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

Decision of the Panel

Introduction

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

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

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

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

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

6. Lupus UK was represented by:
   Ms Jane Dunnage
Professor David Isenberg  
Professor Ian Bruce  

7. The Primary Care Rheumatology Society was represented by:  
Dr John Dickson  
Dr Alastair Dickson  
Dr Peter Lanyon  

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

9. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel:  
Professor Peter Clark  
Professor Jonathan Michaels  
Mr Meindert Boysen  
Ms Helen Knight  
Ms Zoe Garrett  

10. All the above declared no conflicts of interest  

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

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

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

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

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

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

15. Belimumab (Benlysta®, GlaxoSmithKline) is a human monoclonal antibody that inhibits the activity of B-lymphocyte stimulator (BLyS). Belimumab has a marketing authorisation ‘as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy’.

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

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

Professor Valance, for GlaxoSmithKline, stated that belimumab was a medicine with the potential to offer very significant benefits. It was innovative because it was the first drug to target B-lymphocyte stimulator, and therefore to deplete autoreactive B-cells preferentially. That was very different from drugs that depleted all B-cells. There were good clinical trial data showing that belimumab worked, and complementary safety data. It was the only drug shown to be effective in systemic lupus erythematosus. The Company could not understand how the Appraisal Committee had
arrived at the conclusion that they did. He was totally aligned with the need to ensure that NHS used cost-effective treatments. However, the Company could not understand how the cost-effectiveness of belimumab had been judged by comparison with rituximab, which was unlicensed and lacked trial evidence.

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

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

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

Dr A Dickson, for the Primary Care Rheumatology Society, expressed concerns about the use of case series, the
sufficiency of sensitivity analyses, and other matters.

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

Appeal Ground 1: The Institute has failed to act fairly

Appeal Point Ground 1
GlaxoSmithKline

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

21. Professor Tak, for the Company, argued that the Appraisal Committee had failed to take innovation into account. Fatigue, which is difficult to capture in outcome measures, showed a clinically significant improvement at first. Because subjects become acclimatized to their current state, changes are more difficult to show at 12 months.
The medication itself was innovative, as it was directed against a novel target, B-lymphocyte stimulator, that acted to increase autoantibody responses such as occurred in systemic lupus erythematosus. Belimumab really improved the quality of life and reduced disease activity when no other treatment did. Since a significant minority of patients failed to respond to standard treatments, belimumab fulfilled an unmet need.

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

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

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

Fatigue
The Evidence Review Group had reviewed the data on fatigue.
It only improved at one time-point, and was anyway reflected in EQ-5D scores, which were included in the model, and in SF-36 scores.

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

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

Novel mode of action
The Committee was mindful of belimumab’s mode of action.

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

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

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

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

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

26. The Appeal Panel therefore dismissed this appeal point.

Appeal Point Ground 1

GlaxoSmithKline

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

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

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

The Appraisal Committee had considered the amended continuation rule in great detail. The SELENA-SLEDAI score, which was not routinely used in clinical practice, included both patient symptoms and laboratory measures. Clinical experts had told the Appraisal Committee that they would be reluctant to cease treatment if a patient had shown an improvement of 4 points on the SELENA-SLEDAI score, since that had been
judged a clinically significant improvement by, among others, the United States Food & Drug Administration. The Appraisal Committee was therefore worried that the amended continuation rule would be difficult to apply in practice; and the six-year continuation study had suggested that belimumab leads to continual improvement over time, so that even the 4 point continuation rule might be difficult to implement. There were also concerns that stopping treatment at six months would lead to disease flares, as happened with hydroxychloroquine.

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

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

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

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

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

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

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

31. The Appeal Panel therefore upheld this appeal point.

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

Appeal Point Ground 2
Lupus UK

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

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

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

In summary, the degree of uncertainty made the decision unreasonable.
Professor Clark explained that the manufacturer has submitted an economic model based on the Johns Hopkins cohort, and the Evidence Review Group agreed that this was reasonable.

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

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

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

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

All the more plausible incremental cost-effectiveness ratios were outside the acceptable range.
Professor Bruce offered the Registry he had described, suggesting it would allow a path through the uncertainty by contributing to evidence collection—a form of research.

