Executive Summary

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

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

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

<table>
<thead>
<tr>
<th>Description of Scenario</th>
<th>Scenario Details</th>
<th>Incremental Cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Revised Base Case: Same as original base case but with a six year maximum belimumab treatment duration</strong></td>
<td>Time horizon = lifetime; 6 year maximum belimumab treatment duration; treatment continuation criterion at 24 weeks defined as SS score reduction ≥4 points; and health effects discount rate of 3.5%</td>
<td></td>
</tr>
<tr>
<td>More stringent treatment continuation criterion</td>
<td>As revised base case but with treatment continuation criterion at 24 weeks of SS score of ≥6 and health effects discount rate of 3.5%</td>
<td></td>
</tr>
<tr>
<td>Health effects discount rate of 1.5%</td>
<td>As revised base case but with health effects discounting rate of 1.5%.</td>
<td></td>
</tr>
<tr>
<td>More stringent treatment continuation criterion with discount rate of 1.5%</td>
<td>As revised base case but with treatment continuation criterion at 24 weeks defined as SS score of ≥6 points; and health effects discount rate of 1.5%</td>
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The revised health economic modelling, incorporating our patient access scheme (PAS), results in a revised base case ICER of  per QALY gained, with further reductions in the ICERs from
additional key scenarios presented in Table 1. Therefore, given we believe that the health effects discount rate of 3.5% used in the base case is too high for this technology appraisal, the true assessment of cost-effectiveness is likely to lie within the range of [ ] per QALY gained.

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

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

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

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

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

1. **Do you consider that all of the relevant evidence has been taken into account?**

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

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

**Duration of treatment with belimumab – Revised Base Case**

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

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

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

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

2. Treatment Continuation Criterion
In our original base case (and also our revised base case) we included a treatment continuation rule (stopping criterion) after six months. This rule was specifically included in the model to try and represent how patients could be managed on belimumab in clinical practice as recommended in the SmPC. The SmPC states that “Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment”. For the health economic model an objective measure was required to determine for each patient whether belimumab should be continued or discontinued after six months
treatment. Our continuation rule required patients to demonstrate a reduction of at least 4 points in SELENA-SLEDAI (SS) score. A minimum reduction of 4 points in SS score is accepted as a clinically relevant improvement in disease activity (Gladman et al. 2000). We are aware that the Committee felt this continuation rule was arbitrary and may not be adhered to in clinical practice (see ACD Section 4.12). An SS score reduction of 4 or more was a pre-specified component of the composite primary endpoint of the BLISS trials and the main driver of efficacy. The SELENA-SLEDAI is a validated, robust measure (Griffiths et al. 2005) and a decrease of 4 or more points relates to a clinically meaningful change in disease activity (Gladman et al. 2000). We have consulted with lupus experts and have been advised that incorporating a treatment continuation rule in clinical practice as part of the management of patients on belimumab would be easily achievable and acceptable if it was a stipulated requirement in NICE guidelines. As reflected by the clinicians at the Appraisal Committee Meeting, it would in fact be valuable to introduce objective assessment of SLE routinely in clinical practice. It is also worth considering that patients in our proposed target population will be managed in only a small number of specialist lupus centres. This will help ensure that clinicians adhere to any specific requirements for prescribing belimumab as detailed in the guidance that NICE issues.

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

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

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

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

There are some aspects of the interpretation of the clinical evidence that we believe require further clarification and consideration. The main issues that we would like the committee to consider further relate to:
i) the representativeness of our target BLISS SLE population and their likelihood of developing significant long-term organ damage which has an impact on survival

ii) the relevance of the SELENA-SLEDAI tool to patient selection and management

iii) health effects being underestimated in the health economic model and

iv) the cost and efficacy comparison with rituximab.

