This briefing presents the key issues arising from the manufacturer’s submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:

- confirm that the target population defined in the manufacturer’s decision problem is a subgroup of the expected licensed population
- further explain why a comparison against rituximab could not be undertaken quantitatively, and describe any approaches and provide any analyses undertaken to attempt to compare the treatments quantitatively
- provide further trial data on the target population, including: demographics; baseline disease characteristics; systemic lupus erythematosus (SLE) manifestations at baseline; SLE improvements by organ system; results of the efficacy endpoints and mean of the change in Safety of Estrogen in Lupus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score
- clarify how standard care in the trials relates to that in the UK for the high disease activity population and how it differs between trial centres
- provide a table listing all the model assumptions
- explain why the incremental cost-effectiveness ratio (ICER) reduces with the age of the patient
- clarify the reasons for non-responder status and what has been assumed for belimumab non-responders in terms of changes in their SELENA-SLEDAI score and steroid dose over time
- provide patient numbers continuing treatment, and the patient numbers continuing with treatment by responder status.
Licensed indication
Belimumab (Benlysta, GlaxoSmithKline) has a marketing authorisation as add-on therapy in adult patients with active autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy.

Disease overview
SLE is an autoimmune rheumatic disease. It affects the skin and joints, but more serious manifestations can involve the lungs, heart, central nervous system and kidneys. The key aspects of SLE that affect patients’ health-related quality of life include: disease flares, with symptoms such as joint and muscle pain, skin rash, and fever; chronic fatigue or malaise; and in more severe disease, the morbidity associated with organ damage and the side effects associated with corticosteroid therapy.

Key issues for consideration

Clinical effectiveness

- The manufacturer’s submission focused on a subgroup of the licensed indication (defined as the target population). The target population includes patients with positive anti-dsDNA, low complement and a SELENA-SLEDAI score of equal to or greater than 10. Is the target population appropriate and identifiable in clinical practice?
- The Belimumab International SLE Study (BLISS) clinical trials included patients with a broader set of characteristics than both the marketing authorisation and the target population. Can inferences be made about the effectiveness of belimumab in the target population based on the clinical trial data?
- The two BLISS clinical trials were completed in different geographical regions and enrolled patients with differing characteristics.
  - Is it appropriate to pool the phase III data from the BLISS studies?
Are the trial results from the pooled data generalisable to a UK setting?

- The patients in the BLISS trials had a relatively narrow range of SLE manifestations (mainly restricted to musculoskeletal and mucocutaneous problems). Can the effect of belimumab be applied to all SLE manifestations?
- The manufacturer provided a quantitative analysis comparing belimumab with standard care from the BLISS trials. No such analysis was considered possible for the comparison of belimumab with rituximab; instead a narrative comparison was presented.
  - Is rituximab an appropriate comparator, or should it be standard care?
  - For the comparison with standard care, how should standard care be defined, are the BLISS trials representative of standard care in the UK?
  - For the comparison against rituximab, are the manufacturer’s reasons for not providing an indirect or mixed treatment comparison considered acceptable?
  - What inferences can be drawn about the relative effectiveness of belimumab in comparison with rituximab?

Cost effectiveness

- Does the manufacturer’s model adequately represent the natural history of SLE and the likely effect of treatment with belimumab on the condition?
- The ERG raised a number of uncertainties about the estimation of the effect of belimumab and calculation of costs. Does the Committee consider that the calculation of costs and effects is appropriate?
- The model includes assumptions about the maintenance of treatment effect, and treatment continuation and discontinuation.
  - Can it be assumed that treatment effect is maintained over time?
  - Is an annual rate of 8% natural discontinuation considered appropriate?
  - Is the use of a continuation rule of a change equal to or greater than 4 points in SELENA-SLEDAI score at 24 weeks appropriate?
• The manufacturer’s model draws on data from a range of sources including the literature and an observational cohort from Johns Hopkins University.
  - Is the use within the model of the Johns Hopkins cohort for predicting the natural history of the disease appropriate?
  - Are the other estimates from the literature (such as those used for the standard mortality ratios) considered appropriate?
• The manufacturer has agreed a patient access scheme with the Department of Health. How does the patient access scheme affect the cost effectiveness of belimumab?
• A comparison of costs of belimumab and rituximab is provided. If belimumab is compared with rituximab, what relative cost effectiveness between the two treatments is expected?
1 Decision problem

1.1 Decision problem approach in the manufacturer’s submission

<table>
<thead>
<tr>
<th>Population</th>
<th>Evidence was provided on two populations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Phase III trial population: adults with active autoantibody-positive SLE.</td>
</tr>
<tr>
<td></td>
<td>• High disease activity subgroup: adults with active autoantibody-positive SLE with evidence for serological disease activity (low complement, positive anti-dsDNA) and SELENA-SLEDAI ≥10.</td>
</tr>
</tbody>
</table>

| Intervention | Belimumab 10 mg/kg administered as an intravenous infusion over a 1-hour period on days 0, 14 and 28, and at 4-week intervals thereafter in addition to standard therapy. |

<table>
<thead>
<tr>
<th>Comparators</th>
<th>There were two comparators:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Standard care, which comprises (alone or in combination): antimalarials, non-steroidal anti-inflammatories [NSAIDs], corticosteroids, or other immunosuppressants (azathioprine, methotrexate, and mycophenolate mofetil).</td>
</tr>
<tr>
<td></td>
<td>• Rituximab plus standard care, for the more severe SLE subgroup.</td>
</tr>
</tbody>
</table>

| Outcomes | Disease activity, incidence and severity of flares, mortality, health-related quality of life, disease progression in terms of long-term organ damage, fatigue and adverse events of treatment. |

| Economic evaluation | The cost-effectiveness of belimumab was expressed as a cost per quality-adjusted life year (QALY). A lifetime time horizon was used. Costs were considered from an NHS and PSS perspective. |

1.2 Evidence Review Group comments

1.2.1 Population

The ERG explained that the decision problem in the manufacturer’s submission specified two populations: the phase III trial population (adults with active autoantibody-positive SLE), and a high disease activity subgroup.
There was also a third population, the population proposed in the marketing authorisation, but this was not covered in detail in the submission.

