

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Belimumab for treating active autoantibody-positive systemic lupus erythematosus

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

1 Guidance

1.1 Belimumab is recommended as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus in adults only if all of the following apply:

- There is 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 despite standard treatment;
- Treatment with belimumab is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more;
- The company provides belimumab with the discount agreed in the patient access scheme;
- Under the conditions for data collection, monitoring, patient consent, cost to the NHS, and review by NICE as laid out in sections 5 and 6 of this document.

1.2 This guidance is not intended to affect the position of patients whose treatment with belimumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements

were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Belimumab (Benlysta, GlaxoSmithKline) is a human monoclonal antibody that inhibits the activity of B-lymphocyte stimulator (BLyS). Belimumab has a marketing authorisation 'as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy'.
- 2.2 According to the summary of product characteristics, adverse reactions with belimumab include bronchitis, viral gastroenteritis, cystitis, pharyngitis, nasopharyngitis, leukopenia, hypersensitivity reactions, depression, insomnia, migraine, diarrhoea, nausea, pain in extremity, infusion-related reactions and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 Belimumab is available as a 120 mg or 400 mg powder for intravenous infusion in solution. The recommended dose regimen is 10 mg/kg belimumab on days 0, 14 and 28, and at 4-week intervals thereafter. The summary of product characteristics states that discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. The list price of belimumab is £121.50 for a 120 mg vial and £405 for a 400 mg vial (excluding VAT; British national formulary [accessed June 2015]). Assuming vial wastage, the drug cost per administration for a person weighing 65–76 kg is £769.50. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of belimumab. The level 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 company's submission

- 3.1 The Appraisal Committee (section 9) considered evidence submitted by GlaxoSmithKline, reviews of the submissions by the Evidence Review Group (ERG; section 10) and evidence provided in the Decision Support Unit report (DSU; section 10).
- 3.2 The company's submission focused on a subgroup of the patients whose disease met the criteria specified in the marketing authorisation. The company explained that, being aware of NHS resources and to identify people who are most likely to benefit from belimumab, the submission focused on a high disease activity subgroup (hereafter referred to as the target population). The target population is adults with active autoantibody-positive systemic lupus erythematosus with evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10.
- 3.3 The company 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 company's target population.

Clinical effectiveness

- 3.4 The main evidence for the clinical effectiveness of belimumab was from 2 phase III clinical trials. The BLISS-52 (n=865) and BLISS-76

(n=819) trials were randomised, double-blind, placebo-controlled, parallel-group studies with follow-up at 52 weeks and 76 weeks respectively. In these trials, belimumab plus standard care (hereafter referred to as belimumab) was compared with placebo plus standard care (hereafter referred to as standard care). Standard care included: non-steroidal anti-inflammatory drugs, antimalarials, corticosteroids or other immunosuppressants (azathioprine, methotrexate and mycophenolate mofetil) either alone or in combination. Although each of the BLISS trials were 3-arm trials (belimumab 10 mg/kg, belimumab 1 mg/kg and placebo), only results for the 10 mg/kg belimumab dose were presented in the company's submission because this is the dose covered by the marketing authorisation.

- 3.5 Adult patients (aged 18 years or older) who met the American College of Rheumatology criteria for systemic lupus erythematosus and had active autoantibody-positive disease and a SELENA-SLEDAI score of 6 or more at screening were eligible for enrolment in the BLISS trials. Patients with severe active lupus nephritis or central nervous system lupus were excluded from the trials. Of the patients in the standard care and belimumab 10 mg/kg arms (n=1125), 52% (n=585) had disease that met the criteria for the marketing authorisation and 35% (n=396) had disease that met the criteria for the target population.
- 3.6 The BLISS-52 trial recruited patients from South America, Asia and eastern Europe, whereas the BLISS-76 trial recruited patients from the USA, Canada, Europe (western and eastern) and Israel. In the BLISS-52 trial, approximately 42% of the target population were Asian. In the BLISS-76 trial most of the target population were white (around 65%). Over 90% of the target population included in the trials were women and most (approximately 85%) were aged 45 years or younger. In the target population, over 90% of the

patients had at least 1A or 1B British Isles Lupus Assessment Group (BILAG) organ involvement and approximately 70% had at least 1A or 2B BILAG organ involvement. For the target population, mean SELENA-SLEDAI score was approximately 13 in both trials. About 85% of patients in the target population had a physician's global assessment score of between 1 and 2.5. Most of the patients had a range of manifestations of systemic lupus erythematosus, mainly involving mucocutaneous, immunological and/or musculoskeletal damage.

- 3.7 The company presented results from the BLISS-52 and BLISS-76 trials separately and pooled. The primary outcome of both studies was the response rate at week 52 compared with baseline, assessed with the Systemic Lupus Erythematosus Responder Index (SRI). With the SRI criteria, a response was defined as: a reduction of at least 4 points in SELENA-SLEDAI score (regarded as clinically meaningful); no new BILAG A organ domain score; no more than 1 new BILAG B organ domain score; and no worsening in physician's global assessment score (increase of less than 0.3).
- 3.8 For the primary outcome of SRI response at 52 weeks, statistically significant differences were observed between belimumab and standard care in both trials. In the BLISS-52 trial, for the target population, 67% of patients on belimumab had disease that responded compared with 41% of patients on standard care (odds ratio [OR] 3.0; 95% confidence interval [CI] 1.7 to 5.2). In the BLISS-76 study, for the target population the response was 57% for belimumab compared with 34% for standard care (OR 2.5; 95% CI 1.3 to 4.6). In the pooled analysis for the target population, 63% of the patients on belimumab had disease that responded, compared with 38% of those on standard care (OR 2.7; 95% CI 1.8 to 4.1). In the BLISS-76 trial, the target population showed a statistically

significant difference in response rate between belimumab and standard care at 76 weeks ($p=0.02$).

- 3.9 For the individual components of the SRI, which were secondary outcomes in the trials, a greater proportion of patients on belimumab in both BLISS trials had a reduction of at least 4 points in SELENA-SLEDAI score compared with standard care. In the pooled analysis for the target population, 65% of patients on belimumab had a reduction of at least 4 points in SELENA-SLEDAI score compared with 41% on standard care (OR 2.6; 95% CI 1.7 to 3.9), which was statistically significant. For the outcomes of no new BILAG 1A or 2B organ domain involvement and no worsening in physician's global assessment, results from BLISS-52 for the target population showed a statistically significant improvement with belimumab compared with standard care, whereas results from BLISS-76 did not. However, there was a statistically significant improvement for both these outcomes in the pooled analysis for the target population.
- 3.10 For other secondary outcomes, in the pooled analysis of the target population 16% of patients on belimumab compared with 7% of patients on placebo (OR 2.43; 95% CI 1.05 to 5.65) had an average prednisone dose reduction of greater than or equal to 25% from baseline, to less than or equal to 7.5 mg per day, during weeks 40 to 52. There were no differences in the Systemic Lupus International Collaborating Clinics (SLICC) index of organ damage in BLISS-52, BLISS-76 or the pooled analysis.
- 3.11 Quality-of-life measures, the SF-36 and EQ-5D, were also collected as secondary outcomes. At week 24 in the pooled analysis of the target population, there was a statistically significant mean change from baseline EQ-5D index for belimumab compared with standard care, but this was not maintained at week 52. The pooled analysis of the target population showed no statistically significant difference

in mean SF-36 physical component summary scores between belimumab and standard care at weeks 24 or 52. In the pooled analysis of the target population for functional assessment of chronic illness therapy (FACIT)-fatigue scores, the difference in scores was statistically significant at weeks 8 and 12 but not thereafter. In the individual trials, there was a statistically significant difference in FACIT-fatigue scores for the total population in favour of belimumab in the BLISS-52 trial at week 52 but not in the BLISS-76 trial.

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

3.13 Adverse event data were taken from the total population included in the BLISS trials (that is, not just the target population) and from a phase II extension study (LBSL99). Over 90% of patients in each arm experienced 1 or more adverse events. The most frequent (occurring in more than 10% of patients) events were headache, upper respiratory tract infection, arthralgia, nausea, urinary tract infection, diarrhoea and fatigue. Of these events, only diarrhoea and nausea occurred slightly more frequently in the belimumab groups than in the standard care groups. Serious adverse events were experienced by 17% in the 10 mg/kg belimumab group, compared with 16% in the standard care group. Across the double-blind treatment periods, 14 people died, including 3 (0.4%) in the standard care group, 5 (0.7%) in the 1 mg/kg group and 6 (0.9%) in the 10 mg/kg belimumab group. Four deaths were infection-related:

1 in the standard care group, 1 in the 1 mg/kg belimumab group and 2 in the 10 mg/kg belimumab group. Infection may have contributed to the deaths of 2 further patients (1 in the 1 mg/kg belimumab group and 1 in the 10 mg/kg belimumab group). There were 2 suicides, both in patients receiving belimumab (1 in the 1 mg/kg group and 1 in the 10 mg/kg group), and 1 cancer-related death in a patient receiving 1 mg/kg belimumab. In the long-term open-label extension phase of the phase II study, the incidence of adverse events and severe adverse events remained stable or declined over time through 5 years of exposure.

