Chair, Appeal Committee  
National Institute for Health and Clinical Excellence  
MidCity Place  
71 High Holborn  
London WC1V 6NA

Dear [Name],

RE: FINAL APPRAISAL DETERMINATION – BELIMUMAB FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION ISSUED BY THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE ON 27 APRIL 2012

EXECUTIVE SUMMARY

GlaxoSmithKline (GSK) is advancing an appeal under Ground 1 (procedural unfairness) and Ground 2 (unreasonableness) of the grounds permitted in accordance with NICE’s Guide to Technology Appraisal Appeal Process.

Ground 1 (Procedural unfairness)

- The Appraisal Committee has failed adequately to take into account the innovative nature of belimumab in the context of this appraisal and/or its reasoning relating to innovation is not explained.
- The Committee’s decision to reject GSK’s proposal that discontinuation of treatment with belimumab after week 24 should be considered if there was no improvement in a patient’s SELENA-SLEDAI score of 6 points or more is not explained.
- The Appraisal Committee’s finding that belimumab has not been shown to represent a cost-effective use of NHS resources compared with rituximab, acts to
protect continued use of a product which is not authorised for the condition under consideration, contrary to the medicines licensing regime and the European Court decision in Case C-185/10 European Commission v. Republic of Poland.

Ground 2 (unreasonableness)

- The Committee’s findings in relation to the clinical and cost-effectiveness of belimumab compared with rituximab are unreasonable in the context of the available evidence and the licence status of rituximab.
- The Committee’s conclusion that the choice of a maximum treatment duration of 6 years could not be considered sufficiently robust for decision making is unreasonable.
- The Appraisal Committee’s conclusion that there is uncertainty about whether the treatment effect of belimumab is maintained over time does not reflect the available evidence and is therefore unreasonable.

INTRODUCTION

Belimumab (Benlysta) is a human immunoglobulin G1λ monoclonal antibody that has a novel mode of action and has been specifically developed for the treatment of systemic lupus erythematosus (SLE). It binds to soluble human B-lymphocyte stimulator (BLyS) and inhibits its biological activity, thereby promoting apoptosis in autoreactive B-lymphocyte cells. By blocking the action of BLyS, belimumab reduces the life span of B-lymphocytes, which reduces the inflammation and organ damage that occur in SLE.

The product is the subject of a marketing authorisation granted by the European Commission on 15 July 2011, under the centralised procedure. It is indicated as an add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity (such as positive anti-double-stranded DNA (dsDNA) and low complement) despite standard therapy.

PROCEDURAL HISTORY OF THE APPRAISAL

The single technology appraisal of belimumab for the treatment of SLE was referred to NICE in November 2010 and the final Scope was issued in February 2011. The comparators identified in the Scope were: (a) standard therapy alone; (b) rituximab plus standard therapy; and (c) cyclophosphamide plus standard therapy. However, both GSK in their submission and the Evidence Review Group (ERG) agreed that cyclophosphamide was not an appropriate comparator as it was used in a different population to the licensed population for belimumab.

A submission was prepared by GSK in accordance with NICE’s STA specification and provided to NICE on 13 April 2011. Warwick Evidence, at the Health Sciences
Research Institute, Warwick Medical School was appointed ERG for this appraisal and prepared a report, based on the submission by GSK, completed on 26 June 2011.

The first meeting of the Appraisal Committee took place on 26 July 2011. Following this meeting, an Appraisal Consultation Document (ACD) was issued by the Committee and provided to consultees, together with the evaluation report, on 23 September 2011. The Appraisal Committee’s preliminary recommendations as set out in the ACD were: “Belimumab is not recommended as add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy.”

GSK’s response to the ACD was provided to NICE on 21 October 2011. The company addressed the main points raised by the Committee and the clinical specialists to support the use of belimumab within the NHS and submitted a revised cost-effectiveness analysis which incorporated a maximum treatment duration for belimumab of 6 years and the same patient access scheme offering. GSK also submitted new six-year data on steroid dose reduction from the Phase II belimumab extension study.