The high disease activity subgroup was termed the ‘target population’ and was the focus of the manufacturer’s submission. The identification of the target population, and the evidence for clinical effectiveness of belimumab in the target population, came from post hoc analyses of the two BLISS trials. The target population represented a subpopulation (~64.5%) of the population covered by the expected marketing authorisation. The target population was defined as ‘Adults with active autoantibody-positive SLE with evidence for serological disease activity (low complement, positive anti-dsDNA) and SELENA-SLEDAI ≥ 10′ (manufacturer’s submission, page 53).

1.2.2 Intervention

The intervention described in the manufacturer’s submission matches that in the final scope issued by NICE.

1.2.3 Comparators

The manufacturer’s submission did not quantitatively consider rituximab or cyclophosphamide as comparators; only standard care was formally assessed. The manufacturer’s submission did not quantitatively compare rituximab and belimumab because there has been no head-to-head trial of rituximab versus belimumab; outcome measures used in rituximab and belimumab trials differ to the extent that there is little possibility of undertaking meaningful indirect comparison. A comparison was made of the costs of belimumab (with the application of a patient access scheme) and rituximab, assuming equal efficacy. The manufacturer noted that this may be a conservative assumption given that the trial of rituximab did not achieve statistical significance compared with placebo.

The manufacturer did not consider that cyclophosphamide was a suitable comparator because, while it is used in the more severe SLE patient
population, it is largely reserved for the treatment of lupus nephritis (which is not the proposed target population for belimumab).

1.2.4 Outcomes

The ERG considered that the manufacturer’s decision problem matches the scope issued by NICE, because it includes the outcome measures: disease activity, incidence and severity of flares, mortality, health-related quality of life including fatigue, and adverse effects of treatment. A novel composite outcome measure called the SLE Responder Index (SRI) was developed and was the primary outcome measure used in the phase III clinical trials.

1.2.5 Economic evaluation

The ERG found that the manufacturer’s economic analysis was in line with that stipulated in the scope. The manufacturer’s submission presented its economic assessment in terms of incremental cost per QALY and modelled outcomes using a lifetime horizon. Costs were considered from an NHS and PSS perspective.

1.2.6 Other relevant factors

The ERG noted that special considerations and issues raised in the manufacturer’s decision problem include: the innovative nature of belimumab for SLE; the insensitivity of the utility measure used for capturing health-related quality of life of SLE patients; and the impact of SLE on particular ethnic groups and on women of childbearing age. The ERG noted that these issues were not included in the final scope as issued by NICE, and that the draft Summary of Product Characteristics specifies that belimumab should not be administered to pregnant women or those planning pregnancy.
2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer’s submission

The manufacturer identified two phase III clinical trials for inclusion in its submission to NICE. The BLISS-52 and BLISS-76 trials were randomised, double-blind, placebo-controlled, parallel group studies with follow-up of 52 weeks and 76 weeks respectively. In the trials, belimumab plus standard care was compared with placebo and standard care. Standard care included: antimalarials, NSAIDs, corticosteroids or other immunosuppressants (azathioprine, methotrexate, and mycophenolate mofetil) either alone or in combination (see table A12.1 in the clarification response). In the BLISS-52 trial, 290 people received belimumab 10 mg/kg, 288 received belimumab 1 mg/kg and 287 received placebo. In the BLISS-76 trial, these were 273, 271 and 275 people respectively. Although each of the BLISS trials were three arm trials, only results for the 10 mg/kg belimumab dose are presented in the manufacturer’s submission because this is the dose submitted for marketing authorisation. Belimumab was administered by intravenous infusion on days 0, 14 and 28, and every 28 days thereafter, for 48 weeks in BLISS-52 and for 72 weeks in BLISS-76.

Adult patients (aged 18 years or older) who met the American College of Rheumatology criteria for SLE and had active disease (score 6 or more at screening on SELENA-SLEDAI) were eligible for enrolment in the BLISS trials. In addition, patients had to have unequivocally positive antinuclear antibody (titre 1:80 or more) or anti-dsDNA antibody (30 IU/ml or more), and to have been on a stable treatment regimen for at least 30 days before the first study dose. Patients with severe active lupus nephritis or central nervous system lupus were excluded. Of the trial populations, 52% met the criteria for the marketing authorisation (that is, had positive anti-dsDNA and low complement) and 34% (n = 396) met the criteria for entering the high disease
activity subgroup (that is, had positive anti-dsDNA and low complement and SELENA-SLEDAI of 10 or more). The patient characteristics and results for the manufacturer’s target population, that is the high disease activity subgroup, are described in this premeeting briefing.

Baseline demographics of the patient population can be found in table A3.1 of the manufacturer’s clarification response. In summary, the BLISS-52 trial recruited people from the Americas’ excluding the USA and Canada, from Asia and from Eastern Europe, whereas the BLISS-76 trial recruited people from the USA, Canada, Europe (Western and Eastern) and Israel. In the BLISS-52 trial, the majority of people were Asian or of Hispanic origin, whereas in the BLISS-76 trial the majority of people were white. Over 90% of the people included in the trials were female and the majority (>80%) were aged 45 years or younger.

In both trials, over 90% of the participants had at least 1A or 1B British Isles Lupus Assessment Group (BILAG) involvement and over 60% had at least 1A or 2B involvement. Mean SELENA-SLEDAI score was approximately 13 in both trials. Approximately 85% of people in the trials had a Physician’s Global Assessment (PGA) score of between 1 and 2.5. Average prednisolone dose was between 10 mg/day and 14 mg/day.

2.1.1 Results

The primary outcome of both studies was the response rate at week 52, assessed with SRI. With the SRI criteria, a responder was defined as having: a reduction of at least 4 points in the SELENA-SLEDAI score (defined as clinically meaningful); no new BILAG A organ domain score; no more than 1 new BILAG B organ domain score; and no worsening in PGA score (increase of less than 0.3) at week 52 compared with baseline (see appendix B). Figure 1 shows the differences in SRI response between the different subgroups.
The major secondary outcomes were: percent of patients with a 4-point reduction or more in SELENA-SLEDAI at week 52; mean change in PGA at week 24; percent of patients with prednisone (equivalent) reduction 25% or more from baseline to 7.5 mg/day or less during weeks 40–52 (in patients whose prednisone equivalent dose was more than 7.5 mg/day at baseline); and mean change in SF-36 Physical Component Summary at week 24. In BLISS-76, SRI at week 76 was also assessed.

