEEN 30 MONTHS AND 42 MONTHS

Imagine you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 30 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 30 months. We would like you to consider the likely discontinuation rates for the period 30 to 42 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 4

Discontinuations between 30 and 42 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 5 – BELIMUMAB DISCONTINUATION BETWEEN 42 MONTHS AND 54 MONTHS

Imagine you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 42 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab treatment after 42 months. We would like you to consider the likely discontinuation rates for the period 42 months to 54 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 5

Discontinuations between 42 and 54 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 6 – BELIMUMAB DISCONTINUATION BETWEEN 54 MONTHS AND 66 MONTHS

Imagine you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 54 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 54 months. We would like you to consider the likely discontinuation rates for the period 54 months to 66 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 6

Discontinuations between 54 and 66 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 7 – BELIMUMAB DISCONTINUATION AFTER 66 MONTHS

Imagine you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 66 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 66 months. We would like you to consider the percentage of patients who are likely to discontinue treatment each year after 66 months. Please also provide a 95% credible interval.

Response 7

Annual discontinuations after 66 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE. PLEASE EMAIL THE COMPLETED QUESTIONNAIRE TO [redacted]

UK Biologics BILAG Registry

Background to Registry:

- British Isles Lupus Assessment Group (BILAG) Registry was set-up in 2011 and is currently in use in the UK, led by Prof. Ian N Bruce, Arthritis Research UK Epidemiology Unit and The Kellgren Centre for Rheumatology, University of Manchester. The overarching aim is to study the use of novel biological therapies in the treatment of Systemic Lupus Erythematosus (SLE) via a multi-centre, prospective, observational study.

http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/pharmacoepidemiology/bilagbr/

Roles of interested parties:

- The University of Manchester is the sponsor, BILAG 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 operates independently from direct industry involvement
- Funding from industry including GSK

Details of Current Biologics Study

Objective:

- To study the safety and 'real-world' efficacy of biological agents in the management of SLE in the UK
- Primary endpoint of interest: infection requiring hospitalisation

Centres and Patient Cohort:

- 16 specialist centres around UK currently participating. Plan to include renal, rheumatology and paediatric centres
- Includes major lupus centres in the UK
- Patients aged 5 yrs or older
  - ***Biologics***: Newly treated with a biologic therapy (or treated in the last 12 months)
  - ***Standard therapy group:*** Newly treated with a standard therapy (azathioprine, MMF or cyclophosphamide)
- 220 patients per group required for the current study.

Safety Outcomes:

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

Other Data:

- Efficacy Outcomes:
  - BILAG Index 2004, SLEDAI – 2K, SLICC Damage Index
- Prior therapy
- Concomitant medications (including steroid use and dose over time)

- Comorbidities
- Laboratory parameters

Patient Reported Outcomes:

- EQ5D (The EuroQol Group 1990); SF-36 LupusQoL (McElhone et al, 2007); lifestyle questionnaire (e.g. drinking, smoking, employment status), patient diary (recording hospital admissions, visits to outpatients and medications)

Assessments:

- 'Pre-assessment' prior to re-treatment or new biologic added
- Follow-up:
  - Clinical assessment at 3, 6, 12 months; annual assessment thereafter
  - Six-monthly questionnaires to patients for 2 years; annual assessment thereafter

<u>As of May 2013:</u>

- 104 patients recruited (87 biologics and 17 standard therapy). Of the 87 on biologics therapy, 5 are patients who have been prescribed belimumab.

<u>Auditing the conduct of the study and research governance</u>

The following coordinated program will aid quality control:

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