The second meeting of the Appraisal Committee took place on 22 February 2012, and the Final Appraisal Determination (FAD) was issued on 27 April 2012. The Appraisal Committee’s recommendations for belimumab were unchanged from those set out in the ACD.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): BACKGROUND INFORMATION

Systemic lupus erythematosus (SLE) and its treatment are considered in detail in the original submission to NICE by GSK. The following comprises a brief summary provided to assist the Appeal Panel.

SLE is an uncommon, complex and poorly understood autoimmune condition characterised by an unpredictable clinical course, autoantibody production, abnormal B-lymphocyte function and chronic inflammation. The disease affects many tissues and body systems, resulting in chronic debilitating ill-health, with disease activity fluctuating between periods of exacerbation (flares) and relative quiescence.

Clinical manifestations vary widely, however many patients experience general symptoms of fever, malaise, fatigue, anorexia, weight loss, skin rashes and muscle and joint pains. In addition to the immediate impact of SLE on quality of life, more than 50% of affected patients develop permanent and progressive organ damage. Renal disease is one of the commonest and most serious manifestations of the condition, occurring in 40-75% of affected persons. SLE is therefore associated with
very substantial morbidity as well as a 2.4 fold increased mortality compared with the general population.

SLE is approximately 10 times more common in women than men (although affected men tend to have more severe disease), and is more prevalent in African - Caribbean, South Asian and Chinese populations than in Caucasians. The disease onset is generally between the ages of 15 and 44 years, suggesting that SLE affects predominantly women during their childbearing years. In the UK, prevalence has been estimated at 41 per 100,000 persons.

There is currently no cure for SLE; treatments aim to control inflammatory disease activity, prevent further organ damage and reduce symptoms. There is also no accepted treatment algorithm and no relevant NICE guidance. Agreeing on best practice poses a significant challenge owing to the heterogeneous nature of the disease. Patients potentially receive a range of treatments (including non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressants and disease-modifying agents (e.g. hydroxychloroquine)), used either alone or in different combinations. This current standard of care may be associated with undesirable effects, either from chronic use of steroids (osteoporosis, diabetes and cardiovascular disease) or side effects associated with immunosuppressants (toxicity, infection and infertility).

In addition, a significant number of patients with advanced SLE do not respond to current treatments even at high doses and many patients receive therapies which are not licensed for use in SLE. For example, rituximab (MabThera), a biologic product is frequently used, but while this has appeared to show benefit in some patients in clinical practice, it has failed to demonstrate statistically significant efficacy in Phase 2 or 3 clinical trials in SLE, and is not licensed for the treatment of SLE.

**GROUND OF APPEAL**

Ground 1: The Institute has failed to act fairly

1.1 **The Appraisal Committee has failed adequately to take into account the innovative nature of belimumab in the context of this appraisal and/or its reasoning relating to innovation is not explained**

Directions from the Secretary of State require the Appraisal Committee to take into account “the potential for long-term benefits to the NHS of innovation” when formulating its recommendations (paragraph 1.11 of the STA Guide).

In January 2009, Sir David Cooksey wrote in his “Review and Refresh of Bioscience 2015” that “Currently, the perceived problem for UK industry is that NICE appraisals do not operate in a way that is supportive of innovation, or uptake and access to medicines and therefore dissuade companies from investing in the UK”. The Cooksey Report was followed by a Report prepared
by Sir Ian Kennedy for NICE “Appraising The Value Of Innovation And Other Benefits”. In response to the observations of Sir David Cooksey, Sir Ian concluded “NICE should build on its reputation as leading the world in the appraisal of products to establish itself also as a world leader in promoting innovation and the early adoption of treatments”.

These assessments of how NICE should act, in the interests of the NHS, were followed by a decision by NICE’s Board, in March 2010, that the innovative nature of a product should be taken into account during the scoping process of an appraisal, and that the Appraisal Committee would investigate its potential to make a significant and substantial impact on health-related benefits and how use of the product might improve the way that a current need is met. Where the Appraisal Committee is satisfied that the product represents a ‘step change’, it will be expected to demonstrate either that the product’s identified innovative characteristics have been taken into account in the QALY calculation or, if not, how it has separately evaluated them and what their impact is (if at all) on its judgement of the most plausible ICER (paragraph 3.7, Response to Sir Ian Kennedy’s Report, Appendix B).