![Figure 1 SRI response at week 52 by subset of trial participants. Adapted from figure 5.3 of the manufacturer’s submission (page 96)](image-url)

The results for the high disease activity subgroup from the two trials and the combined trial data are shown in table 1. For the primary outcome of SRI at 52 weeks, statistically significant differences were observed between the belimumab arm and standard care arm in both trials and within the combined analysis. In the combined analysis, 63% of the participants in the belimumab arm, compared with 38% of the standard care arm, were responders.
according to the SRI criteria, with an odds ratio (OR) of 2.7 (95% confidence interval [CI]: 1.8–4.1). The BLISS-76 trial demonstrated that a statistically significant difference in response rate between the arms of the trial remained after 76 weeks, with an OR of 2.1 (95% CI: 1.1–3.9).

Table 1 Efficacy endpoints. Adapted from table A6.1 of the manufacturer’s clarification responses, n (%). Bold indicates statistically significant result (p < 0.05)

|                  | BLISS-52                  | BLISS-76                  | Combined BLISS
|------------------|---------------------------|---------------------------|---------------------------
|                  | SC (n = 107)               | Bel (n = 112)              | SC (n = 96)               | Bel (n = 81)              |
| SRI at week 52   | 44 (41.1%)                 | 75 (67.0%)                | 33 (34.4%)                | 46 (56.8%)                |
|                  | (95% CI)                   | (95% CI)                  | (95% CI)                  | (95% CI)                  |
|                  | 3.0 (1.7, 5.2)             | 2.7 (1.8, 4.1)            | 2.5 (1.3, 4.6)            |
| SRI at week 76   | –                          | –                          | 30 (31.3%)                | 40 (49.4%)                |
|                  | –                          | –                          | (95% CI)                  | (95% CI)                  |
|                  | 2.1 (1.1, 3.9)             | –                          | –                          | –                          |
| SLEDAI           |                            |                            |                            |
| (reduction 4 or more) | 47 (43.9%) | 76 (67.9%) | 37 (38.5%) | 49 (60.5%) |
|                  | (95% CI)                   | (95% CI)                  | (95% CI)                  | (95% CI)                  |
|                  | 2.8 (1.6, 4.8)             | 2.5 (1.3, 4.4)            | 2.4 (1.3, 4.4)            |
| No new           |                            |                            |                            |
| BILAG 1A/2B      | 68 (63.6%)                 | 88 (78.6%)                | 57 (59.4%)                | 57 (70.4%)                |
|                  | (95% CI)                   | (95% CI)                  | (95% CI)                  | (95% CI)                  |
|                  | 2.3 (1.2, 4.2)             | 1.6 (0.9, 3.1)            | 1.6 (0.9, 3.1)            |
| No worsening in PGA | 64 (59.8%) | 86 (76.8%) | 55 (57.3%) | 58 (69.1%) |
|                  | (95% CI)                   | (95% CI)                  | (95% CI)                  | (95% CI)                  |
|                  | 2.3 (1.3, 4.2)             | 1.6 (0.9, 3.0)            | 1.6 (0.9, 3.0)            |
| Prednisone usagea | 4 (5.3%)  | 15 (15%)    | 5 (10.0%)  | 5 (11.1%)  |
| (n at risk)      | (n = 76)                   | (n = 81)                  | (n = 50)                  | (n = 45)                  |
|                  | (95% CI)                   | (95% CI)                  | (95% CI)                  |
|                  | 4.11 (1.29, 13.2)          | 0.88 (0.21, 3.60)         | 20 (15.9%)                |
|                  | (n = 50)                   | (n = 45)                  | (n = 126)                 |
|                  | 2.43 (1.05, 5.65)          | 9 (7.1%)                  | 20 (15.9%)                |
|                  | (n = 126)                  | (n = 126)                 | (n = 126)                 |

* Prednisone reduction by 25% or more from baseline to 7.5 mg/day or less during weeks 40–52.
Bel, belimumab; BILAG, British Isles Lupus Assessment Group; OR, odds ratio; PGA = Physician’s Global Assessment; SC, standard care; SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment trial – Systemic Lupus Erythematosus Disease Activity Index; SRI, SLE Responder Index.

For the components of the SRI, a greater number of patients had a reduction of at least 4 points in the SELENA-SLEDAI score in the belimumab arm compared with the standard care arm, in both trials. In the combined BLISS data set, 65% of patients had a reduction of at least 4 points in the SELENA-SLEDAI score compared with 41% in the standard care arm, with an OR of 2.6 (95% CI: 1.7–3.9), which is statistically significant.
For the outcomes no new BILAG 1A/2B, no worsening in PGA, and prednisone usage, trial results from BLISS-52 showed a statistically significant difference between treatment groups, whereas trial results from BLISS-76 did not. The combined data from both trials showed that overall there is a statistically significant difference between the treatment groups.

For the group of people who were black (defined as African American or African heritage) the percentage meeting the primary endpoint was higher in the placebo group (44%) than in the belimumab arm (36%). This compares with the overall rate of response, which was 39% in the placebo group and 51% in the belimumab group (see table 5.21 in the manufacturer’s submission, page 140). For all other races, the belimumab group responded in the expected direction.

Quality-of-life measures, the SF-36 (p117 of the manufacturer’s submission) and EQ-5D (p132 of the manufacturer’s submission), were also collected during the two phase III trials as secondary outcomes. At week 24, a significant mean change from baseline EQ-5D index was reached in the belimumab arm compared with the placebo arm, but this was not maintained at week 52. The pooled trial data for the high disease activity subgroup showed no significant difference in mean SF-36 physical component summary score between the arms of the trial at weeks 24 or 52.

