BELIMUMAB (BENLYSTA®) FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

ELICITING ESTIMATES OF LONG-TERM TREATMENT DISCONTINUATION RATES

REPORT BY THE DECISION SUPPORT UNIT

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1. INTRODUCTION

1.1 BACKGROUND TO THE APPRAISAL

NICE is currently developing a technology appraisal on belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (SLE). The Summary of Product Characteristics (SmPC) for belimumab states that the recommended dose regimen is 10 mg/kg on days 0, 14 and 28, and at 4-week intervals thereafter.[1] Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after the first 6 months of treatment.

In the manufacturer's submission, the belimumab BLISS clinical trials[2] informed the likelihood of response at Week 24 and the rate of discontinuation thereafter. In the manufacturer's model, patients discontinued treatment after Week 24 if they did not have an improvement in SELENA-SLEDAI (SS) score of 4 points or more. Using an SS score of ≥4, the annual discontinuation rate in those responding to treatment was estimated to be 8% per year, based on *post hoc* subgroup estimates from the BLISS trials. Scenario analyses were presented by the manufacturer assuming alternative discontinuation rules and assuming no discontinuation rule. These scenario analyses used alternative annual discontinuation rates, also based on the BLISS trial data.[2] However, clinical specialists at the NICE Appraisal Committee meeting considered that a lifetime treatment with belimumab and the durations of treatment predicted in the model were unrealistic.

In response to consultation, the manufacturer presented long-term efficacy and safety data for belimumab from an open-label, Phase II extension study (LBSL02/99 - Merrill *et al*. 2011; Merrill *et al*. 2012[3;4]). In their response, the manufacturer reported that an annual discontinuation rate of approximately 13% was observed in this study (based on a conference presentation only). This estimate of 13% was subsequently revised by the ERG to be 11.6% based on new availability of 7-year data and what they perceived to be an error in the calculation of the previous 13% estimate. In October 2012, 4-year data from this study were published in full;[4] within this paper, the authors indicated that the overall rate of discontinuation during the first year of belimumab exposure was 16% and the rate decreased during years 2–4 of the long-term continuation study (range 9–14%). The two most common reasons for discontinuation in year 1 (adverse events and patient request) were reported to decrease over time.[4] This study does not however relate specifically to the *post hoc* subgroup reflected within the manufacturer's model.

In addition, following an appeal, the manufacturer presented a scenario analysis that included a variable annual discontinuation rate of 13% up to Year 5 and 30% each year thereafter. The manufacturer stated that the variable discontinuation rate more closely represented the distribution of

treatment durations likely to be prescribed in clinical practice for patients in the target population and that other immunosuppressants for SLE are prescribed only for between 2 and 5 years. The manufacturer stated that belimumab would likely be used in the same way as other immunosuppressants, that is, patients will discontinue belimumab as early as possible once sustained disease control was achieved. This does not however reflect the licensed indication for belimumab, or the conduct of the trial. It should be noted that the manufacturer has thus changed their assumptions to handling belimumab discontinuation in the model twice since their original submission.

The manufacturer's economic model is sensitive to the rate of annual discontinuation assumed, whereby higher rates of annual discontinuation lead to more favourable estimates of cost-effectiveness for belimumab. The NICE Decision Support Unit (DSU) was asked by NICE to explore the range of possible rates of annual discontinuation, taking into consideration those that have been used in the analyses submitted for the appraisal, and to explore whether there are alternative evidence sources available that could inform the value(s) used in the economic model.

This report presents the methods and findings of additional work undertaken by the DSU to elicit estimates of natural discontinuation rates for SLE patients treated with belimumab, with the intention of reducing, or better expressing, the uncertainty surrounding this quantity.

1.2 QUESTIONS TO BE ADDRESSED BY THE DSU

Taking into account the marketing authorisation describing the continuous use of belimumab, the DSU was asked to address the following questions:

1. What is the expected discontinuation rate of belimumab in people whose active autoantibody-positive systemic lupus erythematosus has responded to treatment?
2. Would discontinuation rates differ depending whether an SS score improvement of 4 or 6 was required at Week 24? If so, how may those discontinuation rates differ?
3. Is there any further supporting evidence about belimumab treatment discontinuation that has not already been provided to NICE, for example from registries and similar datasets?
4. In the absence of any further evidence regarding discontinuation rates for belimumab, is there any other evidence for use of immunosuppressants in SLE or other conditions, that can be drawn on to inform estimates of the rate of annual discontinuation for belimumab?
5. What are the estimated ICERs (including appropriate scenario/sensitivity analyses) for belimumab compared with standard care when incorporating any alternative values identified for the discontinuation rate?