Despite NICE’s stated commitment to recognising and taking account of the benefits of innovation, GSK believes that the innovative nature of belimumab has not been appropriately taken into account in this appraisal. Belimumab has a novel mode of action and it is the first medicinal product in its class to be authorised; it has been developed as a targeted therapy for a specific aspect of SLE pathology through genomic science. Belimumab addresses an area of significant unmet need in the management of SLE patients who have severe highly active disease, despite being managed on current standard of care. There has been little therapeutic innovation in the treatments for SLE, with no evidence leading to the development of new licensed treatments for several decades. Belimumab is the only treatment to be developed specifically, and shown to be effective, for the management of this condition and represents, we suggest, a “step-change” in its management. This is the first ever technology appraisal completed for SLE, and no relevant NICE guidance exists.

The current NICE Guide to the Methods of Technology Appraisal 2008 (the Methods Guide), confirms that the Appraisal Committee is expected to take into account the Directions issued by the Secretary of State (paragraph 6.1.3) and reiterates that “it is crucial that the Appraisal Committee’s decisions are explained clearly” (paragraph 6.1.5). The Methods Guide outlines factors to be taken into account when considering technologies associated with an ICER over £20,000 per QALY gained, including “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”. It is significant that this version of the Methods Guide
was issued before the Cooksey report and the report by Sir Ian Kennedy and
does not therefore take into account the statement by NICE’s Board or the
heightened requirement to recognise innovation as a result of those matters.

However, there is no indication that the innovative nature of belimumab was
recognised at the scoping stage of this appraisal or during the two Appraisal
Committee meetings. While the FAD records that the Committee “discussed
the innovative nature of belimumab” (paragraph 4.28), there is no reference to
the innovative nature of the product, or the unmet need that it meets. In
particular, there is no explanation as to how the 2010 direction from NICE’s
Board was taken into account, or how the decision that “the issues identified
around innovation did not change [the Committee’s] conclusions about the
cost effectiveness of belimumab” was reached. In particular, the Committee
does not appear to have taken into account at least the following matters,
including aspects of value not fully accounted for in the estimate of cost-
effectiveness:

(a) The impact of disease flares

SLE is a relapsing and remitting disease that includes periods of
exacerbation or “flare”. Disease flares (which are highly predictive of
accrual of organ damage\(^1\)), by their nature, may not be captured in the
specific periods when quality of life is recorded i.e. at pre-determined
time-points during the clinical trial. In addition, disease flares are not
specifically included in the health economic model due to the additional
complexity this would introduce. 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 in reducing the frequency and/or severity of
flare episodes.

While the Appraisal Committee recognised that disease flares had not
been included in the economic modelling, it referred simply to the fact
that, in the BLISS trials, differences in EQ-5D were not statistically
significant at 52 weeks. However, as noted above and in GSK’s original
submission, EQ-5D may not be the most sensitive measure to assess the
true impact of SLE on quality of life, specifically because it does not
allow for the effect of disease flares. The BLISS trials demonstrated a
significant reduction in the risk of flares; in the high disease activity
subgroup (who would be most likely to receive belimumab in clinical
practice) the hazard ratio for risk of flares overall in patients receiving
belimumab was 0.7 as compared with standard care, and the hazard ratio
for severe flares was 0.55. These results are consistent with sustained
improvement in quality of life, even though they are not reflected in the
utility values used in the context of this appraisal and should have been
taken into account by the Committee in the context of its consideration of innovation.

(b) Chronic fatigue

Fatigue constitutes a serious impairment to the quality of life of SLE patients, with severe consequences on normal day-to-day activities and ability to work. However, while the benefits of belimumab in reducing fatigue are consistent with its effects in terms of reducing disease activity, these are not adequately captured in the EQ-5D measure and are not therefore reflected in the utility values used in this appraisal. At paragraph 4.28 of the FAD, the Appraisal Committee dismissed this benefit, stating only that the FACIT-fatigue scores obtained from patients receiving belimumab in the target (high disease activity) population in the clinical trial were not statistically different from those in patients receiving standard care at 52 weeks. The Committee disregarded the fact that, in this group, belimumab was associated with statistically significantly improved fatigue scores compared with standard care at weeks 8 ($\Delta=1.87$, $p=0.034$) and 12 ($\Delta=1.88$, $p=0.039$), and a greater improvement at week 52 which only just fell short of being statistically significant ($\Delta=1.75$, $p=0.075$). The Appraisal Committee’s dismissal of the benefits of belimumab treatment in terms of reduction in fatigue do not therefore adequately reflect the data from the BLISS trials.