2.1.2 Adverse effects

Adverse event data were taken from the entire dataset (that is, not just the high disease activity subgroup) from the two phase III clinical trials and from a phase II trial. Over 90% of patients in each arm experienced at least one adverse event. Serious adverse events were experienced by 17% in the 10 mg/kg belimumab group, compared with 16% in the placebo group. Across the double-blind treatment periods, there were 14 deaths, including 3 (0.4%) in the placebo groups, and 6 (0.9%) in the 10 mg/kg belimumab groups. Infections were the most frequent event leading to death in all treatment
The most frequent (occurring in more than 10% of patients) events were headache, upper respiratory tract infection (URTI), arthralgia, nausea, urinary tract infection (UTI), diarrhoea, and fatigue. Of these events, only diarrhoea and nausea occurred slightly more frequently in the belimumab groups. There were four infection-related deaths, one with placebo, one with 1 mg/kg belimumab and two with 10 mg/kg belimumab, and infection may have contributed to the deaths of two further patients (one each of 1 mg/kg and 10 mg/kg). There were two suicides, both in patients receiving belimumab (one each of 1 mg/kg and 10 mg/kg), and one cancer-related death in a patient receiving 1 mg/kg belimumab (likely pre-existing condition). In the long-term open-label extension of the phase II trial (LBSL99), the incidence of adverse events and severe adverse events remained stable or declined over time through 5 years of exposure.

### 2.1.3 Comparison against rituximab

The manufacturer explained that many patients with more severe, highly active SLE routinely receive rituximab. However, no studies were identified that directly compare belimumab with rituximab. In a study identified by the manufacturer, which compared rituximab with placebo (the EXPLORER trial), no difference was noted in major clinical responses or partial clinical responses between the rituximab group (12.4% had a major clinical response, and 17.2% had a partial clinical response) and the placebo group (15.9% had a major clinical response, and 12.5% had a partial clinical response) relative to the overall response rate (29.6% versus 28.4%). In addition, the rituximab trial demonstrated no difference in secondary endpoints between the rituximab group and the placebo group over 52 weeks of treatment, in patients with moderate-to-severe SLE. The manufacturer stated that differences in the endpoints considered and the patient populations precluded the conduct of any meaningful indirect and mixed treatment comparisons between the belimumab and rituximab studies (see section 5.7, page 143 of the manufacturer’s submission, and clarification response A2).
The manufacturer also provided data assessing the efficacy and safety of rituximab as part of an analysis of a prospective observational data registry from France. Overall response, defined as a reduction in SELENA-SLEDAI score of 3 or more measured over a period of 6 ± 3 months, was observed in 80 of 113 patients (71%). Efficacy was not found to differ significantly depending on whether patients received rituximab monotherapy or rituximab combination therapy.

2.2 Evidence Review Group comments

2.2.1 Clinical effectiveness

The ERG highlighted a number of concerns with the methods used to conduct the systematic review. However, it concluded that studies relevant to the decision problem had been identified and the studies representing belimumab appeared complete.

The proposed licensed population and the high disease activity target population that formed the focus of the clinical effectiveness evidence were subgroups identified from post hoc analyses aimed at identifying patients with the greatest response to belimumab in the pooled phase III trial populations. The ERG considered that the results from these trials should be viewed with some caution, as the observed results from the BLISS trials may not be the same as those that would have been seen from a randomised controlled trial in which only the target population was studied.

The ERG explained that the SRI had been developed in consultation with the US Food and Drug Administration and designed to avoid the possibility that improvement in some particular SLE manifestation or manifestations might mask deterioration in overall disease activity or involvement of new organ damage. The ERG considered that this was a positive aspect of the manufacturer’s approach. However, the ERG highlighted that according to
expert clinical opinion the SELENA-SLEDAI (a component of the SRI) is not commonlly used to define high disease activity in clinical practice.

The ERG considered that while both trials included adults with active autoantibody-positive SLE, the population in BLISS-76 is more likely to be similar to that in England and Wales than that in BLISS-52, and so the results from BLISS-76 may be more generalisable to the UK. The ERG found that for the target population the results from the BLISS-52 trial were more favourable to belimumab than those from BLISS-76 and additionally BLISS-52 provided more patients to the pooled target population than BLISS-76 (55% versus 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 patient populations in England and Wales.

The ERG identified that the primary endpoint (52-week SRI) was statistically significant (p < 0.05) in both the two phase III randomised controlled trials. In BLISS-76, of the five pre-specified secondary endpoints, a statistically significant reduction in SELENA-SLEDAI score of 4 points or more at week 52 was shown; however, none of the other major secondary outcomes were found to be statistically significant. In addition, none of the other submitted secondary outcomes were found to be statistically significant, including: time to first flare, time to first severe flare, change in Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) organ damage score at week 52, fatigue status (FACIT change from baseline), and quality of life (EQ-5D change).

A literature search undertaken by the ERG revealed published information on SLEDAI and SF-36 changes in the EXPLORER trial which could have been used for comparison with the BLISS trials. In addition, randomised controlled trials for both rituximab and belimumab recorded BILAG changes, thus offering the potential for undertaking an indirect comparison.
2.3 **Statements from professional/patient groups and nominated experts**

SLE was described as a rare disease with a small patient population, which is ideally managed in specialist clinics. It was explained that there is a real need for new agents in the treatment of lupus – no drug has been licensed for over 50 years, the only licensed drugs are prednisolone and hydroxychloroquine and there are no licensed products for people with severe disease.

European guidelines exist on management principles of SLE, but there is likely to be variation in the treatment of SLE. SLE is treated according to the severity of the disease, both globally and depending on which organ systems are involved. Treatment ranges from symptomatic to immunomodulatory to immunosuppressive. With more overt arthritis and pleuritic pain, for example, moderate doses of corticosteroids (10–20 mg per day), together with a drug like azathioprine and/or methotrexate are widely used. The more serious manifestations, particularly renal disease, are often treated with high doses of steroids (20 mg or more) and mycophenolate or intravenous cyclophosphamide. Rituximab is used in refractory disease.

Belimumab is thought to be appropriate for people with moderate to severely active seropositive disease, particularly people with refractory disease or for those intolerant to existing treatments, and also those who have been on high doses of corticosteroids for many years. Possible subgroups of patients include: certain ethnic groups, particularly those with aggressive disease (such as with renal involvement) at diagnosis and patients who present late with existing disease damage.

It was considered that administration of belimumab would require: day-case stay on a monthly basis for an intravenous infusion; monitoring during infusions; and training for staff in the use of belimumab.
Treatment with belimumab may reduce the steroid dose that is needed and/or may reduce the need for increases in steroid doses. Steroids are used in all treatment regimens for lupus of any severity but are thought to be the cause of much of the long-term damage accrued in patients with lupus and may account for a significant part of the increased risk of premature cardiovascular disease in patients with lupus. It was thought that any agent with proven steroid sparing/reduction capability in SLE is likely to have short- and long-term benefits.