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

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

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

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

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

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

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

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>SoC</th>
<th>Belimumab</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Death (years)</td>
<td>66.3</td>
<td>69.3</td>
<td>3.0</td>
</tr>
<tr>
<td>SLICC at Death</td>
<td>3.9</td>
<td>3.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Average Mean SLEDAI</td>
<td>5.8</td>
<td>4.77</td>
<td>-1.0</td>
</tr>
<tr>
<td>Average Monthly Steroid (mgs)</td>
<td>235.3</td>
<td>213.2</td>
<td>-22.1</td>
</tr>
<tr>
<td>Life Years (undiscounted)</td>
<td>28.35</td>
<td>31.31</td>
<td>3.0</td>
</tr>
<tr>
<td>Life Years (discounted)</td>
<td>15.65</td>
<td>16.79</td>
<td>1.1</td>
</tr>
<tr>
<td>QALYs (undiscounted)</td>
<td>15.28</td>
<td>17.12</td>
<td>1.8</td>
</tr>
<tr>
<td>QALYs (discounted)</td>
<td>8.91</td>
<td>9.74</td>
<td>0.8</td>
</tr>
</tbody>
</table>
ii) Relevance of SELENA-SLEDAI Instrument

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

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

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

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

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

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

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

ACD Section 4.9. In this section it is stated that the Committee noted the limited steroid sparing effect observed in the BLISS studies. It is very likely however, that a greater steroid sparing effect would in fact be seen with belimumab in clinical practice. Given the double-blind nature of the study it is highly probable that the BLISS trialists were cautious in reducing the steroid dose too much or too quickly in the RCTs due to concern of the impact this could have on inducing a flare. Indeed, in the BLISS trials only patients who had improving SLE disease activity for at least eight weeks could, at the investigator’s discretion, reduce the steroid dose, targeting a reduction to 7.5 mg/day or lower after the Week 24 visit. Therefore in terms of steroid sparing effect, the benefits that belimumab could offer are likely to have been underestimated. This is supported by recent results from the Phase II belimumab extension study (LBSS99) (Petri et al. 2011) which showed that for patients remaining in the study with steroid data recorded, the dose of steroid gradually and significantly reduced over time (Figure 1). By the end of Year 6 the steroid dose had reduced by an average of 4.7mg/day, an average of 34.4% from the baseline dose (Petri et al. 2011). In this study there were no restrictions on steroid use and it was left to the physicians’ discretion as to whether it was appropriate to reduce a patient’s steroid dose. Therefore this reflects more accurately how steroid tapering would be managed in clinical practice for patients receiving belimumab. This is important when considering HRQoL, because, although there was a clear improvement in disease activity with belimumab in the trials, this benefit may not have been fully realised by the patients if they were still experiencing side effects from high dose steroid use. Additionally, reducing steroid use may have important long-term benefits with reducing future steroid -related organ damage.
As detailed in our original submission, we believe that the EQ-5D underestimates the impact of SLE on HRQoL. Certain relevant dimensions of health are not directly included in the EQ-5D instrument, such as fatigue or sensory impairment. This has also been discussed by the NICE Decision Support Unit in their report ‘The incorporation of health benefits in cost utility Analysis using the EQ-5D’ (Wailoo et al. 2010). Chronic fatigue is one of the most prevalent clinical manifestations of SLE and severely affects HRQoL (Thumboo et al. 2007; Zonana-Nacach et al. 2000). It is nearly always a major factor in the life of a patient with SLE; it can be debilitating and difficult to treat. In the high disease activity subgroup, the pooled data from both studies showed that belimumab 10 mg/kg was associated with significantly improved fatigue scores compared with placebo at Weeks 8 and 12 (p < 0.05) and although at Week 52 a statistically significant difference with placebo was not seen, the mean change from baseline in the belimumab group (4.9 points) was superior to that seen in the placebo group (3.3 points). We further note that both clinical experts and patient groups at the first appraisal committee meeting specifically pointed to the significant impact of fatigue and sensory impairment on patients with SLE.

iv) Comparison with rituximab
- The costs presented for rituximab based on the doses used in their clinical trial and presented in our original submission are appropriate and justifiable for comparison with belimumab costs.
The current available RCT evidence for both drugs demonstrates that belimumab met its primary endpoint whereas rituximab failed to do so. Thus our approach of assuming belimumab is at least as effective as rituximab is conservative.