- 3.14 The company explained that some people 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 (EXPLORER) 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 company stated that differences in the end points considered and the patient populations precluded any meaningful indirect comparison between the belimumab and rituximab studies.

Further evidence and proposed evidence collection provided by the company after the fourth Committee meeting

- 3.15 The company acknowledged the uncertainties in the evidence base for belimumab and the assumptions used in the economic modelling. It considered that some of this uncertainty could be addressed by collecting real-world evidence that would inform a future review of the technology appraisal guidance. It submitted a

proposal to collect additional evidence on belimumab over a minimum of 3 years through the British Isles Lupus Assessment Group (BILAG) registry, which has 29 specialist centres around the UK and has already enrolled over 200 patients with systemic lupus erythematosus. It stated that this would generate real-life data for belimumab as prescribed in UK clinical practice for the target population of patients with highly active systemic lupus erythematosus despite current standard of care.

3.16 The company's research proposal included details about sample size, data collection and timing of assessments:

- It was anticipated that, based on current recruitment rates, around 9–11 patients receiving belimumab would enroll in the registry each month, with an estimated total of 300 patients after 3 years.
- The data collected for belimumab would be consistent with those already being collected in the registry for biological treatments:
 - Efficacy data comprising clinical response (measured by BILAG Index 2004 and SLEDAI-2K) and organ damage accrual (using the SLICC Damage Index and BILAG Index 2004).
 - Incidence of serious adverse events such as hospitalisation for infection, malignancy and death.
 - Patient-reported outcomes using EQ-5D, SF-36 and LupusQoL.
 - Other data such as previous and concomitant treatment.
- Patients would be assessed before receiving a new biological treatment or before re-treatment. Further clinical assessment would be at 3, 6, and 12 months, and then annually.
- Patients would complete questionnaires every 6 months for 2 years and annually thereafter.

- 3.17 The company considered that the data would address many areas of uncertainty that had been identified by the Committee, such as treatment duration, type of standard of care in clinical practice in England, treatment benefit for the full range of disease manifestations, steroid-sparing effect, impact on quality of life, stopping rule adherence, maintenance of treatment effect, development of organ damage and safety data.
- 3.18 The company also submitted further supportive evidence, including organ damage and 5-year safety data from 2 open-label, phase III extension studies that included people who had completed the BLISS-52 and BLISS-76 studies.

Cost effectiveness

- 3.19 A de novo decision-analytic model was developed by the company. The model is a micro-simulation that incorporates the interaction between patient characteristics, disease activity, medication (corticosteroid use), risk of organ damage development (a person with systemic lupus erythematosus could potentially develop damage in 12 different organ systems) and mortality. The company 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.
- 3.20 The health states in the model were informed by data from the BLISS trials, observational cohort data (the Johns Hopkins cohort, see section 3.22), and other data from the literature. A patient's baseline characteristics were simulated based on the pooled target population characteristics in the BLISS trials. The BLISS clinical trials were used to inform the likelihood of response at week 24 (based on a SELENA-SLEDAI score decrease of 4, this being the

basis for the company's proposed continuation rule in which belimumab would be continued for people whose disease had such a response after 24 weeks), the change in SELENA-SLEDAI score up to week 52, the likelihood of discontinuation, and the effect of SELENA-SLEDAI score on utility and treatment costs. Data from the literature were used to inform the standardised mortality rate for a given SELENA-SLEDAI score, and quality-of-life and cost impacts of long-term damage to each organ system.

3.21 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.

3.22 Prediction models based on data from the Johns Hopkins cohort were used to predict change in adjusted mean SLEDAI score (which is used as a proxy for SELENA-SLEDAI score), average corticosteroid dose per year, risk of organ damage and risk of death. The Johns Hopkins cohort reported data on a large population of patients with systemic lupus erythematosus from Baltimore, Maryland, USA, of whom 93% were women, 52% were

white and 38% were black. Analyses were conducted on a dataset of 1282 people, with follow-up of greater than 2 years and data after 1992. Mean age at diagnosis was 33 years and mean SLEDAI score at first visit was 3.32. Few people with SLEDAI scores of 10 or more remained at the end of this observational study.

- 3.23 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 company adjusted the constant in the regression to obtain a better fit to the data.
- 3.24 Corticosteroid use was calculated based on a regression equation from the Johns Hopkins cohort, with disease activity as measured by mean SLEDAI score as the sole independent variable. For each organ system contained within the SLICC Damage Index, the probability of damage during that year was calculated based on the patient's characteristics and disease activity at that time. The company 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.

3.25 The baseline quality of life assumed in the cost-effectiveness analysis was determined by a regression equation (which accounted for age, family origin and SELENA-SLEDAI score), which was derived from the BLISS trials. Disutility multiplier values for each type of organ damage were identified from a search of the literature. These disutility multipliers were applied to the utility score if a patient developed organ damage in the model cycle. Costs in the analysis were limited to direct medical costs and costs associated with disease activity and long-term organ damage. Total resource use varied according to disease severity and was determined using a linear regression analysis. A literature search was conducted to identify the cost of organ damage. All costs were inflated to 2010 values. The base case considered only the additional acquisition costs for belimumab. Because belimumab is given in addition to standard care, it was assumed that the costs for standard care treatments would be the same for people on belimumab as for those not on belimumab and so were not included. The administration cost of £126 for belimumab was calculated based on 2 hours of senior hospital staff nurse time (£63 per hour): 1 hour for the infusion and another 1 hour for patient preparation and monitoring post-infusion. It was assumed that the first year annual cost of treatment and administration of belimumab was £10,918 and, in subsequent years, was £10,138, based on a cost of belimumab of £114.30 for a 120 mg vial and £381 for a 400 mg vial. At the time of submission, the vial price for belimumab had not been finalised, so the expected vial list price was used in the base-case analyses. The effect on cost effectiveness of a maximum expected vial price for both the 120 mg and 400 mg vials was investigated in a scenario analysis. The

inclusion of a cost for standard care and different costs of administration were also explored in scenario analyses.

- 3.26 The model showed lower disease activity for patients on belimumab than in patients on standard care only, which led to decreased corticosteroid dose and decreased risk of organ damage, and contributed to a difference in mortality risk. The model predicted that patients on belimumab live longer than those on standard care. Although a decreased duration of damage was shown for organs on which belimumab has a large effect (cardiovascular, pulmonary and renal), the duration of damage for other organ systems is increased because of the prolonged life expectancy.
- 3.27 The model predicted that patients treated with belimumab, in the target population, live on average 2.9 years longer (34.9 compared with 31.9 years), have a reduction in average adjusted mean SLEDAI score, have a reduced cumulative monthly corticosteroid dose and similar total SLICC organ damage score compared with those on standard care only. Treatment with belimumab provided an estimated additional 1.1 life years and 0.8 quality-adjusted life years (QALYs) (both discounted values). For both treatment groups, the organ damage costs were the highest expense. In total, the organ damage costs were lower for patients treated with belimumab. The costs related to disease activity were similar in the 2 treatment arms. Because of their increased life expectancy and the cost of belimumab treatment, costs were higher for patients receiving belimumab than for those on standard care.
- 3.28 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.

- 3.29 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.
- 3.30 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 company'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.
- 3.31 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.

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

Further evidence submitted by the company after the first Committee meeting

3.33 In response to consultation, the company 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 company showed a mean reduction in corticosteroid use of 4.7 mg per day, an average reduction of 34.4% from the baseline dose, by the end of 6 years of follow-up. The company calculated that based on 6-year follow-up the annual discontinuation rate was approximately 13% in this trial.

3.34 As well as further clinical evidence, in response to consultation the company 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 company's revised base case resulted in an ICER of £47,342 per QALY gained, with an incremental cost of £28,705 and incremental QALYs of 0.61. In a scenario analysis conducted by the company on the revised base-case analysis, the continuation rule for belimumab was changed

from a SELENA-SLEDAI score of greater than or equal to 4 to greater than or equal to 6 and the health effects discount rate lowered from 3.5% to 1.5%. These scenarios had the effect of lowering the ICER to £40,863 and £31,988 per QALY gained respectively. When both scenarios were applied together, they lowered the ICER to £27,807 per QALY gained, with an incremental cost of £20,766 and incremental QALYs gained of 0.747.