1.3 CONSTRAINTS IMPOSED BY THE MANUFACTURER'S MODEL STRUCTURE

It should be noted that there are two versions of the GSK health economic model:

- "Model 1" - the original version of the model submitted at the beginning of the NICE appraisal process, and;
- "Model 2" a modified version of the model submitted post-appeal.

Model 1 characterises the natural discontinuation parameter as a single probability which is applied from 6-months until the end of the model time horizon. Model 2 is more flexible as it includes the possibility of variable rates for individual years since starting treatment. This represents a different structural assumption between the models - only Model 2 is structurally capable of handling time-dependent discontinuation probabilities.

2. METHODS

2.1 METHODS FOR THE IDENTIFICATION OF EXISTING EMPIRICAL RESEARCH ON LONG-TERM DISCONTINUATION RATES FOR BELIMUMAB

The DSU contacted two Rheumatoid Arthritis (RA) registries to enquire whether they held additional relevant data concerning long-term belimumab discontinuation rates for patients with SLE. These registries were the European SLE International Collaborating Clinics Programme (Manchester contingent – see http://www.cmft.nhs.uk/) and the US National Databank on Rheumatic Diseases (http://www.arthritis-research.org/).

The lead for the UK contingent of the SLICC, Professor Ian Bruce, stated that the registry did not hold relevant data on patient discontinuation for belimumab since the drug had not been approved by NICE. Consequently, uptake has been on an exceptional basis only. He also noted that registry itself is still in the early phases of development. The US registry also informed the DSU that they have not had any patients on belimumab for any substantive period of time. Following advice received from Professor Bruce, Dr Anca Askanase at Bellevue Hospital, New York, was contacted as she has undertaken some work on belimumab use amongst US physicians. However, Dr Askanase's study does not yet contain long-term follow-up data beyond 6 months.

Other published empirical studies relating to belimumab discontinuation were *not* sought as (i) the DSU felt that all relevant published evidence would have been identified during the appraisal process and (ii) initial timescales for the delivery of the report precluded a full systematic search and review process.

Given the absence of other relevant data on belimumab discontinuation, the DSU sought to elicit estimates using expert clinical opinion from UK experts, as detailed below.

2.2 METHODOLOGICAL ISSUES SURROUNDING THE ELICITATION OF DISCONTINUATION RATES

Initially, it had been envisaged that formal face-to-face elicitation would be undertaken, facilitated by expert statisticians within the DSU using the Sheffield Elicitation Framework (SHELF) (http://www.tonyohagan.co.uk/shelf/). There are a number of different ways of designing such exercises within a formal elicitation framework. Whilst planning this elicitation exercise, the DSU considered the Roulette Method[5;6] to be the most applicable to this particular decision problem. Using the Roulette method, the expert provides probabilities of the uncertain quantity of interest (denoted θ – in this case, this quantity relates to the proportion of patients who discontinue belimumab treatment within a particular time interval). The experts' subjective belief that θ lies within particular probability intervals is elicited by specifying intervals as 'bins' and by allocating `gaming chips' to that bin. Thus, the expert distributes n chips amongst m bins, with the proportion of chips allocated to a particular bin representing her subjective belief about the probability of θ. m is fixed within the structure of the exercise, whilst n is chosen by the respondent. This method therefore enables the respondent to construct a graphical representation of their prior beliefs regarding uncertain quantity θ.

It should be noted that in this instance we are not solely interested in eliciting a single distribution for discontinuation rate θ; whilst the original submitted manufacturer's model (Model 1) assumed a fixed discontinuation rate (dependent on initial SS response), the model submitted post-appeal (Model 2) included the facility for this probability to be time-dependent. Therefore, there is uncertainty not only around the value of θ, but also in how other covariates influence this discontinuation rate. The key issues in structuring the elicitation exercise relate to:

(i) The level of detail to which the discontinuation parameter θ is specified (elicitation of a single constant discontinuation parameter or elicitation of multiple discontinuation parameters by cause e.g. lack of efficacy, adverse events, non-compliance, other etc.);
(ii) The nature of the discontinuation parameter(s) defined in (i) over time;
(iii) The conditionality of natural discontinuation specified in (i) and (ii) according to initial response as measured by SELENA-SLEDAI score (SS≥4 or SS≥6);
(iv) The design of more qualitative information collection to explain and justify the quantitative values elicited.