(c) Delay in organ damage

At paragraph 4.23 of the FAD, the Appraisal Committee notes that the utility values used for the purposes of this appraisal are likely to underestimate some of the benefits associated with delaying certain types of organ damage (e.g. renal damage). However, this important benefit was not taken into account by the Committee in the context of its consideration of the innovative nature of belimumab and targeted mode of action, even though we believe it represents precisely the type of effect, difficult to quantify, which should be reflected in the Committee’s analysis of innovation.

(d) The potential steroid sparing effect

A major secondary endpoint in the BLISS trials was the percentage of subjects whose average prednisolone (equivalent) dose was reduced by $\geq$ 25% from baseline to $\leq$ 7.5mg/day during weeks 40-52 in the subgroup of patients who were receiving $> 7.5$mg /day prednisolone at baseline. As noted in paragraph 4.10 of the FAD, a statistically significant reduction in steroid use was observed in the pooled analysis, confirming the beneficial effect of belimumab in reducing steroid dose. Furthermore, while this
endpoint did not reach statistical significance in either of the two studies considered individually, the magnitude of the steroid sparing effect was similar in both studies. In the high disease activity subgroup, belimumab 10mg/kg achieved the highest steroid sparing effect (15.9% compared with 7.1% in patients treated with standard care alone (p= 0.0389)). In clinical practice, it is likely that the reduction in steroid use may be greater than that observed in the randomised controlled trials (RCTs). This is because in the RCTs, due to their double-blind nature, it is highly probable that the BLISS trialists were cautious in reducing the steroid dose too much or too quickly in case it induced a flare in the standard care only arm.

The steroid sparing effects of belimumab are also demonstrated by data from the open-label Phase II belimumab extension study which showed a mean reduction in steroid use of 4.7mg/day (an average of 34.4% from baseline) after 6 years of follow-up (described at paragraph 4.11 of the FAD). This was new data submitted to NICE that was available after the original GSK submission.

As explained in GSK’s responses to the ACD, 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 (with associated increased use of healthcare resources) would also be reduced. Any reduction in the clinical dosage of steroids will therefore be a benefit both to patients, and the available healthcare resources. However, when considering innovation, the Committee seemingly did not take into account these benefits or, if they were considered, the FAD provides no explanation for the Committee’s conclusions in this context.

(e) The novel mode of action of belimumab and the clinical need of patients with SLE

Finally, while the Appraisal Committee recognises that few medicinal products have been investigated and licensed for use in SLE, that there is a high level of clinical need for effective treatments, and that belimumab represents a novel therapy specifically designed to target the pathology of this condition, there is no explanation in the FAD as to how, if at all, these matters were taken into account in reaching the conclusion in the FAD, that “the Committee concluded that the issues identified around innovation did not change its conclusions about the cost-effectiveness of belimumab” (paragraph 4.28). This lack of reasoning prejudices GSK in its ability to understand and respond to the Committee’s conclusions and is inconsistent with paragraph 6.1.5 of the Methods Guide, particularly in circumstances where the absence of explanation relates to two of the
matters (clinical need and innovation) which the Secretary of State has directed NICE to take into account when issuing guidance.

GSK requests that the Appraisal Committee is directed to reconsider this appraisal specifically taking into account the innovative nature of belimumab and the health benefits that are not adequately captured in the QALYs, and fully to explain its conclusions in this regard.

1.2 The Committee’s decision to reject GSK’s proposal that discontinuation of treatment with belimumab after week 24 should be considered if there was no improvement in a patient’s SELENA-SLEDAI score of 6 points or more is not explained

In order to target those patients who derive maximum benefit from belimumab therapy, GSK proposed that treatment with belimumab should be discontinued after week 24 in patients who did not achieve an improvement in the SELENA-SLEDAI score of 6 points or more. The effect of limiting continued treatment to those patients who show the greatest response is important because it improves the cost-effectiveness of belimumab and reduces the ICER by almost £5,000 per QALY gained.