- 3.35 The company 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 company supported the use of belimumab for up to 6 years with the newly available long-term data for belimumab from the phase II extension study (see section 3.33). The company 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 company 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.
- 3.36 According to the company it was appropriate to use NICE's clarification to section 5.6 of the Guide to the methods of technology appraisal 2008 on the discounting of health benefits in special circumstances for a number of reasons; namely, the nature of systemic lupus erythematosus and the fact that belimumab has been shown to result in clinically important reductions in disease activity, and has the potential to provide important long-term

benefits including reduced organ damage, reduced use of high-dose corticosteroids, along with their associated risks, and consequently improved survival. Therefore, the company considered that the discount rate of 1.5% for health effects rather than the 3.5% normally applied in technology appraisals was appropriate. Furthermore, the company stated that by applying a continuation rule at 24 weeks of a SELENA-SLEDAI score greater than or equal to 6 rather than 4, a more efficient use of NHS resources could be made.

Further evidence provided by the company after the appeal

- 3.37 After the appeal, the company submitted a further revised base case using a revised patient access scheme. This used the same assumptions as in the original base-case model (that is, lifetime treatment with a continuation rule of a SELENA-SLEDAI score greater than or equal to 4), but incorporated an annual discontinuation rate of 13% and an administration cost of belimumab of £154, reflecting the infusion administration cost used in NICE's technology appraisal guidance on [tocilizumab for the treatment of rheumatoid arthritis](#). The total costs were £146,056 for belimumab and £105,366 for standard care. Total QALYs were 10.47 for belimumab compared with 9.81 for standard care. The incremental costs were therefore £40,691, and the incremental QALYs 0.66. This resulted in an ICER of £61,328 per QALY gained. ICERs with the patient access scheme were also provided. These were marked commercial in confidence because of the confidential nature of the patient access scheme.
- 3.38 The company also presented scenario analyses including a maximum treatment duration of 6 and 10 years, alternative treatment continuation rules and a range of treatment discontinuation rates. The alternative discontinuation rates included the 8% discontinuation rate used in the original base case, and a

variable discontinuation rate of 13% up to year 5 and a 30% rate afterwards. The company stated that the variable discontinuation rate more closely represented the distribution of treatment durations likely to be prescribed in clinical practice for people in the target population. The company's additional evidence also included a cost comparison between rituximab and belimumab.

Further evidence provided by the company after the fourth Committee meeting

3.39 The company submitted additional economic analyses for belimumab compared with standard care in which the base-case maximum treatment duration was 3 or 5 years. They incorporated a treatment continuation rule at 6 months of a change in SELENA-SLEDAI score of 4 or more, a discontinuation rate of 8% in year 1 and 11.7% thereafter and assumed that people who stopped having belimumab reverted to average SELENA-SLEDAI score for standard care. Scenario analyses that included different continuation rules were also provided. The base-case results and those of the scenario analyses are confidential and cannot be presented here. The company noted that the base-case ICERs for belimumab compared with standard care with a maximum treatment duration of 3 or 5 years were lower than those it had previously submitted.

3.40 The company asserted that a robust comparison of the relative efficacy of belimumab and rituximab was not feasible because of a lack of direct or indirect data from randomised controlled trials.

Evidence Review Group's critique of the company's original submission

3.41 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 people with the greatest response to belimumab. The ERG noted

that, according to clinical opinion, the SELENA-SLEDAI (a component of the SRI and 1 of the measures used to identify people in the target population) is not commonly used to define high disease activity in clinical practice.

- 3.42 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.
- 3.43 The ERG highlighted that information on SLEDAI and SF-36 changes in the rituximab EXPLORER trial were available, and that randomised controlled trials for both rituximab and belimumab recorded BILAG score changes.
- 3.44 The ERG considered that the company's model was complex, though generally well constructed. It noted that the model conformed to the NICE reference case and that the longer-term effects of systemic lupus erythematosus had been modelled well, using the Johns Hopkins cohort. An ERG cross-check of the

probabilistic modelling for the target population resulted in a central estimate for the ICER of £65,530 per QALY gained.

3.45 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 company 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.

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

both between week 24 and 52 and beyond week 52, leading to an underestimation of the ICER.

- 3.47 The ERG noted that a higher adjusted mean SLEDAI score was associated with an increased probability of the patient dying and of a patient developing particular organ involvement. The economic modelling did not take into account a patient's history before entry into the trial and this may also have exaggerated the impact that changes in SELENA-SLEDAI score had on the adjusted mean SLEDAI score for belimumab compared with standard care, with the likely result that the base-case ICER was an underestimate. This is potentially important when comparing the Johns Hopkins cohort, in which most patients had SELENA-SLEDAI scores of less than 10, with the target population, who all had scores of greater than 10 at baseline.
- 3.48 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 company 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.
- 3.49 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 company to 3.0 to improve the fit to belimumab trial data after week 52. Sensitivity analyses by the company showed that using the original value of the constant term increased the ICER by approximately £29,000, to £93,654 per QALY gained.

- 3.50 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 (NICE's technology appraisal guidance on [tocilizumab for the treatment of rheumatoid arthritis](#)), 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.
- 3.51 The ERG completed an exploratory analysis that used the estimates from the individual BLISS trials in the disease activity regression equation rather than the pooled estimate. This analysis demonstrated that the economic model was not particularly sensitive to the use of estimates from the individual trials. Using BLISS-76 as the source of the regression increased the ICER by approximately £2000, to £66,318 per QALY gained.

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

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

there is a substantial degree of uncertainty over whether the effects observed in the data would translate into longer-term effects.

3.53 The ERG reviewed and critiqued the company's additional economic analysis submitted after consultation. The ERG noted that the company's revised base-case model was based on 6 years maximum treatment duration, while the original model had some patients on 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 company's revised base-case model also assumed that while the SELENA-SLEDAI scores for the patients at the end of year 6 revert to scores expected for patients receiving standard care, the adjusted mean SLEDAI score continues to show benefit, which could indicate a sustained reduction in organ damage in the treatment arm. The ERG also noted that, given an annual discontinuation rate of 8% (as in the original submission) or the rate observed in the phase II extension study (13% annual discontinuation rate), if a maximum treatment duration of 6 years was imposed, a considerable number of patients benefiting 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 company 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.

3.54 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 get 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.

- 3.55 The ERG noted that the company 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 company considered that this early effect of belimumab, together with the observed 34% reduction in corticosteroid usage, would translate into long-term benefit by reducing the development of organ damage. The ERG commented that the extent to which short-term benefits translated into longer-term benefits was uncertain and presented data showing that in the economic modelling 63% of the incremental QALY gain (undiscounted) was accrued within 30 years.
- 3.56 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.
- 3.57 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.

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

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

3.59 The ERG reviewed the company's revised base case and confirmed that no structural changes were made to the model originally submitted and that only inputs were changed. It noted that, in 1 scenario, an error in the calculations resulted in an incorrect value, which when corrected raised the ICER slightly. The ERG stated that many of its previous concerns about the economic model had not been addressed in the additional evidence and that, if justified, these would increase the estimates of cost

effectiveness. The ERG also highlighted the sensitivity of the model to estimates of pulmonary damage and uncertainties in these costs. With respect to the comparison of costs presented by the company, the ERG noted that there was still no research data that would allow for either a direct or an indirect comparison between belimumab and rituximab. The ERG noted that, in a recent systematic review of rituximab therapy in systemic lupus erythematosus, most observational studies used less rituximab than used in the rituximab EXPLORER trial.

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

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

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

3.62 For a scenario assuming no continuation rule, the ERG estimated an ICER of £68,986 per QALY gained. For a scenario assuming a continuation rule of SELENA-SLEDAI score of greater than or equal to 4, the ERG estimated an ICER of £59,946 per QALY gained. For a scenario assuming a continuation rule of SELENA-SLEDAI score greater than or equal to 6, the ERG estimated an

ICER of £52,517 per QALY gained. ICERs with the patient access scheme were provided. These are commercial in confidence because of the confidential nature of the patient access scheme.

Critique by the ERG of the company's further evidence provided after the fourth Committee meeting

3.63 The ERG provided a review of the economic analyses provided by the company. It confirmed that the analyses had been conducted correctly (that is, as described by the company), but queried the relevance of the proposed maximum treatment durations. It also presented additional scenario analyses, including the company's base case combined with a lifetime maximum treatment duration and an assumption that patients whose condition does not respond to belimumab revert to the same SELENA-SLEDAI score as those whose condition did not respond to standard care. The results of these exploratory analyses are confidential and cannot be presented here.

NICE Decision Support Unit work after the appeal

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

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

NICE Decision Support Unit work after the fourth Committee meeting

3.66 The DSU provided a review of the company's proposed evidence collection using advice in the [Guide to methods of technology appraisal 2013](#) and a framework developed by Claxton et al. (2012). It found that the proposal accurately described the BILAG registry and would provide some data that could be used to resolve the Committee's uncertainty and might be particularly valuable in collecting data on adherence to the proposed stopping rule (because this is not being used in any other country). It noted that several other ongoing studies described in the company's submission would provide data to address some of the other uncertainties identified by the Committee.