The DSU sought advice on these structural issues surrounding the elicitation exercise from Dr Mohammed Akil, Consultant Rheumatologist, Royal Hallamshire Hospital, Sheffield. Dr Akil advised

that specific causes of discontinuation may be important and that it is reasonable to believe that these may vary over time. The questions asked by NICE (see Section 1.2) also required the elicitation of separate estimates according to initial SS score. As a consequence, this introduces considerable complexity to the elicitation exercise as a number of alternative estimates of discontinuation parameter θ are required.

2.3 PRACTICAL ISSUES SURROUNDING THE ELICITATION OF DISCONTINUATION RATES

Ideally, elicitation exercises should be undertaken in a face-to-face setting whereby the facilitator help the respondent fully express the uncertainty surrounding their beliefs, as well as ensuring that the respondent is fully aware of what they are being asked to do. Furthermore, the use of a graphical interface means that the respondent can immediately see their beliefs expressed as a crudely stated probability distribution for uncertain quantity θ. This has further benefits in ensuring that the respondent's expressed beliefs are stated as they intended.

However, these benefits also carry several costs – in particular, such exercises are time-consuming, requiring an initial training exercise to help respondents think about uncertainty and for them to familiarise themselves with the structure of the exercise, and typically around 1-day of elicitation time per expert (overall time requirements are dependent on the number of estimates of θ to be elicited). Given the need to estimate θ at different timepoints as well as for separate SS subgroups, we concluded that such an exercise would be very unlikely to be feasible in practice across more than 5-6 clinical experts. As an alternative, we also considered the feasibility of undertaking the elicitation exercise via telephone interview individually or within small groups, however this would still have considerable time implications for each participating clinician. The DSU takes the view that it is unlikely that many clinicians would have consented to participate in such an exercise for practical reasons alone.

For reasons of pragmatism, and to allow us to reflect the views of a wider pool of SLE experts, we decided that a survey-based approach would be quicker and more feasible for participants and would produce more generalisable information for the NICE Appraisal Committee.

2.4 SURVEY METHODS

Forty one lupus experts were invited to complete the survey questionnaire. Clinical experts were identified through their membership of either the British Isles Lupus Assessment Group (BILAG, contact details provided by Dr Akil) and/or the St Thomas' Lupus Trust (http://www.lupus.org.uk/contact/find-a-specialist). All experts were expected to have experience treating patients with SLE, but not necessarily to have experience treating SLE patients with

belimumab. Experts were sent an electronic version of the questionnaire via an email from NICE together with a cover letter explaining the anticipated role of the questionnaire in informing the technology appraisal. A reminder email was later sent with the intention of increasing the number of survey respondents.

Within the questionnaire, potential respondents were asked to provide information on the following:

- Personal information (name, role, whether they have treated lupus patients, whether they have treated patients with belimumab)
- The mean proportion of patients expected to discontinue belimumab within a given 12-month time interval
- The upper and lower 95% credible intervals for the discontinuation proportions
- The number of hypothetical patients upon which each discontinuation proportion is based as a further measure of their uncertainty surrounding their beliefs (note – this information was elicited separately to the credibility interval around the mean discontinuation rate)
- Whether the respondent believes the discontinuation probability to be time-dependent.

Separate estimates were requested for patients with an initial SS score ≥4 and initial SS score ≥6. The final survey questionnaire sent to invited participants is presented in Appendix 1. All responses were anonymised within the analysis.

3. SURVEY RESULTS

3.1 RESPONSE RATE

Of the 41 clinicians invited to complete the survey questionnaire, 14 (34.1%) clinicians responded. However, of these only 3 clinicians (7.3%) completed the questionnaire, either in part or in full.

3.2 REASONS FOR NON-COMPLETION

The reasons given for non-completion of the questionnaire are presented in Table 1. The responses provided by the non-completers suggest that the principal reason for non-completion was that belimumab is not approved in the UK, hence they found it difficult, if not impossible, to provide credible estimates of long-term discontinuation rates with any degree of uncertainty.