The Methods Guide envisages the limitation of treatment to patients who achieve a specified response to treatment (paragraph 5.10.12), and identifies factors to be taken into account when considering such “continuation rules”. These include:

- the costs and health consequences of factors such as any additional monitoring associated with the continuation rule;
- the robustness and plausibility of the endpoint on which the rule is based;
- whether the ‘response’ criteria defined in the rule can be reasonably achieved;
- the appropriateness and robustness of the time at which response is measured;
- whether the rule can be incorporated into routine clinical practice;
- whether the rule is likely to predict those patients for whom the technology is particularly cost effective;
- issues with respect to withdrawal of treatment from non-responders and other equity considerations.

At paragraph 4.17 of the FAD, the Appraisal Committee noted that the SmPC for belimumab requires that discontinuation of treatment should be considered if there is no improvement in disease control after 6 months therapy, and that the clinical specialists indicated that this would be consistent with clinical
practice. The inclusion of a continuation rule in the context of this appraisal satisfies the criteria listed at paragraph 5.10.12 of the Methods Guide and introduces no costs over and above those that would be required in accordance with the SmPC. The Committee accepted that the application of continuation rules is appropriate in the context of belimumab and clinical experts have indicated that they would welcome a defined framework for the review/monitoring of patients with SLE and that this would benefit patient treatment.

When assessing how the continuation rules should operate, the Appraisal Committee stated that, for the purposes of the assessment, patients should continue therapy if the SELENA-SLEDAI score showed an improvement of at least 4 points, but “that it was not appropriate to consider using the more restrictive rule of a SELENA-SLEDAI score improvement of 6 or more as the base-case analysis for decision making”. No reasons for this conclusion of the Appraisal Committee are provided and it is wholly unclear why, having accepted the premise that a stopping rule is appropriate, the Committee has rejected applying the rule so as to target those patients who obtain the highest benefits from therapy. In the absence of an explanation for the Committee’s conclusions in this regard, GSK is unable to understand why its case has failed and is prejudiced in its ability appropriately to respond to the FAD.

For completeness, while the FAD states that clinical specialists “would prefer the lower continuation rule of an improvement of 4 points in the SELENA-SLEDAI score... unless it reduces the base-case ICER to an acceptable level”, physician preference would not explain why patients who demonstrate enhanced benefits should be denied therapy if it is only in these patients that the product may be regarded as cost-effective.

GSK therefore requests that the Appraisal Committee is directed to reconsider this appraisal, specifically taking into account discontinuation of treatment after week 24 if there was no improvement in a patient’s SELENA-SLEDAI score of 6 points or more, or alternatively, to explain why a continuation rule based on a SELENA-SLEDAI score of 4 or more is acceptable, but one based on a score of at least 6 is not.

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

The statement at paragraph 4.27 of the FAD that “the Committee did not consider that belimumab with the patient access scheme had been shown to be
a cost-effective use of NHS resources as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity .....despite standard therapy, compared with rituximab” has the inevitable result that patients will continue to receive rituximab, which is not authorised for this indication, rather than licensed belimumab.

The position of strategies which have the effect of supporting use of unlicensed products, despite the availability of licensed alternatives, was recently considered by the European Court in Case C-185/10 European Commission v. Republic of Poland. While this case arose from the importation of an unlicensed product and the application of the derogation under Article 5(1) of Directive 2001/83 from the requirement for a marketing authorisation, in circumstances where a licensed version of the product was available, the judgement of the Court made clear that financial considerations alone cannot be the basis for a Member State to endorse the use of an unlicensed medicinal product over a licensed one.

Applying the reasoning of the European Court, it is GSK’s position that guidance which has the effect of recommending use of a product outside the terms of its marketing authorisation, in circumstances where a licensed alternative is available, on financial grounds, is not permitted. In the case of belimumab, the Appraisal Committee has not reached a finding that rituximab is more clinically effective than belimumab and the recommendation in the FAD is based simply on a finding that GSK has not demonstrated that belimumab is more cost-effective than rituximab (i.e. on financial grounds). While GSK does not believe that this conclusion is reasonable (see section 2.1 below), we also believe that, as a result of the decision of the European Court, it is no longer permissible.