3.67 Full details of all the evidence are in the [Committee papers](#).

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 experts. 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 experts on the clinical signs and symptoms associated with systemic lupus erythematosus. The Committee heard from clinical experts 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 experts 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 people with systemic lupus erythematosus would welcome an additional treatment option specifically for this disease. Furthermore, it was highlighted that many people 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 people with high disease activity 'despite standard therapy'. The Committee heard from clinical experts that 10–15% of people with systemic lupus erythematosus continue to have high disease activity despite standard therapy and that a proportion of these patients are currently treated with rituximab. The Committee understood that rituximab is used in people with severe disease to reduce the levels of disease activity (that is, to induce remission) and to reduce the amount of corticosteroids and other immunosuppressants prescribed. The Committee also heard from the clinical experts that rituximab treatment is repeated in such people when the disease shows signs of a significant increase in activity and that the re-treatment interval with rituximab varies from person to person. The clinical experts explained that they considered that rituximab would be a relevant comparator for belimumab. The Committee noted that since September 2013 rituximab has been provided by NHS England through an interim clinical commissioning policy statement. The Committee therefore concluded that standard care and rituximab should be comparators for belimumab.

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

4.5 The Committee discussed how belimumab would be used in clinical practice. It noted that the marketing authorisation stated that treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of systemic lupus erythematosus. It heard from the clinical experts that continuous use of belimumab for a long time would be very unlikely. The clinical experts explained that, as with other immunosuppressants, one of the aims of treatment with belimumab would be to work towards coming off the treatment. Once a person 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 person became symptomatic or if the serological tests signalled that this was likely. The company explained that there were no data available that reflected the scenarios described by the clinical experts, such as treatment holidays or tapering of treatment. However, the Committee noted that the European Medicines Agency has requested that the company address uncertainties about the effect of stopping treatment with belimumab (treatment holidays) as well as the risk of rebound phenomena, as part of the routine pharmacovigilance programme. The Committee was aware that belimumab is indicated as an add-on treatment in people with a high degree of disease activity despite standard therapy and it also observed that the European Medicines Agency's European Public Assessment Report for belimumab acknowledged that the BLISS studies were not designed for evaluating whether remission was induced, but rather for evaluating maintenance of remission. In addition the Committee noted that the most recent data supporting longer-term use of belimumab used a continuous schedule of administration over 7 years in people whose disease responded to treatment. Although the company had presented data supporting the continuous use of belimumab in people whose disease

responded, the Committee concluded that, in clinical practice, belimumab might be used in the same intermittent way as rituximab, although there are no efficacy data for such an approach and the likely treatment durations and discontinuation rates are not known.

- 4.6 The Committee discussed the population in the company's decision problem. It noted that the company focused on a target population comprising a post hoc subgroup of the population covered by the marketing authorisation and the BLISS clinical trials. The target population was identified by a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10 and evidence of serological disease activity. The Committee noted that although a SELENA-SLEDAI score of greater than or equal to 10 had been a pre-specified stratification factor in the BLISS clinical trials, when combined with the marketing authorisation criterion of a high degree of serological disease activity, this was not a group that had been pre-specified in the BLISS clinical trials. However, the Committee heard from the clinical experts 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 experts also explained that the biomarkers mentioned in the marketing authorisation (that is, low complement and positive anti-double-stranded DNA antibodies), would be used for demonstrating evidence of serological disease activity and would detect changes in disease activity. The Committee concluded that, although specifying a SELENA-SLEDAI

score of greater than or equal to 10 may be considered arbitrary, the specified target population is clinically relevant.

Clinical effectiveness

- 4.7 The Committee discussed the company's submission of clinical evidence, noting that most of the evidence in the company's submission was from the 2 BLISS trials (BLISS-52 and BLISS-76) that compared belimumab against standard care. The Committee considered the composite end point of the Systemic Lupus Erythematosus Responder Index (SRI) used in the BLISS trials. It noted that this end point was developed in conjunction with the Food and Drug Administration in the USA. The Committee heard from the clinical experts that the SELENA-SLEDAI score, a component of the SRI, is a relatively crude tool and that the experts considered the use of the composite tool, which also includes the British Isles Lupus Assessment Group (BILAG) tool (as well as the physician's global assessment), was reasonable. The Committee accepted the evidence from the clinical experts that the SRI was an appropriate end point in the trials.
- 4.8 The Committee discussed whether the individual BLISS trials were representative of the UK population, in particular, whether data from the BLISS-52 trial were as relevant to UK practice as data from the BLISS-76 trial. The Committee noted that the BLISS-52 trial recruited people from eastern Europe, South America and Asia, and that the BLISS-76 trial recruited people from Europe (western and eastern), the USA, Canada and Israel. The clinical experts explained that, because the UK is a multi-ethnic country and systemic lupus erythematosus affects many ethnic groups more severely than white populations, data from different populations would still be relevant to the UK. Furthermore, the Committee understood from the clinical experts that clinical practice varies between countries, for example, in the USA higher doses of

corticosteroids are used than in the UK. Therefore, there may also be issues about the relevance of the data from BLISS-76. On balance, the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52. However, data from BLISS-52, and therefore from the pooled analysis would be relevant.

4.9 The Committee discussed the characteristics of the patients in the BLISS trials. It noted that the patients in the BLISS trials had mainly immunological, mucocutaneous and musculoskeletal manifestations of systemic lupus erythematosus at baseline. The Committee noted comments from consultation that the range of manifestations in the BLISS clinical trials was similar to those in clinical practice in the UK. Furthermore, it noted comments that serological manifestations are indicative of wider systemic disease activity. The Committee discussed whether, on this basis, belimumab may be expected to also show benefits for other manifestations. The Committee heard from clinical experts that if the experience of belimumab was like rituximab, then benefits for the range of manifestations may be expected. However, there remained uncertainty, and initially belimumab may be more likely to be used in people with predominantly musculoskeletal and mucocutaneous involvement. The Committee concluded that currently the effect of belimumab on the full range of manifestations of systemic lupus erythematosus was uncertain.

4.10 The Committee discussed baseline standard care in the 2 BLISS trials. It noted variations in treatments 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 experts that, in the UK, people for whom treatment with belimumab would be considered would have active

disease despite standard therapy, and that standard therapy for most people would include an immunosuppressant. The Committee concluded that there was uncertainty about the extent to which standard care in the belimumab trials represented UK clinical practice, for the target population for whom belimumab is intended.

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

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

4.13 The Committee explored the comparison of belimumab with rituximab and the evidence available to support the comparison, noting that head-to-head data comparing belimumab with rituximab were not available. It discussed the available evidence including

the uncontrolled observational data and the comparative data for rituximab and placebo from the EXPLORER trial. It considered whether any indirect analysis of the EXPLORER and BLISS data could be conducted. The Committee heard from the clinical experts that the EXPLORER trial included patients with more severe disease (that is, in terms of corticosteroid use and dose, and existing organ damage) than those in the BLISS studies, so the trial populations were different. The Committee heard from the ERG that there were 3 outcomes for which an indirect comparison could be completed (that is, BILAG, SLEDAI and SF-36 scores), but data were only available in the public domain for the SF-36. The ERG also highlighted the differences in the trial populations, which it considered meant that the results of an indirect comparison were not meaningful. The Committee concluded that there were no data that would allow a robust calculation of the relative clinical efficacy of belimumab compared with rituximab.

Cost effectiveness

- 4.14 The Committee discussed the economic model submitted by the company that informed both the original and revised analyses. The Committee noted that short-term outcomes from the BLISS studies were linked to long-term outcomes, using data from the Johns Hopkins cohort. The Committee considered the similarity of people in the Johns Hopkins cohort to those in the BLISS trials and noted that the people in the BLISS trials had higher SELENA-SLEDAI scores than the average SLEDAI scores in the Johns Hopkins cohort, indicating that the populations in the trials had more active disease than in the Johns Hopkins cohort. The Committee noted that the SLEDAI scores from the Johns Hopkins cohort were used to inform the equation for disease activity, corticosteroid use, mortality and organ involvement, but that only the equation for disease activity was adjusted so that it more closely matched the BLISS trial populations. The Committee heard from the company

how the model was driven by changes in the SELENA-SLEDAI score based on data from the Johns Hopkins cohort and that cost effectiveness was not particularly driven by other factors, such as by corticosteroid use. The Committee accepted that attempting to link short-term outcomes to long-term outcomes was appropriate and recognised that there were limited data sources available with which to do this. However, it concluded that there was uncertainty about whether the equations derived from the Johns Hopkins data could be reliably applied to the target population because of differences in study populations.