Table 1: Reasons given for non-completion of the questionnaire

Resp. no.	Reason for non-completion
R1	I never received your original e-mail but did receive a lot of e-mails from colleagues in the BILAG group who had received it. The general consensus appeared to be that due to the very small number of patients with lupus treated with belimumab so far in the UK it was difficult to give meaningful answers to these questions and I think you will have received letters from several people explaining this.
R2	As you will be aware the situation in the UK is that the drug has been restricted quite significantly because while it has a European licence it has got no current NICE guidance to support its use, therefore we have had a very limited experience of using the drug. This is also compounded by the fact that the UK did not have a large number of centres involved in the actual clinical trial programme. The scenarios therefore posed within your questionnaire are therefore too speculative for me to actually put realistic numbers on particularly given the fact that there is likely to be a major decision making process around these figures. My own estimates would be based only on the literature and not from personal experience.
R3	... I could not answer the questionnaire as I have only had one patient on belimumab. I do not have enough experience of this drug to make reasonable estimates. For what it is worth my patient had failed all other medications before and did very well with this drug over first 12 months, and managed to reduce steroids significantly for her from 20mg to 10mg daily.
R4	I am very sorry to say that I am not able to answer your survey with any certainty and indeed this might reasonably be viewed as unanswerable with any degree or range of certainty given the lack of experience which anyone currently has in the UK in the use of this agent, which is likely to cause problems with the validity of any responses.
R5	Many thanks for the questionnaire. I fear that you are going to find it very difficult to get information from this. Most rheumatologists have experience of 1 or 2 patients on belimumab if any. In general SLE patients have flares of severe life threatening disease that can be controlled over several months. However, there are a group of very severe disease who require continuous therapy for years. Sorry I can't help more.
R6	Thank you very much for asking me to participate in this survey. Unfortunately, despite my interest in the field I have so far not used Belimumab and all that I know about this drug comes from published data from clinical trials. I did not participate in these trials and therefore my experience with this drug is nil. Therefore, I think I will not be able to answer the questions raised in your survey. Sorry that I am not able to help on this occasion.
R7	I'm sorry to say that I am unable to answer the survey questionnaire sent to me from NICE regarding the discontinuation of belimumab in the different scenarios posed. I have not used belimumab nor was I involved in the clinical trials and I do not assess my SLE patients using the SELENA-SLEDAI. In any case the change of 4 or 6 is rather arbitrary. Therefore, I am sorry that I am unable to answer the questionnaire sent out by NICE regarding Belimumab.
R8	I received your request to complete the survey questionnaire in relation to the use of Benlysta but I am sorry to have to tell you that I really feel unable to answer it. I would like to explain why. In the past, as new drugs ranging from cyclosporine in the early 1980s to mycophenolate in the late 1990s and, in the last decade to rituximab, have become available, treating a modest number of patients enabled you to get a feel for the period of time necessary to treat, the response rate, the relapse rate etc. I have treated precisely one patient with Benlysta and I simply have no idea how the patients that I might prescribe it for and who, incidentally, are likely to have more than just the skin and joint involvement which Benlysta is approved for, will respond. How could I possibly be expected to know this?? I am also rather flummoxed by your division into SELENA/SLEDAI responses of more than 4 or more than 6. Could I with any degree of accuracy distinguish a patient with a response of 5 SELENA/SLEDAI points compared to one who has a 7 point response? I very seriously doubt it. I think your questions might have made some more sense if you attempted to distinguish patients say of 4 point SELENA/SLEDAI response and one with more than 10. With apologies, I just don't find this questionnaire credible. Finally, I am used to using the BILAG

	system for assessment not the SLEDAI system but this is a relatively minor point.
R9	I see a lot of lupus patients, but I have no experience yet of using Belimumab as other consultants in our dept currently manage these patients
R10	I have not been able to prescribe belimumab so can't help with your expert survey
R11	As you might know the current UK wide experience with belimumab in SLE is very small. We only have one patient in our unit who has been just started on belimumab and I doubt that other lupus units in the UK will have enough numbers to address the points raised in your questionnaire. I have great difficulty in predicting likely discontinuation rates during the period 6 months to 18 months based on imaginary number of patients. I am no statistician but have to raise my concern whether this is a scientifically acceptable way of assessing a drug which has the potential to benefit patients with SLE? I can only assume that approval by the FDA is commensurate with the view that belimumab has something to offer some but not all lupus patients. Can NICE not consider looking at the possibility of allowing the use of belimumab on named patient basis for a defined period of time (18 months) according to a strict protocol and hopefully that will address the issues of efficacy and short term safety in real-life situation. It will also address the issue of drop-outs over the period. Any drug no matter how cheap or expensive will only establish itself in clinical practice when it proves its therapeutic worthiness and no responsible clinician will continue to use a drug that has no therapeutic benefits or is unsafe irrespective of its cost or molecular sophistication. Thanks again for giving us the opportunity to engage with NICE.