GSK requests that the Appraisal Committee is directed to reconsider this appraisal in the context of the European Court’s decision in European Commission v. Republic of Poland.

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

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

Rituximab was accepted as a comparator in this appraisal and, at paragraph 4.3 of the FAD, the Committee acknowledged that a proportion of SLE patients who continue to have high disease activity despite standard therapy (i.e. the group of patients who would be eligible for treatment with belimumab) are currently treated with rituximab. Rituximab is unlicensed for the treatment of
SLE and the only clinical trials which have investigated use in this indication, failed to demonstrate a benefit. Accordingly use of rituximab in SLE patients often takes place through individual funding requests. At paragraph 4.12 of the FAD, the Committee concluded that there are no reliable data to show the relative clinical effectiveness of belimumab and rituximab. At paragraphs 4.26 - 4.27 of the FAD, the Committee considered the cost-effectiveness of belimumab compared with rituximab; its comments included that: (a) the dosing schedule for rituximab could be lower than that used in clinical trials; and (b) administration/pharmacy costs for belimumab were likely to be higher than for rituximab because belimumab is given more frequently. The Committee concluded that “there was no sound case presented to it on the cost-effectiveness of belimumab compared with rituximab” and that “the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity …...despite standard therapy, compared with rituximab”.

GSK believes that the conclusions of the Appraisal Committee do not represent a reasonable view of the available evidence:

- The only available data for the benefits of rituximab in SLE are provided by the EXPLORER trial, which failed to demonstrate any statistically significant benefits of rituximab as compared with placebo, as acknowledged at paragraph 3.13 of the FAD. In contrast the BLISS trials have established the benefits of belimumab, albeit in a slightly different trial population.

- Considering simply cost-effectiveness, as the Appraisal Committee does at paragraphs 4.26-4.27 of the FAD, it is unreasonable:
  
  ▪ to base guidance on speculation that the dose of rituximab may be less than that used in clinical trials; the uncertainty regarding the dosage regime for rituximab is a reflection of the lack of regulatory approval for this indication, and the Committee may not reasonably rely on any other doses than those used in the clinical trial programme. Further, while there are some anecdotal reports suggesting that rituximab may be efficacious at a lower dose in certain patients, such evidence does not form a proper basis for decision making and it is unreasonable to consider the lower dose in the context of this appraisal, in circumstances where the higher dose used during the EXPLORER trial failed to establish efficacy in SLE;

  ▪ to take account of differing administration/pharmacy costs for the two products, but then to disregard the additional costs and clinician
time associated with the individual funding requests that must be made in each case where rituximab is prescribed for use in SLE patients.

The ERG concluded that there will never be a large head to head comparison of rituximab with belimumab in SLE patients. Therefore it is unreasonable for NICE to fail to issue adequate guidance based on the evidence available. The recommendations in the FAD have the effect that patients will continue to receive unproven rituximab, used outside the terms of its marketing authorisation, rather than belimumab, which has a marketing authorisation as a result of demonstrating benefits in clinical trials. This result is arbitrary and irrational and neither in the interests of patients or the NHS.

It is also worth noting that there are limited safety data available for rituximab in the treatment of SLE: in 2006 the independent Data Monitoring Committee (DMC) suspended enrolment into the open-label extension of the EXPLORER trial for rituximab until more data on the benefit/risk profile was available. To date, we understand that this study has not re-started enrolment and no marketing authorisation has been applied for. In contrast, in addition to belimumab’s marketing authorisation, a detailed risk management plan, agreed with the CHMP, is in place. As a result of these arrangements, the safety of belimumab will be continually monitored and further long-term safety data will be generated. GSK believes that any recommendations by the Appraisal Committee should take into account important safety implications associated with its guidance and that the apparent failure by the Committee to consider such issues in the context of rituximab for SLE is arbitrary and therefore unreasonable.

GSK requests that the Appraisal Committee is directed to reconsider the comparison of belimumab with rituximab in the context of the matters identified above.