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

6 years. The Committee heard from the company that, taking into consideration the evidence from clinical experts at the first Committee meeting and from other consultations with clinicians, it was likely that in clinical practice belimumab would not be used continuously over a lifetime. The company stated that belimumab would probably be used in the same way as other immunosuppressants in systemic lupus erythematosus, that is, people would discontinue belimumab as early as possible once sustained disease control was achieved. The company 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 experts that, because of the heterogeneity of systemic lupus erythematosus, some people may need treatment continuously for longer than 6 years. But for most, it was more probable that belimumab would be used for less than 6 years, once a person's disease was in remission. The Committee considered the implications of stopping belimumab treatment at 6 years. The Committee noted that the data from the phase II extension study suggested there could be a possibility of continued benefit with continued treatment at 6 years because approximately 50% of patients on treatment with belimumab at the end of the second year were still on it at the end of the sixth year. The results of this study therefore suggested a rationale for continued use of belimumab in a significant proportion of patients beyond 6 years. The Committee was also aware that the ERG had identified 7-year data in relation to the belimumab phase II extension study. The Committee concluded that, although the 6-year maximum treatment duration modelled in the company's revised analyses improved the cost effectiveness of belimumab, the rationale for the choice of a maximum treatment duration of 6 years could not be considered sufficiently robust for use as the basis of decision-making.

4.17 The Committee discussed the annual discontinuation rates for belimumab after the first 24 weeks assumed in the original and revised economic models. The Committee noted that, in the original model, the company had based the annual discontinuation rate of 8% on data from the BLISS trials and that, in the company's additional evidence, the revised base case used a rate of 13%, based on longer-term 6-year data provided from the phase II extension study. The Committee understood that the 13% rate had been revised by the ERG to 11.7% using the 7-year data. The Committee also noted that the company had included a scenario analysis that used a variable annual discontinuation rate of 13% for the first 5 years and 30% thereafter. The Committee heard from the company that it considered the variable annual discontinuation rate better reflected the expected use of belimumab in UK clinical practice, in which clinicians had suggested that belimumab would be used like other immunosuppressants and most people would not receive belimumab beyond 6 years. The Committee discussed the use of the variable discontinuation rate noting that it was not presented with any evidence supporting an increased rate of discontinuation after 5 years. The Committee heard from the NICE Decision Support Unit that the results of its survey of experts in lupus in the UK did not reduce the uncertainty surrounding the discontinuation rates or have more credibility than the estimates available from the BLISS or phase II extension studies (see sections 3.64–3.65). The Committee also heard from the clinical experts that, without any long-term evidence on the use of belimumab in clinical practice, it was difficult to provide estimates for the rate of discontinuation with belimumab. The Committee considered that, because the effects of stopping belimumab treatment (rebound phenomena in patients whose disease has responded to belimumab) were not fully understood and because there was no evidence on treatment holidays and the efficacy of re-

treatment with belimumab, this could make clinicians less willing to stop. The Committee was therefore not persuaded that the proposed variable discontinuation rate was plausible.

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

4.19 The Committee considered the continuation rules applied in the economic model, noting that the summary of product characteristics states that discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. The Committee noted

that the original economic model applied a rule that patients would continue treatment after week 24 if there was an improvement in their SELENA-SLEDAI score of 4 points or more and that, after consultation, an additional analysis using a more stringent rule needing an improvement of 6 points or more on the SELENA-SLEDAI scale had been proposed by the company. The Committee understood that the SELENA-SLEDAI scale was not widely used in clinical practice, but noted comments that its introduction could improve patient care. The Committee heard from the clinical experts that if the person had not shown any benefit from treatment with belimumab after 6 months of treatment, then they would be likely to discontinue treatment as per the summary of product characteristics. The Committee heard that the clinical experts indicated that a gain of 4 points on the SELENA-SLEDAI score was generally considered to be a reasonable improvement and that if there was some benefit of treatment at 24 weeks, but less than 4 SELENA-SLEDAI points, the patient may continue treatment with belimumab. The Committee then discussed the difference between the 4 and 6 point continuation rules. It noted that the BLISS trials had included a gain of 4 points on the SELENA-SLEDAI as a secondary outcome and as part of the composite primary outcome (SRI response) because it was regarded as clinically meaningful. It heard from the clinical experts that they would prefer the lower continuation rule of an improvement of 4 points in the SELENA-SLEDAI score, but would use the higher continuation rule of 6 points if it reduced the base-case ICER to an acceptable level. The Committee agreed that specifying a continuation rule using an improvement in SELENA-SLEDAI score of either 4 or 6 points at 24 weeks could be considered arbitrary, but noted that these could help identify a population for which belimumab was more cost effective. It considered that a clinician's reluctance to discontinue belimumab in a person whose disease has responded but had not

reached a fall in SELENA-SLEDAI score of 4 at 24 weeks would be magnified with a continuation rule of 6 points. On balance, it was persuaded that the application of continuation rules was appropriate, but concluded that, given the uncertainties about the application of SELENA-SLEDAI in clinical practice and the specification of 4 rather than 6 points as part of the primary end point in the clinical trials, it was not appropriate to consider using the more restrictive rule of a SELENA-SLEDAI score improvement of 6 or more as the basis for the most plausible ICER. However, because the application of the SELENA-SLEDAI score improvement of 6 or more improved the cost effectiveness of belimumab, it agreed that this alternative scenario should still be considered when it examined the range of estimates of the ICER.

- 4.20 The Committee discussed the assumption in the economic model that the effect of belimumab was maintained over time. The Committee heard from the clinical experts that there were limited data available about the maintenance of treatment effect in systemic lupus erythematosus. The clinical experts explained that, in other conditions such as rheumatoid arthritis, people on biological treatments can experience a reduction in the response to treatment over time. However, the clinical experts explained that, in their experience with systemic lupus erythematosus, those people whose disease responded to rituximab and who needed re-treatment with rituximab at a later stage had shown a good response to re-treatment. The Committee was aware that the only longer-term data identified by the company and the ERG in relation to the benefit of belimumab was the open label phase II extension study that had been reported in conference abstracts and a journal publication (Petri et al. 2011, Merrill et al. 2012a, Merrill et al. 2012b). The Committee concluded that there was still some uncertainty in the evidence about whether it was appropriate to assume that treatment effect was maintained over time. If the

treatment effect was not maintained over time, this would lead to an increase in the ICER.

4.21 The Committee discussed the modelling of response in the economic model. The Committee noted the ERG comments that, for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, it was assumed that at week 52 they had the mean benefit observed in the standard care group. The ERG stated that, because the standard care group included both patients whose disease had responded and not responded to standard care, this was likely to overestimate the benefit of belimumab. The ERG stated that a more appropriate approach would have been to model the changes for the group of patients whose disease did not respond to standard care. The Committee heard from the company that, rather than reflecting the trial protocol treatment, the economic model was reflecting expected clinical practice with the introduction of a continuation rule, whereby patients whose disease does not respond to belimumab are switched to standard care and therefore get the benefits associated with standard care. The Committee agreed that, in patients whose disease has not responded to belimumab at 24 weeks, some response was likely when the patient was switched to standard care, but the size of this effect was uncertain. The Committee concluded that the company's approach may have overestimated the treatment effect of belimumab, and that alternative scenarios exploring the impact on the ICER with respect to the assumed mean benefit experienced by the patients whose disease did not respond to treatment in the belimumab group would help to better reflect the level of uncertainty.

4.22 The Committee noted that the model outputs in the original base-case analysis demonstrated a gain in survival of 2.9 years from treatment with belimumab compared with standard care. The

Committee considered the predicted survival from the model, noting that there was no evidence from the trials to support this modelled outcome and that in the trials there was a trend towards higher mortality in the belimumab arms compared with standard care. The company 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 experts that people with higher disease activity are more likely to have organ damage and die than people with lower disease activity. However, the clinical experts stated that this was likely to be dependent on the site of organ damage. For example, treatment for people with mainly musculoskeletal or mucocutaneous damage was unlikely to result in a survival benefit. The Committee was also aware that, because of the prolonged life expectancy of people treated with belimumab, the duration of damage for the other organ systems is increased, affecting cost and health-related quality of life. The Committee also discussed how survival time in the model was predicted to be longer in the target population than in the overall trial population (31.9 years in the standard care arm of the target group compared with 30.5 years in the overall standard care arm in the overall pooled BLISS populations), even though the target population had more severe disease. The Committee noted comments from consultation that this was because of the different baseline ages of the target and trial populations. The Committee considered that, although the different ages at baseline accounted for the survival difference, it noted that the age of death remained the same for both age groups. This was considered to be an unexpected finding given the longer disease history of the younger age group. The Committee considered that the company should have explored uncertainty around the estimate of survival in the model and its impact on the ICER by exploring a scenario that assumed no

survival gain for treatment with belimumab compared with standard care. The Committee concluded that, although gains in survival from reduced organ damage were plausible, there was considerable uncertainty around the validity of the modelled gains in survival and that alternative scenarios exploring the impact to the ICER around this parameter would better reflect the level of uncertainty.