3.3 ELICITED ESTIMATES OF DISCONTINUATION

Table 2 presents elicited estimates of discontinuation rates for patients receiving belimumab.

Table 2: Elicited estimates of belimumab discontinuation

Respondent no.	R12	R13	R14
Background information			
Experience in treating lupus patients?	Yes	Yes	Yes
Experience in using belimumab?	Yes	No	Yes
Believed nature of dropout rate over time	Increasing	Increasing	Increasing
Initial response SELENA-SLEDAI 4 (mean proportion, lower CrI, upper CrI), number of patients			
p(discontinue) 6-18 months	**~25%** (NR,NR), 6	**8%** (2%,15%), 50	**15%** (10%,20%), 100
p(discontinue) 18-30 months	**~25%** (NR,NR), 6	**12%** (5%,20%), 25	**20%** (15%,25%), 100
p(discontinue) 30-42 months	**75%** (NR,NR), 6	**15%** (7%,35%), 25	**25%** (20%,30%),50
p(discontinue) 42-54 months	**100%** (NR,NR), NR	**17%** (8%,40%), 20	**30%** (25%,35%), 50
p(discontinue) 54-66 months	**100%** (NR,NR), NR	**20%** (8%,40%), 20	**50%** (45%,55%), 30
p(discontinue) annual >66 months	**100%** (NR,NR), NR	**20%** (10%,45%), 15	**55%** (50%,60%), 50
Initial response SELENA-SLEDAI 6 (mean proportion, lower CrI, upper CrI), number of patients			
p(discontinue) 6-18 months	**~25%** (NR,NR), 6	**8%** (2%,15%), 50	**10%** (5%,15%), 80
p(discontinue) 18-30 months	**~50%** (NR,NR), 6	**12%** (5%,20%), 25	**15%** (10%,20%), 80
p(discontinue) 30-42 months	**75%** (NR,NR), 6	**15%** (7%,35%), 25	**25%** (15%,25%), 20
p(discontinue) 42-54 months	**90%** (NR,NR), NR	**17%** (8%,40%), 20	**25%** (20%,30%), 30
p(discontinue) 54-66 months	**100%** (NR,NR), NR	**20%** (8%,40%), 20	**40%** (35%,45%), 30
p(discontinue) annual >66 months	**100%** (NR,NR), NR	**20%** (10%,45%), 15	**50%** (45%,55%), 30

CrI – credible interval; p(discontinue) – probability of discontinuation

All three participating respondents had experience of treating lupus patients, although only two of these (R12 and R14) had experience in treating patients with belimumab. Two of the three participating respondents (R12 and R14) believed that initial SS response would lead to different long-term discontinuation probabilities; the third respondent (R13) believed that these probabilities of discontinuation would be independent of initial response.

All three participating respondents believed that discontinuation rates would increase over time. Respondent R13 cited disease flares (relapses) and patient tolerability/inconvenience as the main reasons for discontinuation; this respondent also noted that there will be a smaller subgroup with an excellent response in whom all features of disease have gone and there will be patient and physician pressure to discontinue belimumab. Respondent R14 stated that nearly all therapies used in SLE patients are associated with an increased drop-out rate over time. The respondent cited the increased risk of sepsis associated with prolonged immunosuppression, patient preference, pregnancy planning and loss of clinical effect as the main reasons for discontinuation.

The elicited estimates presented in Table 2 indicate a substantial degree of discordance between the three participating respondents. For patients with an initial response of ≥4 SS points, estimates of discontinuation within year 1 range from 8% to 25% with the degree of discordance increasing with each additional 12-month interval. It is also noteworthy that the credible intervals provided by Respondents R13 are particularly wide although these do overlap with the credible intervals from Respondent R14 up to 42 months. One respondent (R12) did not complete these fields of the questionnaire. Overall, this indicates that amongst the responders who completed the questionnaire, there are no strong prior beliefs independent of published data which can help resolve the problem. Whilst based on very few experts' responses, these results indicate considerable uncertainty surrounding their beliefs about the true discontinuation rates. However, given the low completion rate for the questionnaire, limited confidence can be placed on the relative credibility of these estimates over and above those already available in the literature.

4. DISCUSSION

The purpose of this short study was to elicit estimates of natural discontinuation rates for SLE patients treated with belimumab in order to reduce, or better express, the uncertainty surrounding this parameter. Whilst a formal elicitation exercise was originally planned as the means of deriving these subjective judgements, we did not believe this would be feasible for practical reasons. Instead we developed a survey questionnaire to elicit the same type of information. Unfortunately, the completion rate for the questionnaire was very low (3 respondents, 7.3% of the invited sample) and no further model analysis was undertaken by the DSU. Given the reasons for non-completion presented in Table 1, it is reasonable to speculate that those individuals who did not complete the questionnaire would have also refused to consent to participate in the elicitation exercise. The DSU do not believe that the results of this survey have more credibility than other estimates available within the published literature.