Alternative treatments to belimumab include rituximab and cyclophosphamide. According to the professional submissions, there is a sense that rituximab is an effective agent, particularly for refractory disease, but it failed to show effect in two randomised controlled trials. Nevertheless, the submissions point out that in clinical practice, rituximab has shown promising results, especially in those with renal lupus. Rituximab is payment by results (PbR) excluded, so the decision to fund it is subject to local funding decisions and is based on whether there is exceptional case for a specific patient. Cyclophosphamide has major disadvantages, especially for the treatment of young women, as the side effects include infection, bone marrow toxicity, and infertility.

The two BLISS studies that provide the evidence base for belimumab are thought to have been well conducted, undertaken in diverse geographical settings and in patients being treated with local standard care, and so are thought to reflect UK current practice. The trials were conducted on a large scale and belimumab was shown to meet its primary endpoints. However, belimumab has principally been used to treat patients with mucocutaneous, musculoskeletal and respiratory problems: it has not yet been established how effective it will be in treating patients with renal or cerebral disease.

Two issues were identified in the design of the clinical trials. The first was that concomitant medications were limited within the trial (ACE inhibitors or angiotensin receptor blockers and statins to reduce cholesterol). The second
issue was in the use of the SRI to evaluate outcomes, which is a composite responder index involving clinical scoring that is not routinely used. However, there is recognition that such scoring is required and the introduction of a more formal, systematic assessment of disease activity and damage is likely to have a secondary impact of improving the standard of care for these patients (by focusing clinicians on outcome), regardless of drug utilisation.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer’s submission

The manufacturer identified no relevant studies on the cost effectiveness of belimumab in its review of the literature. Therefore the manufacturer developed a de novo decision-analytic model. The model is a micro-simulation model that incorporates the interaction between: patient characteristics, disease activity, medication (corticosteroid use), risk of organ damage development (a patient with SLE could potentially develop damage in 12 different organs) and mortality, as shown in figure 2.

Figure 2 Schematic overview of interdependencies between baseline characteristics, treatment and outcomes in the microsimulation model. Adapted from figure 6.2 of the manufacturer’s submission
3.1.1 Model states

The model states (see figure 3) are informed by data from the BLISS trials, observational cohort data, and other data from the literature.

A patient's baseline characteristics are simulated based on the population characteristics in the BLISS trials including: age, gender, ethnicity, SLE disease duration, SLICC damage index (SDI) score and SELENA-SLEDAI score (see section 6.3, page 186 of the manufacturer’s submission for further details). They then enter the model in which their lifetime SLE history is simulated. A patient is 'cloned' and enters both the belimumab 10 mg/kg and standard care treatment arms and then works through the model cycle as shown in figure 3. As well as the baseline population characteristics, the BLISS clinical trials inform the likelihood of response at week 24 (based on a patient demonstrating a SELENA-SLEDAI score decrease of 4), the change in SELENA-SLEDAI score up to week 52, likelihood of discontinuation and the effect of SELENA-SLEDAI score on utility and treatment costs (see summary of data sources on page 93 of the ERG report).
Figure 3 Patient flow through the micro-simulation model. Adapted from figure 6.3 of the manufacturer's submission

*a if inadequate response to belimumab, the patient switches to standard care and continues through the model’s yearly cycles on standard care until death
To inform other model states, prediction models are used based on data from the Johns Hopkins cohort. These are used to predict: change in mean SLEDAI score (which is used as a proxy for SELENA-SLEDAI score), average steroid dose per year, risk of organ damage and risk of death. The Johns Hopkins lupus cohort reports data on a large population of SLE patients from Baltimore, Maryland. Patients in the Johns Hopkins cohort visit the clinic every 3 months from cohort entry. 765 participants were excluded from the analysis, leaving a final sample size of 1282 patients. Of these, 93% were female, and 52% were white, and 38% of black ethnicity. Mean (standard deviation (SD)) age at diagnosis was 33 (13) years and mean age of entry into the study was 38 (13) years. SLEDAI score at first visit was 3.32 (3.7). See table 6.7 of the manufacturer’s submission (page 198) for further details.

Further 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 each organ involvement.

For a patient entering the model and assigned to either belimumab or standard care, it is first determined whether the patient survives for that year. This is based on data from the Johns Hopkins cohort adjusted by standardised mortality ratios from the literature. For a surviving patient on belimumab, it is then established whether the patient continues belimumab medication. In the model belimumab treatment can be stopped due to natural discontinuation or insufficient response after the first 6 months. Figure 4 shows the estimated percentage of patients on belimumab through time.
Figure 4 Discontinuation from belimumab (including death). Adapted from figure 6.35 of the manufacturer's submission

Having determined continuation of belimumab, disease activity is updated in the model. In the first year of the simulation, the effects on disease activity measured by SELENA-SLEDAI score as observed in the BLISS trials are applied. A linear regression model based on data from the BLISS trials was used to predict the change in SELENA-SLEDAsi score at 52 weeks. For subsequent cycles, disease activity is predicted using regression equations based on the natural history data from the Johns Hopkins cohort.

For each organ system contained within the SLICC Damage Index (SDI) (see appendix B), the probability of damage during that year is calculated based on the patient’s characteristics and disease activity at that time based on Johns Hopkins data (see table 6.14 in the manufacturer’s submission, page 212).

3.1.2 Model inputs

Average costs and utilities calculated from regression analyses are assigned to a patient’s health state for that particular year. Costs and utilities are then recorded together with clinical outcomes for that patient. Time is then
increased by 1 year and the process is repeated for the lifetime of the patient. These yearly cycles continue until a patient dies. Utilities and costs are discounted at 3.5%. A NHS and PSS perspective was adopted. Adverse events were not included in the model because the trials did not find any important differences between the incidence of adverse events in treatment groups in the BLISS trials.

Mean EQ-5D from the BLISS trials was 0.70 (SD = 0.26) and this was used to inform the baseline utilities in the economic model. The baseline quality of life assumed in the cost-effectiveness analysis was determined by the following regression equation, which was derived from the BLISS trials:

\[ U = 1.275 - 0.140 \log_e (\text{AGE}) - 0.036 \times \text{BLACK} - 0.009 \times \text{SS} \]

where \( \text{AGE} \) is the current age of patient, \( \text{BLACK} \) is 1 if a patient is of black African ethnicity, or 0 otherwise, and \( \text{SS} \) is the SELENA-SLEDAI score during the particular model yearly cycle. The above equation was used to determine a patient’s utility (\( U \)) without organ damage.