- 4.23 The Committee considered the standardised mortality ratios used by the company and the alternative values identified by the ERG. The Committee heard from the ERG that the values it identified were unpublished data from an English cohort of patients. The Committee heard from the clinical experts that they considered that the standardised mortality ratios provided by the company 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 company in its decision-making.
- 4.24 The Committee discussed the administration costs used in the economic model. It noted that in the original model a cost of £126 had been used, based on 2 hours of specialist nurse time. The Committee noted that that this may be an underestimate of the costs of administration and noted that the ERG had completed a number of scenario analyses using values based on day-case codes and also values used in previous appraisals of intravenous monoclonal antibodies for rheumatoid arthritis (£154). Furthermore, the Committee noted comments from consultation that pharmacy preparation time had not been included in the economic analyses. The Committee noted that the company included the updated

administration cost of £154 in its revised submission. The Committee concluded that the administration cost of £154 was appropriate to use in its consideration of the most plausible ICER.

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

4.26 The Committee considered the cost effectiveness of belimumab in comparison with standard care. The Committee recognised that a scenario reflecting lifetime continuous treatment may not accurately capture how belimumab would be used in clinical practice. It noted that the company presented updated base-case ICERs with 3- and 5-year maximum treatment durations that incorporated the patient

access scheme, and were based on the Committee's previously preferred assumptions. It observed that they were within the range normally considered a cost-effective use of NHS resources, and that this was also the case when using the company's non-responder scenario. However, the Committee considered the assumption that all patients stopped at the appropriate time, regardless of the benefit they were receiving, to be unlikely and that it did not reflect clinical practice. The Committee noted that there is no evidence of the effectiveness of such a strategy. It also noted that the ERG's exploratory analysis based on the company's non-responder scenario with a lifetime maximum treatment duration increased the ICER beyond the range normally considered to be cost effective. The Committee considered that the estimated ICERs with the revised patient access scheme may have been underestimated because of a number of uncertainties. These included linking the short-term trial outcomes to long-term data with differing study populations, the annual discontinuation rate, the maintenance of the treatment effect, the mean benefit assumed for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, and validity of the modelled gains in survival that remained in the economic modelling (see sections 4.14, 4.17–4.22). The Committee agreed that, because of the considerable uncertainty that remained in the economic modelling, it was unable to conclude that the true value of the ICER incorporating the revised patient access scheme was within or outside a range in which belimumab could be considered a cost-effective use of NHS resources compared with standard care.

- 4.27 The Committee considered the cost effectiveness of belimumab compared with rituximab. The Committee had previously discussed the clinical effectiveness of rituximab in comparison with belimumab (see section 4.13) and concluded that no reliable data were available to demonstrate the relative efficacy of belimumab in

comparison with rituximab. It recalled that although rituximab was not licensed for treating systemic lupus erythematosus, it was available in the NHS because it was funded by NHS England via an interim clinical commissioning policy statement. The Committee concluded that without any comparison of the clinical effectiveness of belimumab with rituximab, it could not reach a conclusion as to the cost effectiveness of belimumab compared with rituximab as an add-on therapy in adults with active autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy. It further concluded that collecting data for belimumab and rituximab via the BILAG registry could provide data for a future comparison of the cost effectiveness of the 2 treatments when the NICE technology appraisal guidance on belimumab for systemic lupus erythematosus is reviewed.

- 4.28 The Committee discussed the innovative nature of belimumab. It specifically noted the comments from clinical experts and patient experts that few drugs are licensed for treating systemic lupus erythematosus, and the comment from the company that belimumab was developed to target the underlying pathology of this disease. The Committee also discussed whether any health-related quality-of-life benefits may not have been captured in the calculation of the QALY. It was aware that disease flares had not been fully included in the economic modelling and that the company stated that this could underestimate the benefits of treatment. The Committee noted that in the BLISS trials differences in EQ-5D were demonstrated between treatment groups but that this was not statistically significant at 52 weeks, the longest follow-up time for which quality-of-life data are available for the target population. Furthermore, there were no statistically significant differences at week 52 for FACIT-fatigue scores in the target population in people receiving belimumab compared with people

receiving standard care. The Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life from belimumab had not been adequately captured. The Committee concluded that the issues identified around innovation did not change its conclusions about the cost effectiveness of belimumab.

- 4.29 The Committee was aware of a potential equality 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.

Proposed managed access arrangements

- 4.30 The Committee discussed the general concept of a managed access arrangement, which described the arrangements and responsibilities for the use of and further data collection for belimumab for treating active autoantibody-positive systemic lupus erythematosus, would be useful. It reviewed the structure of the proposed managed access arrangement that had been developed. It concluded that this approach was a useful tool that should be used to achieve consensus among the key stakeholders in the event of a positive recommendation with further evidence collection in the NHS in England.
- 4.31 The Committee heard from the company that, if belimumab was recommended by the Committee, the NHS would be able to recruit people with active autoantibody-positive systemic lupus

erythematosus to the UK BILAG registry and collect real-world evidence on the safety and efficacy of belimumab to address the key uncertainties, including rates of discontinuation. The Committee noted that the data could inform a future comparison of belimumab and rituximab. The Committee considered the nature of the evidence that could be collected from the BILAG registry according to the company's proposal and whether this would be useful in future decision-making. The clinical experts acknowledged that observational registries have limitations, and that randomised controlled trials are the gold standard. However, the Committee heard from a clinical expert that there are challenges to conducting randomised controlled trials in this therapy area, such as the small number of patients in the UK and ethical constraints in balancing corticosteroid use, high-quality care and demonstrating a treatment effect. The clinical experts emphasised the value of the BILAG registry in providing real-world evidence from UK clinical practice. The Committee heard that few of the patients in the ongoing clinical trials are in the UK, and several of the studies have assessments that are less robust than the registry (for example, physician's global assessment of improvement). The Committee concluded that collecting data via the BILAG registry had the potential to provide additional data that could be useful in a future technology appraisal of belimumab, including a comparison with rituximab.

- 4.32 The Committee discussed the potential sample size and duration of treatment in the registry. The Committee heard that if belimumab were recommended, the clinical experts anticipated that 10–12 new patients receiving belimumab and 6–8 receiving rituximab would join the registry each month. It heard from NHS England that it would expect a licensed, NICE-recommended treatment to be prescribed over one used outside its marketing authorisation, but that the decision would ultimately come down to physician and patient choice. The Committee noted that if the research were

carried out for 3 years, and 10–12 patients were recruited each month, very few patients would have 3-year follow-up data at 3 years. The Committee concluded that a minimum of 3 years would be needed for data collection from the registry and that it was likely that up to 5 years would be needed to collect a meaningful dataset.

4.33 The Committee questioned the benefit of obtaining data from the registry over and above the existing ongoing trials and whether it was needed to inform a review of the guidance. It noted the DSU's opinion that, in relation to most uncertainties, the proposed evidence collection is ongoing in other existing studies. The Committee recalled that the company's economic modelling included a treatment continuation rule that specified belimumab would only be continued in people whose SELENA-SLEDAI score dropped by 4 points or more. It agreed that it was appropriate to introduce this continuation rule in clinical practice (see section 4.19). The Committee understood that belimumab discontinuation practice would therefore be expected to differ in UK clinical practice compared with non-UK trials, and agreed that the data captured should include dose and timing data, discontinuations and adherence to the treatment continuation rule. It agreed that the registry would provide useful data on the treatment continuation rule and would be unique in providing efficacy and safety data for the population affected by it. It also heard that, unlike the clinical trials, the registry would provide lupus-specific data on health-related quality of life. The Committee concluded that although the ongoing clinical trials could potentially address many of its uncertainties, the BILAG registry would provide some unique data, particularly on the treatment continuation rule.

4.34 The Committee queried whether there were any irrecoverable NHS costs associated with establishing the registry. It noted that there

would be clinician and administrator time involved in recruiting and following-up patients and in adding data to the database. However, it heard from the clinical experts that the registry has established funding and has already been set up with NHS England to provide data on existing treatments such as rituximab and standard care. The Committee concluded that there were no significant irrecoverable NHS costs associated with starting the belimumab research.

4.35 The Committee considered what might happen if belimumab were initially recommended (with further evidence collection) but, after a subsequent review of the technology appraisal guidance, was later found not to be cost effective. If belimumab was subsequently not recommended, the Committee considered that it would be clinically unacceptable for belimumab treatment to be withdrawn from all patients after 3 or 5 years. It noted the company's proposed exit strategy, which is confidential and cannot be included here. It emphasised the importance of ensuring high-quality care for patients, and considered that withdrawing belimumab, at an arbitrary time, from people whose disease was responding to the drug, would be both inappropriate and impractical. The Committee concluded that NHS England needed reassurance from the company about how a person's care would continue in these circumstances.

4.36 The Committee discussed whether belimumab met the criteria for recommending a treatment with research according to the [Guide to the methods of technology appraisal 2013](#). In considering each of these criteria, the Committee agreed the following:

- Data collected using the BILAG registry would inform the future development of NICE guidance and clinical practice on using belimumab.