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

The SmPC for belimumab provides for administration on days 0, 14, 28 and at 4 week intervals thereafter. A maximum period of therapy is not specified. During the course of the appraisal, the Appraisal Committee accepted the views of the clinical specialists that continuous treatment over many years was unlikely to reflect how belimumab would be used in clinical practice (paragraphs 4.4 and 4.15 of the FAD). Accordingly, in its response to the ACD, GSK proposed a revised base case which incorporated a maximum 6 year treatment duration for belimumab, reflecting the data from the Phase II
extension study, and consistent with the patterns of treatment seen with other therapies prescribed to patients with SLE.

The revised approach incorporated a maximum of 6 years treatment with belimumab, following which patients continue to receive standard of care treatments and are deemed to revert to the standard of care level of disease activity. While GSK recognised that inevitably, there is some arbitrariness associated with discontinuation of treatment at 6 years, as indicated above, the figure was not random. Long term data, in excess of 6 years, are almost impossible to generate within a clinical trial setting and the FAD acknowledges that, for most patients, “it was more probable that belimumab would be used for less than 6 years until a patient’s disease was in remission” (paragraph 4.16 of the FAD). Therefore, the maximum 6 year treatment period is closer to the likely use of the product in clinical practice. The Committee did not take into account the views of clinicians that many patients will not require treatment for 6 years, but will stop a number of years before this duration. 6 years represents a conservative estimate of a date when the majority of patients will no longer require treatment with belimumab as their disease is controlled.

In these circumstances, we believe that the Committee’s conclusions that “the rationale for the choice of a maximum treatment duration of 6 years could not be considered sufficiently robust for use as the basis of decision making” (paragraph 4.16) were unreasonable.

As explained in GSK’s response to the ACD, the choice of 6 years was based on data received from the long term Phase II extension study, as well as discussions with clinicians about treatment practices. Against a background where long term RCTs over many years are effectively impossible to conduct, the proposal, put forward by GSK, represents a reasonable interpretation of the totality of the available evidence and an appropriate approach to treatment in the proposed target population.

GSK asks that the Appraisal Committee reconsider the appraisal of belimumab in the context of treatment limited to 6 years.

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

At paragraphs 4.18 and 4.25 of the FAD, the Appraisal Committee suggests, based on experience in rheumatoid arthritis, that there remains uncertainty in the evidence about whether it was appropriate to assume that the treatment effect of belimumab is maintained over time. This conclusion is relied upon
to support the possibility that the ICER calculated for belimumab, incorporating the patient access scheme, may be too low.

However, all the evidence available to the Committee argued against a finding that treatment effects were not maintained. In particular, the Committee accepted at paragraph 4.18 of the FAD that the clinical specialists had referred to experience with SLE (rather than rheumatoid arthritis) where the effects of rituximab did not seem to diminish over time. Furthermore data from the 6 year Phase II extension study supported the view that the benefits of belimumab were maintained. For example, in relation to long-term reduction in steroid dose, the FAD acknowledges that the extension study provided additional evidence of the long-term mean reduction in steroid dose at 6 years of 5 mg a day (paragraph 4.11). There will always be uncertainty when a product is initially authorised. However, the data collected during the 6 year extension study provide a large body of evidence to support the safety and efficacy of belimumab for the treatment of SLE, and supported the data collected during clinical trials undertaken for a shorter duration. The expectation that RCTs should be run for very long durations in order to reduce long-term uncertainty in outcomes, prior to obtaining a licence for a medicine, is unrealistic and would be in practice logistically infeasible, particularly in rare diseases. To the extent that the Appraisal Committee wish to suggest that the single arm, open label design of the extension study raises questions over its reliability, this is unreasonable. We believe that a randomised, blinded study of this length in a disease such as SLE would be unethical as soon as it became apparent that belimumab was associated with benefits over standard care.

In summary, we are not aware of any evidence suggesting that the benefits of belimumab are not maintained over time, the Appraisal Committee has not suggested such evidence exists and in these circumstances the conclusion at paragraphs 4.18 and 4.25 is unreasonable.

GSK therefore asks that the Appraisal Committee should be asked to reconsider this appraisal on the basis that the clinical benefits of belimumab are maintained as demonstrated in the Phase II extension study.

THE DETERMINATION OF THIS APPEAL

GSK requests an oral hearing for the determination of this appeal.

References