Disutility multiplier values for each type of organ damage were identified from a search of the literature (see table 2). These disutility multipliers were applied to \( U \) if a patient had developed organ damage in the model cycle. The lowest disutility was used if multiple organs were involved. For example, for a black African SLE patient aged 40 years at entry with a SS score of 10, the baseline utility using the equation above is 0.63. If this person has ocular organ damage, this would give a disutility multiplier of 0.97 (as can be seen from table 2). So the utility for this person would be calculated as 0.63*0.97 = 0.61.
Table 2 Summary of disutility multipliers for the cost-effectiveness analysis. Adapted from table 6.19 of the manufacturer’s submission

<table>
<thead>
<tr>
<th>Organ damage type</th>
<th>Disutility multipliers year</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2a</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.72</td>
<td>0.76</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.91</td>
<td>0.91</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.79</td>
<td>0.91</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0.67</td>
<td>0.74</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>0.68</td>
<td>0.71</td>
</tr>
<tr>
<td>Ocular</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>0.86</td>
<td>0.92</td>
</tr>
<tr>
<td>Premature gonadal failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.69</td>
<td>0.69</td>
</tr>
<tr>
<td>Renal</td>
<td>0.97</td>
<td>0.96</td>
</tr>
<tr>
<td>Skin</td>
<td>0.94</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*Disutility multipliers in year 3 and beyond were generally the same as those in year 2. See manufacturer’s submission for further details. SD, standard deviation.

Costs in the analysis were limited to direct medical costs and costs associated with disease activity and long-term organ damage. Costs related to disease activity were drawn from an analysis conducted in 2009 on the resource utilisation recorded in the 1-year belimumab phase II trial (LBSL02) in which 2005/06 NHS reference costs were used. Costs were inflated to 2010 costs. Total resource use was varied according to disease severity and calculated using a linear regression analysis (see pages 241 to 243 of the manufacturer’s submission).

A literature search was conducted to identify cost of organ damage. Costs were inflated to 2010 costs. Cost for the first and second years after initial damage development are shown in table 3.
Table 3 Costs for organ damage in the first and second year after initial damage development. Adapted from table 6.26 in the manufacturer’s submission

<table>
<thead>
<tr>
<th>Organ damage type</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>£3440</td>
<td>£505</td>
</tr>
<tr>
<td>Diabetes</td>
<td>£2338</td>
<td>£2338</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>£2708</td>
<td>£0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>£6123</td>
<td>£0</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>£5431</td>
<td>£1903</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>£3660</td>
<td>£1144</td>
</tr>
<tr>
<td>Ocular</td>
<td>£1535</td>
<td>£17</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>£2988</td>
<td>£598</td>
</tr>
<tr>
<td>Premature gonadal failure</td>
<td>£0</td>
<td>£0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>£9679</td>
<td>£9603</td>
</tr>
<tr>
<td>Renal</td>
<td>£1765</td>
<td>£2453</td>
</tr>
<tr>
<td>Skin</td>
<td>£0</td>
<td>£0</td>
</tr>
</tbody>
</table>

The base case only considers the additional acquisition costs for belimumab. Because belimumab is given in addition to standard care, it is assumed that the costs for standard care treatments cancel one another out and so were not included (page 247 of the manufacturer’s submission). The administration cost of £126 for belimumab was calculated based on 2 hours of senior hospital staff nurse time (£63/hour) from PSSRU Unit Costs of Health and Social Care 2010 (1 hour for the actual infusion and another 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. This cost assumed a price of belimumab of £114.30 for a 120mg vial and £381 for a 400mg vial. The inclusion of a cost for standard care and different costs of administration were explored in scenario analyses.

3.1.3 Results

The model shows a slower disease activity for belimumab patients than standard care patients, which leads to a decreased steroid dose and a
decreased risk of organ damage and contributes to a difference in mortality risk. The model predicts that in the belimumab arm patients live longer than patients in the standard care arm (as shown in figure 4).

**Figure 4 Survival of patients over time. Adapted from figure 6.36 of the manufacturer’s submission**

Because belimumab patients have an estimated longer life expectancy, the exposure to the risk of organ damage is increased for belimumab patients. For six of the organ damage types (diabetes, gastrointestinal, malignancy, musculoskeletal, neuropsychiatric and ocular) the percentage of occurrence is similar or higher in the belimumab arm than for standard care. However, for cardiovascular, peripheral vascular, premature gonadal failure, pulmonary and renal systems, fewer patients on belimumab develop damage compared with those on standard care. Although a decreased duration of damage is shown for organs on which belimumab has a large effect (cardiovascular, pulmonary and renal), the duration of damage for the other organ systems is increased because of the prolonged life-expectancy.
Table 4 Summary of health economic outcomes. Adapted from table 6.45 of the manufacturer’s submission

<table>
<thead>
<tr>
<th></th>
<th>SC</th>
<th>Belimumab</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>66.2</td>
<td>69.1</td>
<td>2.9</td>
</tr>
<tr>
<td>SLICC at death</td>
<td>4.1</td>
<td>4.0</td>
<td>−0.1</td>
</tr>
<tr>
<td>AMS</td>
<td>5.5</td>
<td>4.55</td>
<td>−0.9</td>
</tr>
<tr>
<td>Average monthly steroid cumulative dose</td>
<td>228.1</td>
<td>207.9</td>
<td>−20.2</td>
</tr>
<tr>
<td>Life years (undiscounted)</td>
<td>31.93</td>
<td>34.87</td>
<td>2.9</td>
</tr>
<tr>
<td>Life years (discounted)</td>
<td>17.05</td>
<td>18.11</td>
<td>1.1</td>
</tr>
<tr>
<td>QALYs (undiscounted)</td>
<td>17.31</td>
<td>19.17</td>
<td>1.9</td>
</tr>
<tr>
<td>QALYs (discounted)</td>
<td>9.81</td>
<td>10.61</td>
<td>0.8</td>
</tr>
</tbody>
</table>

AMS adjusted mean SLEDAI; QALY, quality-adjusted life year; SC, standard care; SLICC Systemic Lupus International Collaborating Clinics.