- Reconsidering the decision in light of research findings would be likely to reduce the uncertainty in the economic model.
- The research will be feasible even if belimumab is recommended for NHS use outside the context of research.
- No significant irrecoverable costs would be incurred when introducing the technology.

The Committee concluded that this meant belimumab was a potential candidate for recommending with further evidence collection, but had reservations about the risks involved.

4.37 The Committee then explored whether the potential value to the NHS of the recommended research is likely to represent good value in the context of limited research resources. It noted that the company proposed funding the research and that NHS England would fund the provision of the technology in the NHS. The Committee considered the 'budget impact' cost comparison between belimumab and rituximab. It heard from the clinical expert that people tend to receive rituximab approximately every 12–15 months on average, and was aware that belimumab's marketing authorisation recommends continuous use. The Committee noted that it had been estimated that there was an additional cost of using belimumab rather than rituximab over 5 years, assuming 1 dose of rituximab per year and using belimumab continuously (that is, as recommended in belimumab's summary of product characteristics). The Committee recalled that it had heard from the clinical experts that belimumab could be used in a similar intermittent way to rituximab in clinical practice (see section 4.5). It considered that this would reduce the costs of belimumab compared with administering it as specified in the summary of product characteristics. The Committee agreed that the company's calculations could overestimate the cost of belimumab, depending on how it is used in clinical practice. The additional cost of using belimumab rather than

rituximab is confidential and cannot be presented here. The Committee concluded that in the context of limited research resources, the proposed research would represent good value, only if NHS England finds the financial arrangements acceptable compared with current alternative biological treatment options.

4.38 The Committee deliberated over making a recommendation on belimumab:

- It agreed that it was unable to conclude if the true value of the ICER incorporating the revised patient access scheme for belimumab compared with standard care was within or outside a range in which belimumab could be considered a cost-effective use of NHS resources (see section 4.26).
- It observed that the clinical and cost effectiveness of belimumab compared with rituximab could not be determined because of a lack of clinical evidence. The Committee recalled that rituximab, which does not have a marketing authorisation for systemic lupus erythematosus, was being routinely funded in the NHS via an interim clinical commissioning policy statement. It acknowledged that belimumab does have a marketing authorisation for treating systemic lupus erythematosus (see section 2.1). It considered that a comparison of the 2 treatments could be made when the guidance is reviewed, informed by evidence collected via the BILAG registry, which would include some unique data that would not be provided through ongoing clinical trials (see sections 4.27 and 4.33).
- It considered that collecting real-world data from UK patients had additional benefits to support the data generated in the global belimumab clinical trial programme, such as better generalisability of the patient population and standard care that more closely represents clinical practice in England (see sections 4.8, 4.10 and 4.31).

- It agreed that belimumab met the criteria for recommending a treatment with research according to [Guide to the methods of technology appraisal 2013](#) (see section 4.36).
- It believed that the proposed research would represent good value in the context of limited research resources, as long as NHS England found the financial arrangements acceptable compared with those for current alternative biological treatment options (see section 4.37).

Taking all of these factors into account, the Committee considered that it was appropriate to grant access to belimumab to enable further evidence collection to inform a comparison with rituximab and reduce the uncertainty in the company's economic modelling when the technology appraisal guidance is reviewed. The Committee concluded that it recommended belimumab as an option, with further evidence collection, for treating active antibody-positive systemic lupus erythematosus in people with evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and SELENA-SLEDAI score of greater than or equal to 10.

- 4.39 The Committee discussed the review of the technology appraisal guidance. It heard that it could take over 6 years to complete evidence collection, data analysis and re-appraisal. The Committee was aware that guidance is normally considered for review 3 years after publication. The Committee recalled that several ongoing trials would provide useful information to inform a re-appraisal, and that potentially many current areas of uncertainty could be addressed without the registry data. The Committee concluded that although the BILAG registry would provide some unique data, NICE should consider the technology appraisal guidance for belimumab for review 3 years after publication, as is standard, to determine whether the main uncertainties could be addressed using clinical

trial data, as well as any early registry data, available at that time. It further concluded that if a review was not considered appropriate at 3 years, a mandatory review should be done no later than 5 years after publication.

4.40 The Committee discussed the implications of belimumab getting a negative recommendation following re-appraisal. The Committee considered that issuing a positive recommendation in the context of a proposed managed access arrangement meant that there was a significant risk of NHS England paying for a treatment that was not cost effective, and noted that this risk could be borne for up to 6 years after guidance publication, depending on when additional data to inform a review become available. It believed that it was unacceptable for NHS England to bear all of this risk and considered it reasonable that NHS England and the company should establish a risk-sharing strategy in the proposed managed access arrangement. It further concluded that it would be inappropriate under these circumstances for belimumab to be withdrawn from patients who already had access in the NHS, and that NHS England and the company should agree an appropriate exit strategy.

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 recommended as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus in adults only if all of the following apply: <ul style="list-style-type: none"> • There is evidence for serological disease activity (defined as 		1.1

<p>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 despite standard treatment.</p> <ul style="list-style-type: none"> • Treatment with belimumab is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more. • The company provides belimumab with the discount agreed in the patient access scheme. • Under the conditions for data collection, monitoring, patient consent, cost to the NHS, and review by NICE as laid out in sections 5 and 6 of this document. 	
<p>As a condition of its positive recommendation, the Committee instructed that data on efficacy, safety and quality-of-life should be collected using the BILAG registry to resolve uncertainties in a future review of this technology appraisal guidance.</p>	<p>4.38, 6.1 – 6.3</p>
<p>The Committee agreed that, because of the considerable uncertainty that remained in the economic modelling, it was unable to conclude that the true value of the incremental cost-effectiveness ratio (ICER) incorporating the revised patient access scheme was within or outside a range in which belimumab could be considered a cost-effective use of NHS resources compared with standard care.</p>	<p>4.26</p>
<p>There are no data that would allow a robust calculation of the relative clinical efficacy of belimumab compared with rituximab. For the comparison of belimumab with rituximab the Committee concluded that, without any comparison of the clinical effectiveness of belimumab with rituximab, it could not reach a conclusion as to the cost effectiveness of belimumab compared with rituximab as an add-on therapy in adults with active autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy.</p>	<p>4.13 4.27</p>

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.	4.2
The technology		
Proposed benefits of the technology	The treatment might be corticosteroid sparing and may reduce the side effects of other drugs, especially corticosteroids.	4.2, 4.11, 4.12
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Few drugs are licensed for treating systemic lupus erythematosus. Belimumab was developed to target the underlying pathology of this disease. However, the Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life from belimumab had not been adequately captured.	4.28
What is the position of the treatment in the pathway of care for the condition?	Between 10% and 15% of people with systemic lupus erythematosus have high disease activity despite standard therapy. The Committee therefore concluded that standard care and rituximab should be	4.3

	comparators for belimumab.	
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 company's submission was from the 2 BLISS trials (BLISS-52 and BLISS-76) that compared belimumab against standard care.	4.7
	There are no data that would allow a robust calculation of the relative clinical efficacy of belimumab compared with rituximab.	4.13
Relevance to general clinical practice in the NHS	The Committee concluded that, although BLISS-76 was more representative of the population of England and Wales than BLISS-52, data from BLISS-52, and therefore from the pooled analysis, would be relevant.	4.8
Uncertainties generated by the evidence	The relevance of both the pooled and unpooled data from the BLISS trials to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, nature of standard of care and effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus.	4.8-4.11
Are there any clinically relevant subgroups for which	The company focused on a target population comprising a subgroup of the marketing authorisation population and BLISS clinical	4.6

<p>there is evidence of differential effectiveness?</p>	<p>trials. The target population was identified by a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10 and evidence of serological disease activity. The Committee concluded that, although specifying a SELENA-SLEDAI score of greater than or equal to 10 may be considered arbitrary, the specified target population is clinically relevant.</p>	
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee concluded that, compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the evidence of effect was observed with greater consistency across outcomes in the BLISS-52 trial. Further, the relevance of both the pooled and unpooled data from the 2 BLISS trials to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, nature of standard care and effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus.</p>	<p>4.11</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company submitted an economic model in which short-term outcomes from the BLISS studies were linked to long-term outcomes, using data from the Johns</p>	<p>4.14</p>

	Hopkins cohort.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The Committee accepted that attempting to link short-term outcomes to long-term outcomes was appropriate and recognised that there were limited data sources available with which to do this. However, it concluded that there was uncertainty about whether the equations derived from the Johns Hopkins data could be reliably applied to the target population because of differences in study populations.</p> <p>The Committee understood that continuous treatment over many years was unlikely to reflect how belimumab would be used in clinical practice. However, the summary of product characteristics for belimumab describes continuous use as the model for administration. Although the 6-year maximum treatment duration modelled by the company in its 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.</p> <p>The Committee concluded that the company may have underestimated the annual discontinuation rate in the original economic model, and therefore overestimated the ICER, and that a higher rate of annual</p>	<p>4.14</p> <p>4.15-4.16</p> <p>4.17 4.18</p>