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

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

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

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

ACD Section 3.29. The text in this section which states “The ERG highlighted that information on SLEDAI and SF-36 changes in the rituximab EXPLORER trial were available, and that randomised controlled trials for both rituximab and belimumab recorded BILAG changes, thus offering the potential for an indirect comparison” is inconsistent with the text in Section 4.10 which states “The Committee heard from the ERG that there were three outcomes for which an indirect comparison
could be completed (that is, BILAG, SLEDAI, and SF-36 scores), but data were only available in the public domain for the SF-36. The ERG also highlighted the differences in the trial populations, which it considered meant that the results of an indirect comparison were not meaningful.” This latter text provides a more complete assessment of the ERG’s opinion as to the inappropriateness of conducting an indirect comparison of efficacy between belimumab and rituximab. Whereas the statement in Section 3.29 suggests that an indirect comparison would be valid.

Other Points for Clarification of Interpretation of the Evidence

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

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

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

<table>
<thead>
<tr>
<th>Years on belimumab</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients starting year</td>
<td>339</td>
<td>274</td>
<td>248</td>
<td>223</td>
<td>208</td>
</tr>
<tr>
<td>% discontinued</td>
<td>19.2%</td>
<td>9.5%</td>
<td>10.1%</td>
<td>6.7%</td>
<td>19.7%</td>
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</tbody>
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ACD Section 4.8. The Committee concluded that there was uncertainty about the extent to which standard of care (SoC) in the BLISS trials was representative of UK clinical practice, with particular reference to the fact that approximately 50% of BLISS patients were receiving immunosuppressants as part of their SoC.
There are no national guidelines for the management of SLE in the UK and the treatment pathway is not ‘step-wise’ as in other conditions such as rheumatoid arthritis. Hence there is considerable variability in standard of care treatment between SLE patients and across UK centres. The lupus experts we have consulted believe that the proportion of patients receiving immunosuppressants in the BLISS trials seems reasonable based on the level of variability in SoC currently evident in the UK. These trials included a variety of different combinations of SoC treatments, all of which could be observed in UK clinical practice and therefore it is reasonable to assume the results are applicable to the UK.

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

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

### 3. Additional Considerations

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

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

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

- Belimumab was specifically designed to treat a rare, severely debilitating disease with a significant unmet need where there has been little innovation for 50 years. It specifically binds to BLYs and inhibits its biological activity thus having a beneficial effect on reducing disease activity as demonstrated in two large RCTs.
- Our proposed target population, which we have identified as a cost-effective subgroup to receive belimumab, is considerably smaller than our licensed SLE population and targets treatment to patients with the most serious disease activity and who are likely to gain the most from belimumab. We would also ask the committee to consider the implications of a restricted treatment duration of six years and the implications of a lower discount rate and more stringent continuation rules.
Moreover, in the absence of these biologics being available on the NHS, SLE patients may be admitted to hospital for alternative more expensive treatments such as Intravenous immunoglobulin (IVIG).

- There are aspects of value not fully accounted for in our estimate of cost-effectiveness. Specifically, the full benefit of belimumab on disease flares and chronic fatigue are not adequately captured in the quality adjusted life years (QALYs) derived from EQ-SD utility values. In addition the implications of new evidence supporting a steroid sparing effect for belimumab have not been considered.

- There is no alternative NICE guidance for any other treatment in SLE. If this appraisal results in a negative recommendation for belimumab patients will continue to receive treatments that have not been rigorously assessed for either clinical or cost-effectiveness within the NHS. Specifically the use of rituximab will continue, which is unlicensed for SLE and has not demonstrated any efficacy benefit in RCTs or shown evidence of being a cost-effective medicine in SLE.

5. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**

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


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