As shown in table 4, the model predicts that belimumab-treated patients, in the subgroup with high disease activity, live on average 2.9 years longer, have a reduction in average mean SLEDAI score, and similar total SLICC organ damage score compared with standard care patients. Treatment with belimumab in the high disease activity subgroup provides an estimated additional 1.1 life years and 0.8 QALYs (discounted).

For both treatment groups, the organ damage costs are the highest expense (see table 5). In total, the organ damage costs are lower for belimumab-treated patients. The costs related to disease activity are similar in the two treatment arms. Overall, the main difference in costs is caused by belimumab acquisition and administration, amounting to £56,067 (89.6%) of the total absolute cost difference of £62,610.
Table 5 Summary of discounted costs over lifetime. Adapted from table 6.46 of the manufacturer’s submission

<table>
<thead>
<tr>
<th>Discounted Costs</th>
<th>SC</th>
<th>Belimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity related costs</td>
<td>£27,882</td>
<td>£28,130</td>
</tr>
<tr>
<td>Belimumab drug acquisition</td>
<td>£0</td>
<td>£47,008</td>
</tr>
<tr>
<td>Belimumab administration</td>
<td>£0</td>
<td>£9059</td>
</tr>
<tr>
<td>Sum of organ damage costs</td>
<td>£77,483</td>
<td>£73,093</td>
</tr>
<tr>
<td>Total direct costs</td>
<td>£105,366</td>
<td>£157,291</td>
</tr>
</tbody>
</table>

SC, standard care.

Belimumab-treated patients are estimated to live longer. However, because of their increased life expectancy and belimumab treatment, costs are higher than for standard care patients. Total costs are £157,291 for belimumab and £105,366 for standard care. Total QALYs are 10.61 for belimumab compared with 9.81 for standard care. The incremental costs are therefore £51,925, and the incremental QALYs 0.806; 2.9 life years are gained (1.05 life years (discounted)). This results in an incremental cost-effectiveness ratio (ICER) of £64,410 per life year gained for the target population (see table 6).

In comparison, the ICER for the population of the marketing authorisation is £66,170 per QALY gained. The ICER for the marketing authorisation population comprises a total cost of standard care of £103,591 compared with £143,895 for belimumab (an incremental difference of £35,584), and 9.55 and 9.98 QALYs respectively (an incremental difference of 0.43 QALYs).

The ICER for the total trial population (which includes a wider population than that specified in the marketing authorisation) is £82,909 per QALY gained. The ICER for the total trial population comprises total cost for standard care £97,583 compared with £133,167 for belimumab (an incremental difference of £35,584), and 9.55 and 9.98 QALYs respectively (an incremental difference of 0.43 QALYs). (See the ERG report page 104).
Table 6 Base-case results. Adapted from table 6.47 of the manufacturer’s submission

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Total costs (£)</th>
<th>Total LYG</th>
<th>Total QALYs</th>
<th>Incremental costs (£)</th>
<th>Incremental LYG</th>
<th>Incremental QALYs</th>
<th>ICER (£) versus baseline (QALYs)</th>
<th>ICER (£) incremental (QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>£105,366</td>
<td>17.05</td>
<td>9.81</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belimumab</td>
<td>£157,291</td>
<td>18.11</td>
<td>10.61</td>
<td>£51,925</td>
<td>1.05</td>
<td>0.806</td>
<td>£64,410</td>
<td>£64,410</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SC, standard care.

The most influential factors on cost effectiveness were found to be: the treatment effect regression to estimate the effect of belimumab after 52 weeks, the natural discontinuation probability and the effect of the adjusted mean SLEDAI (AMS) on mortality. The scatter plot and acceptability curve for the target population are presented in figures 5 and 6 respectively.

![Scatter plot of the PSA](image)

The PSA results show that at a willingness to pay (WTP) of £30,000 per QALY gained, there is a 0% probability that belimumab is cost effective compared with standard care. With a willingness to pay of £60,000 per QALY gained, the ICER is £64,410.

Figure 5 Scatter plot of the PSA. Adapted from figure 6.40 of the manufacturer’s submission

![Figure 5 Scatter plot of the PSA](image)

![Figure 6 Acceptability curve](image)
gained, there is a 35% probability that belimumab is cost effective compared with standard care.

![Figure 6 Acceptability curve of PSA. Adapted from figure 6.41 of the manufacturer’s submission]

A number of scenario analyses were conducted, with resultant ICERs ranging from £50 114 to £77 707 per QALY gained. One of the scenarios explored was an increased vial price to £127.80 for the 120mg vial and £426 for the 400mg vial. This represented the maximum expected vial price. The resulting ICER was £71 297 per QALY gained (see page 301 of the manufacturer’s submission).

### 3.1.4 Patient access scheme

A patient access scheme, which has been accepted by the Department of Health, and provides the 120mg and 400mg vials at a cost of £*** and £*** respectively would make the total cost for a person taking belimumab £******* rather than £157,291 without the patient access scheme. The cost of standard care is £105,366. In the standard care arm, a total of 9.81 QALYs are gained over the course of the model, compared with 10.61 QALYs for the belimumab

---

National Institute for Health and Clinical Excellence
Premeeting briefing – Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus

Issue date: July 2011
arm. This leads to an ICER of £****** per QALY gained compared with £64,410 without the patient access scheme.

### 3.1.5 Comparison against rituximab

The manufacturer stated that the patient access scheme would make belimumab available at a price that is ******** to the cost of providing rituximab (drug acquisition cost). The annual drug cost of belimumab would be £*****, compared with an annual cost of rituximab of £6985. The manufacturer explained that while it is not possible to directly compare belimumab with rituximab, using the assumption that belimumab is as effective as rituximab, it is expected that belimumab would ************************************ in this patient population (see page 28 of the manufacturer’s submission).

### 3.2 Evidence Review Group comments

The ERG considered that the manufacturer’s model was well constructed and conforms to the NICE reference case and that the longer term effects of SLE had been modelled well, using the Johns Hopkins SLE cohort. An ERG cross-check of the probabilistic modelling for the target population resulted in a central estimate of £65,530 per QALY gained.