	<p>discontinuation as observed in the phase II extension study may be more appropriate. The Committee was not persuaded that the proposed variable discontinuation rate of 13% for the first 5 years and 30% thereafter, as presented by the company, was plausible. The Committee heard from the NICE Decision Support Unit that the results of its survey of experts in lupus in the UK did not reduce the uncertainty surrounding the discontinuation rates or have more credibility than the estimates available from the BLISS or phase II extension studies. The Committee also heard from the clinical experts that, without any long-term evidence on the use of belimumab in clinical practice, it was difficult to provide estimates for the rate of discontinuation with belimumab. The Committee considered it preferable to use an annual discontinuation rate from the available trial data and understood that the phase II extension study was the only available long-term data source. The Committee concluded that it was more appropriate to use the ERG's rate of 11.7% annual discontinuation.</p> <p>There was still some uncertainty in the evidence about whether it was appropriate to assume that treatment effect was maintained over time. If treatment effect was not maintained over time, this would lead to an</p>	<p align="center">4.20</p>
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	<p>increase in the ICER.</p> <p>The Committee noted the ERG comments that, for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, it was assumed that at week 52 they had the mean benefit observed in the standard care group. The Committee concluded that the company’s approach may have overestimated the treatment effect of belimumab.</p> <p>Although gains in survival from reduced organ damage were plausible, there was considerable uncertainty around the validity of the modelled gains in survival.</p> <p>Deriving cost data from different sources may have led to some inconsistencies in the estimates and the company may have underestimated some of the benefits associated with delaying certain types of organ damage.</p>	<p>4.21</p> <p>4.22</p> <p>4.25</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been</p>	<p>The Committee also discussed whether any health-related quality-of-life benefits may not have been captured in the calculation of the quality-adjusted life years (QALYs). It was aware that disease flares had not been fully included in the economic modelling and that the company stated that this could underestimate the benefits of treatment. However, the Committee was not persuaded that the clinical evidence submitted strongly</p>	<p>4.28</p>

<p>identified that were not included in the economic model, and how have they been considered?</p>	<p>indicated that the changes in health-related quality of life from belimumab had not been adequately captured.</p>	
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The company focused on a target population, comprising a subgroup of the population covered by the marketing authorisation and the BLISS clinical trials. The target population was identified by a SELENA-SLEDAI score of greater than or equal to 10 and evidence of serological disease activity.</p>	<p>4.6</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee considered that the estimated ICERs with the revised patient access scheme may have been underestimated because of the uncertainties associated with the linking of short-term trial outcomes to long-term data with differing study populations, the discontinuation rate, the treatment effect, the mean benefit assumed for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, and validity of the modelled gains in survival that remained in the economic modelling.</p>	<p>4.26</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee agreed that, because of the considerable uncertainty that remained in the economic modelling, it was unable to conclude that the true value of the ICER</p>	<p>4.26</p>

	<p>incorporating the revised patient access scheme was within or outside a range in which belimumab could be considered a cost-effective use of NHS resources compared with standard care.</p> <p>The Committee concluded that, without any comparison of the clinical effectiveness of belimumab with rituximab, it could not reach a conclusion as to the cost effectiveness of belimumab compared with rituximab as an add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy.</p>	4.27
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health that would provide a simple discount to the list price of belimumab. The level of the discount is commercial in confidence.	2.3
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	4.29

	<p>erythematosus predominantly affects women of child-bearing age from ethnic minority groups. Given that the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations do not limit access to the technology for any specific group, compared with any other group.</p>	
<p>Other</p>	<p>The Committee concluded that collecting data via the BILAG registry had the potential to provide additional data that could be useful in a future technology appraisal of belimumab, including a comparison with rituximab.</p> <p>The Committee concluded that a minimum of 3 years would be needed for data collection from the registry and that it was likely that up to 5 years would be needed to collect a meaningful dataset.</p> <p>The Committee concluded that although the BILAG registry would provide some unique data, NICE should consider the technology appraisal guidance for belimumab for review 3 years after publication, as is standard, to determine whether the main uncertainties could be addressed using clinical trial data, as well as any early registry data, available at that time. It further concluded that if a review was not considered appropriate at 3 years, a review must be done no later than</p>	<p>4.31</p> <p>4.32</p> <p>4.39</p>

	5 years after publication.	
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5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has active autoantibody-positive systemic lupus erythematosus and the doctor responsible for their care thinks that belimumab is the right treatment, it should be available for use, in line with NICE’s recommendations.
- 5.4 The Department of Health and GlaxoSmithKline have agreed that belimumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about

the patient access scheme should be directed to [NICE to add details at time of publication].

5.5 Details of the dialogue between NHS England and GlaxoSmithKline about the costs of providing belimumab to NHS patients (during the period of data collection, during re-appraisal, and in case the re-appraisal is not positive), the cost of data collection through the BILAG registry, and the cost of conducting the required analyses at the end of the data collection period are included in the proposed managed access document that is available from GlaxoSmithKline.

5.6 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [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 data collection

6.1 As a condition of its positive recommendation, the Committee instructed that the following data should be collected using the BILAG registry to resolve uncertainties in a future review of this technology appraisal guidance:

- Efficacy data:
 - Clinical response measured by BILAG Index 2004 and SLEDAI-2K

- Organ damage accrual using the SLICC Damage Index and BILAG Index 2004
- Use of corticosteroids
- Safety data:
 - Incidence of serious adverse events: hospitalisation for infection, malignancy and death, other serious adverse events
- Patient-reported outcomes:
 - EQ-5D
 - SF-36
 - LupusQoL
- Other data:
 - Demographics (age, gender, ethnicity)
 - Belimumab treatment details: date started/stopped/ and restarted, dose and IV frequency, reason for discontinuation (as appropriate)
 - Lifestyle questionnaire (for example, drinking, smoking, employment status)
 - Patient diary (recording hospital admissions, visits to outpatients and medications)
 - Clinical serology – autoantibody profiles
 - Prior therapy
 - Concomitant medications
 - Comorbidities
 - Laboratory parameters.

6.2 The Committee specified that initial assessment in the BILAG registry should take place before starting a new biological treatment, or at re-treatment. Further clinical assessment should be undertaken at 3, 6 and 12 months then annually thereafter. Questionnaires should be given to patients every 6 months for 2 years then annually thereafter.

- 6.3 The Committee expects the proposed managed access arrangement to include a section detailing specific requirements for patient consent.
- 6.4 The Committee acknowledged the company's post-marketing commitment to investigate intermittent treatment with belimumab including time to flare from withdrawal of treatment and response to belimumab at re-treatment, and considered that these studies would be of value.

7 Related NICE guidance

Details are correct at the time the final appraisal determination goes out for appeal and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

There is no related NICE guidance for this technology.

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators. If a review 3 years after publication is not considered appropriate, there will be a mandatory review no later than 5 years after publication.

Gary McVeigh
Chair, Appraisal Committee
May 2016

9 Appraisal Committee members and NICE project team

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 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

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

Professor Gary McVeigh (Chair)

Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)

GP, West Coker Surgery, Somerset

Dr Aomesh Bhatt

Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black

General Practitioner, Mortimer Medical Practice, Herefordshire

Professor David Bowen

Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Ian Campbell

Honorary Consultant Physician, Llandough Hospital, Cardiff

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Dr Alexander Dyker

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

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor John Henderson

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

Dr Malcolm Oswald

Lay member

Professor Femi Oyeboade

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

Dr Mohit Sharma

Consultant in Public Health, Public Health England

Dr Murray D Smith

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

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Richard Diaz, Martyn Burke, Ian Watson and Linda Landells

Technical Leads

Zoe Garrett and Matthew Dyer

Technical Advisers

Kate Moore

Project Manager

10 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)

The NICE Decision Support Unit (DSU) report for this appraisal:

- Tappenden P, Wailoo A, Stevens J et al. Eliciting estimates of long-term treatment discontinuation rates (June 2013)

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 make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- GlaxoSmithKline

II. Professional/expert and patient/carer groups:

- Lupus UK
- National Kidney Federation
- British Association of Dermatologists
- British Health Professionals In Rheumatology
- British Renal Society
- British Society for Rheumatology
- Primary Care Rheumatology Society

- Renal Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III. Other consultees:

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

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

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

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

- Professor David Isenberg, Academic Director of Rheumatology, University College London, nominated by British Society for Rheumatology – clinical expert.
- Dr Liz Lightstone, Consultant Renal Physician, nominated by Renal Association – clinical expert.
- 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.

C. 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 invited to comment on the ACD.

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

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

- GlaxoSmithKline