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

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

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

34. The Appeal Panel therefore rejected this appeal point.

Appeal Point Ground 2
Lupus UK

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

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

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

Ms Dunnage, for Lupus UK, emphasized that rituximab was not the same drug as belimumab. The Final Appraisal Determination was being read by Primary Care Trusts as
saying that rituximab should not be funded as ‘it had not reached its end-point in trials,’ while at the same time failing to recommend belimumab, which had reached its end-points. She supported Professor Bruce’s suggestion of a registry.

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

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

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

38. The Appeal Panel therefore rejected this appeal point.

39. The Appeal Panel asks the Institute Board to consider the inclusion of a standard introductory paragraph reiterating the
nature and purpose of the Single Technology Appraisal in each piece of guidance produced under the Single Technology Appraisal process.

Appeal Point Ground 2
GlaxoSmithKline

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

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

The Appeal Panel heard from Professor Clark for the Committee. Professor Clark explained there were no head-to-head trials of rituximab against belimumab. Within the Single Technology Appraisal process there was no facility for the Committee to itself produce such comparison. The Committee acknowledged that any indirect comparison between the two technologies using the BLISS and EXPLORER data was difficult. Professor Clark noted that the EXPLORER trial of rituximab compared to placebo did not demonstrate efficacy but the bar in that trial was set high compared to the bar in the BLISS trials.
Professor Clark went on to outline the steps the Committee considered the Company could have taken in order to obtain better data about the relative efficacy of belimumab compared to rituximab. The Company could have extracted relevant patient level data from the EXPLORER trial, or could have used the French Registry data.

The Company had suggested that the Committee adopt an assumption of equal effectiveness. Working on that assumption, the issue between rituximab and belimumab was one of cost. The Committee was not able to assess relative clinical effectiveness in the way that it would have liked but the Committee's approach was not unreasonable.

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

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

The Panel noted the comments from Professor Clark that the Company could have done more to explore the relative cost-effectiveness of belimumab, in particular by extracting patient level data from the EXPLORER trial or using the French
Registry data. The Panel noted the statement in the Final Appraisal Determination that the Expert Review Group considered that the results of any indirect comparison between EXPLORER and BLISS would not be meaningful and the Committee's conclusion that "there are no reliable data to show the relative efficacy of belimumab compared with rituximab" [FAD 4.12]. In these circumstances the Panel did not consider it reasonable to require the Company to demonstrate relative clinical and cost-effectiveness when compared with rituximab.

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

The Panel understood from the hearing that the Committee had dealt with the paucity of data on rituximab by adopting an assumption (proposed by the Company) that belimumab and rituximab were equally efficacious. The Committee had then gone on to assess the costs relating to each technology. However, this is not clear from the Final Appraisal Determination which reiterates in its concluding paragraph on relative cost-effectiveness with rituximab that "no reliable data were available to demonstrate the relative efficacy of belimumab compared with rituximab" [4.27]. In that paragraph
the Committee reached a conclusion on cost-effectiveness compared with rituximab: "The Committee concluded that there was no sound case presented to it on the cost-effectiveness of belimumab compared with rituximab. For these reasons, the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources… compared with rituximab." (Panel's emphasis).

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

The Panel understood that the exploration of the costs associated with rituximab was in part necessary. While the Panel appreciated the desire to reduce to a minimum the amount of commercial-in-confidence information that had to be removed from the public version of the NICE Guidance, the priority must be that the Final Appraisal Determination is adequately reasoned. As the Final Appraisal Determination stands, it appears that the Committee has reached a conclusion on the cost-effectiveness of belimumab compared with rituximab based solely on an assessment of costs. If the
costs of rituximab needed to be explored in order to understand the value of the manufacturer's patient access scheme, this should have been stated explicitly and dealt with separately.

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

42. The Appeal Panel therefore upheld this appeal point.

Appeal Point Ground 2

GlaxoSmithKline

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

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

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

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

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

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

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

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

The Appeal Panel therefore rejected this appeal point.

Appeal Point Ground 2

GlaxoSmithKline

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

Professor Tak stated that there were no data to suggest that the effect of treatment waned over time. Since a long-term
randomized controlled trial was very unlikely to gain ethics committee approval, no such data were likely to be forthcoming.