The ERG identified a number of issues that may affect the results. They also did a number of exploratory analyses around key parameters in the model as shown in table 7.
The ERG highlighted that the steroid use data within the trials was not used in the modelling, and that the function used was not subject to sensitivity analysis. The ERG completed a sensitivity analysis that arbitrarily applied a constant steroid dose (10mg) for all patients in both groups regardless of their SELENA-SLEDAI score. This increased the ICER by approximately £4000 to £68,766 per QALY gained.
The ERG considered that there is some lack of clarity around the reasons for patients’ discontinuation and the derivation of the 8% annual discontinuation rate among belimumab week-24 responders, and of the reasonableness of extrapolating using this value. Sensitivity analyses by the manufacturer show that a low discontinuation rate, such as 2% worsens the cost effectiveness of belimumab to an ICER of £85,893, while a higher discontinuation rate, such as 14% improves it, to give an ICER of £54,518 per QALY gained.

The ERG stated that the model assumes that belimumab week-24 non-responders will experience the average SELENA-SLEDAI score within the standard care arm. The ERG considered that this assumption seems likely to have overestimated the average impact on SELENA-SLEDAI scores within the belimumab arm, which would lead to an underestimation of the ICER.

The ERG noted that it is the adjusted mean SLEDAI (AMS) score that contributes to the likelihood of a patient dying and a patient developing particular organ involvement. The economic modelling does not take into account a patient’s history before entry into the trial and this may also exaggerate the impact that changes in SELENA-SLEDAI score have on the AMS for belimumab compared with standard care, with the likely result that the base case ICER is an underestimate.

The ERG stated that the requirement to adjust the Johns Hopkin’s cohort survival model by standardised mortality ratios (SMRs) from the literature is 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 SMR rates used by the manufacturer may not accurately represent a UK cohort. A sensitivity analysis using the lower SMRs derived from the UK study increased the ICER by approximately £6000 to £70,860 per QALY gained.
The ERG highlighted that the constant in the SS change regression equation from the Johns Hopkin’s data was originally 2.0577 but was adjusted by the manufacturer to 3.0 to improve model fit. Sensitivity analyses by the manufacturer show that using the original value of the constant term increased the ICER by £29 000, to £93 654 per QALY gained.

The ERG noted that analysing the observational cost data on a 6-monthly basis in order to relate it to the maximum SELENA-SLEDAI score during that period, and then doubling it to arrive at the annual relationship, appears peculiar given that the observational cost data were collected over a year. The ERG considered that this may have also led to bias, specifically an underestimation of the ICER because of the likely exaggeration of the association between the SELENA-SLEDAI score average over the year and annual treatment costs.

The ERG was concerned that because there were separate estimations of cost per organ involved, this may have double-counted costs estimated within the SELENA-SLEDAI score cost function, the ERG considered that if there was double counting this may have also underestimated the ICER.

The ERG considered the impact of using different administration costs than were used in the model (£126). The ERG found that if costs were in line with those from previous appraisals of rheumatoid arthritis, which had an administration cost of £154, then the ICER would increase by £2500 to £66 907 per QALY gained. If the full day case cost were used (£432) then the ICER would be higher by £27 000, at £91 699 per QALY gained.

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

4 **Equalities issues**

In the scoping workshop consultees considered that children should have access to belimumab. The manufacturer confirmed at the scoping workshop that a marketing authorisation will not be sought for children and therefore an appraisal should focus on adult patients with SLE only. Compliance with the therapy was also raised as a potential equality issue, because patients would need hospital admission to receive this drug.

Consultees noted that certain ethnic minority groups might benefit more from therapy with belimumab than others, because the prevalence of SLE is greater in certain populations. The manufacturer highlighted that SLE is more common in women than in men. It is also more prevalent in African-Caribbean, South Asian and Chinese than in European white populations.

5 **Authors**

Dr Helen Starkie and Zoe Garrett, with input from the Lead Team (Peter Jones, Niru Goenka and Cliff Snelling).
Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:


B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- GlaxoSmithKline

II Professional/specialist, patient/carer and other groups:

- British Association of Dermatologists
- British Society for Rheumatology
- Renal Association
- British Health Professionals in Rheumatology
- Primary Care Rheumatology Society
- Royal College of Nursing
- NHS Bolton
Appendix B: Description of primary and secondary endpoint measures

The SLE Responder Index (SRI) includes: a measure of the reduction in global disease activity (reduction in SELENA-SLEDAI score of 4 or more) and two measures to ensure that the improvement in disease activity score is not offset by worsening of the subject’s condition overall (that is, no worsening in the PGA) or worsening in any specific organ system (that is, no new BILAG A or two new B flares).

Safety of Estrogens in Lupus Erythematosus National Assessment trial – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) aims to capture the subject’s condition over the 10 days before the assessment. Disease activity can range from 0 to 105 (0 = no activity, ≥ 20 very high activity). A reduction of 4 points equates to elimination of a disease manifestation and a demonstration of clinical benefit.

The British Isles Lupus Assessment Group (BILAG) measures changes in disease activity over the past 28 days. A BILAG score ranges from A (very active disease) to D (no current disease activity) through to E (the organ system has never been involved). An A or 2B flare represents either an increase in disease activity sufficient to require alteration of therapy (A) or mild reversible problems in two organ systems (2B).

The Physician’s Global Assessment (PGA) is a semi-quantitative test of the patient’s condition. It uses a 10-cm visual analogue scale from 0 to 3 on which the physician marks his assessment. A score of 1 = mild lupus disease activity, a score of 2–2.5 = moderate disease activity, and a score of 3 = severe disease activity. A change of 1 unit on the PGA is associated with worsening of disease activity. An increase of 1 unit or more from the last assessment resulting in a PGA score of 2.5 or less is considered a mild-
moderate flare. If the increase in PGA is to more than 2.5, it is considered a severe flare.

The SLICC/SDI contains 41 damage items in 12 systems that are specific comorbidities associated with SLE or damage because of toxicity of SLE treatment (cardiovascular disease, diabetes, gastrointestinal, malignancy, musculoskeletal, neuropsychiatric, ocular, peripheral vascular, gonadal failure, pulmonary, renal and skin). Damage items are recorded irrespective of their attribution to SLE. Damage items have to persist for a minimum of 6 months, or be associated with an immediate pathological scar indicative of damage. The total score is the sum of the marked scores and ranges from 0 to 47. Since damage is irreversible, items that are marked will stay marked for the lifetime of the patient.