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

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

50. The Appeal Panel therefore rejected this appeal point.

Appeal Point Ground 2

The Primary Care Rheumatology Society

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

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

The funding of rituximab depended on local discussion with Commissioners, and in the presence of a licensed product for systemic lupus erythematosus, it would be increasingly difficult to persuade Commissioners to fund rituximab; but the Final
Appraisal Determination did not support the use of belimumab. Professor Clark for the Committee explained that the Company, the Evidence Review Group, and the Appraisal Committee agreed that rituximab was used in the NHS to treat patients with systemic lupus erythematosus, and was therefore an appropriate comparator. There was good evidence regarding the principal comparison between belimumab and standard care, and that was modelled by the Company. The comparison between belimumab and rituximab was made on the assumption of equal efficacy put forward by the Company, so that only the relative costs were in fact compared.

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

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

Dr A Dickson suggested that a meta-analysis of results of trials involving rituximab might be helpful, although Professor Clark explained that this was not for the Institute to undertake in the course of a Single Technology Appraisal. Ms Maslen pointed
out that no such analysis was possible, because the two randomized trials of rituximab were in mutually exclusive populations.

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

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

Appeal Ground 3: The Institute has exceeded its powers

Appeal Point Ground 3

GlaxoSmithKline

3.1 [originally ground 1.3]

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

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

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

57. (i) The conclusion that belimumab should not be recommended unless GlaxoSmithKline is able to robustly
demonstrate its cost-effectiveness compared with “off-label” rituximab, despite the lack of any RCT data indicating that rituximab is effective in this indication, undermines the protection to public health provided by the medicines licensing regime (GlaxoSmithKline legal submissions para 17-21).

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

(a) Demonstrating comparative clinical and cost effectiveness

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

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

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

59. **(b) Supporting or preferring off-label use**
The Company referred to its written submissions, which it reiterated at the hearing.

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

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

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

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

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

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

64. (iii) [The Final Appraisal Determination] is inconsistent with the decision of the European Court in Case C-185/10 European Commission v. Republic of Poland.
Dr Adela Williams representing the Company referred to the GlaxoSmithKline legal submissions. In response to the legal advice provided to the Panel by DAC Beachcroft LLP Dr Williams argued that NICE’s role was not outside the scope of the Directive.

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

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

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

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

Extrapolating from the Poland case it was wrong to recommend off-label use of a product over a licensed
alternative or to encourage or support such off-label use.

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

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

(1) to recommend belimumab; or

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

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

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

The Committee’s decision was not based solely on price, as explained in the Final Appraisal Determination.
68. The Panel considered the arguments. It concluded that the *Poland* case was not analogous to this appraisal because:

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

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

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

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

69. Considering the relationship between NICE appraisals and a product receiving a licence, NICE appraises technologies referred to it by the Department of Health. While products appraised by NICE are normally appraised for use within their
licensed indication, so far as NICE is concerned this is a consequence of the referrals that the Department of Health has chosen to make to it.

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

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

72. The Company referred to its legal submissions.

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

Moreover, the Panel was unpersuaded that the nature of the
remedy available to patients suffering harm as a result of treatment with a comparator was relevant to a question of whether NICE has exceeded its powers.

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

Appeal Point Ground 3
Primary Care Rheumatology Society
3.1. The NICE guidance, which indicates that there is no advantage of “licensed” belimumab compared to “unlicensed” rituximab, will potentially lead doctors into a situation which conflicts with advice issued by the General Medical Council (2008) and the MHRA (2009)
75. This point was considered by the Panel alongside GlaxoSmithKline Ground 3.1(ii).
76. For the reasons outlined above in relation to GlaxoSmithKline Ground 3.1(ii) the Appeal Panel rejected this ground of appeal.

Appeal Point Ground 3
Primary Care Rheumatology Society
3.2 The NICE guidance, which indicates that there is no advantage of “licensed” belimumab compared to “unlicensed” rituximab, will potentially lead to severe adverse unintended consequences for lupus patients... Not only will they not be able to access treatment with belimumab, but it is likely that they will now find it much more difficult to access the comparator drug rituximab.
77. Dr John Dickson from the Primary Care Rheumatology Society explained that if the Final Appraisal Determination became NICE guidance it would be very difficult for patients to access belimumab. Dr Alistair Dickson highlighted that the disease affected women in their reproductive years and any extension of life would make a significant difference to families with young children. The Panel noted the concern raised in the
Society’s written submission that if the Final Appraisal Determination becomes guidance, this will potentially lead to reduced patient access to rituximab.

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

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

80. The Appeal Panel rejected this ground of appeal.

Conclusion and effect of the Appeal Panel’s decision

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

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

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