In light of the very limited evidence provided by the survey, there appear to be three possible alternative evidence-based options for estimating the long-term discontinuation rate for belimumab:

1. **Draw on evidence of long-term dropouts from other immunosuppressants used to treat SLE or other autoimmune diseases**. The DSU would caution against this type of approach – as noted by within the manufacturer's submission, there has been little therapeutic innovation in treatments for SLE, with no evidence leading to the development of new licensed treatments for several decades. Interpolating discontinuation rates from evidence for other immunosuppressants in SLE, or even across other autoimmune disorders, may not reflect the actual expected rates for belimumab, would inevitably be subject to considerable uncertainty and may conflict with the licensed indication for belimumab.

2. **Use the BLISS trials to inform discontinuation rates.**[2] This was the approach initially adopted by the manufacturer. The most significant problem with this approach is that the BLISS trials were short in duration and the incentives for patients continuing/discontinuing treatment within the clinical trial protocols may not fully reflect expected NHS practice. If the causes of belimumab discontinuation are time-dependent, as suggested by the long-term extension study and the clinical experts who completed the questionnaire, the use of these trials to inform long-term discontinuation is likely to fail to capture such effects.
3. **Use the long-term open-label study to inform discontinuation rates (LBSL02/99[3]).** This evidence was presented by the manufacturer in response to the consultation. Whilst this study provides much longer follow-up than the BLISS trials, these patients may not correspond well with the target population from the BLISS trials, or the 24-week response criteria adopted by the manufacturer. In addition, the design of this study, which focusses on safety, indicates that there may be other incentives to keep patients on treatment which may somewhat bias observed estimates of belimumab discontinuation.

5. REFERENCES

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APPENDIX 1

Survey questionnaire on the long-term use of belimumab (Benlysta®) for systemic lupus erythematosus (SLE)

NICE Decision Support Unit

Please complete this questionnaire electronically and return to [redacted]

1. BACKGROUND

The National Institute for Health and Clinical Excellence (NICE) makes recommendations to the NHS about the use of new and existing health technologies. NICE has recently undertaken an appraisal of belimumab for the treatment of systemic lupus erythematosus (SLE). This technology appraisal has been subject to a number uncertainties relating to the available short-term randomised trial evidence and the absence of longer-term studies. One particular area of uncertainty concerns the rate at which patients with SLE discontinue treatment with belimumab over time. This discontinuation rate has the potential to substantially influence the expected cost-effectiveness of belimumab. The NICE Decision Support Unit (DSU) has been asked to undertake further work with the intention of better characterising the nature and value of expected belimumab discontinuation rates using opinion from clinical experts. You have been sent this survey questionnaire because you have been identified as an expert in the treatment of patients with SLE. In this questionnaire we would like you to express your subjective beliefs about the expected discontinuation rates for patients with SLE receiving belimumab.

2. EXISTING EVIDENCE ON LONG-TERM DISCONTINUATION RATES FOR BELIMUMAB

In April 2011, GlaxoSmithKline (GSK) submitted evidence relating to the clinical effectiveness and cost-effectiveness of belimumab to NICE. This submission included a summary of available clinical trials and a cost-effectiveness model. The main clinical evidence within the submission was taken from the BLISS trials.[1] The BLISS trials were randomised, double-blind, placebo-controlled,

multicentre trials comparing belimumab 1mg/kg and 10 mg/kg plus standard therapy with placebo plus standard therapy in patients with active SLE.[1] Within the GSK cost-effectiveness model, the BLISS trials were used to inform the likelihood of response at Week 24 and the rate of discontinuation thereafter. The model assumes that patients discontinue belimumab after Week 24 if they do not have an improvement in SELENA-SLEDAI score of 4 points or more. Within the patient subgroup that had an improvement in SELENA-SLEDAI score of 4 points or more, the subsequent annual belimumab discontinuation rate was estimated to be 8% each year, based on unpublished BLISS subgroup data. Clinical specialists at the NICE Appraisal Committee meeting considered that lifetime treatment with belimumab and the durations of treatment predicted in the model were unrealistic. Later in the appraisal process, GSK presented long-term efficacy and safety data for belimumab from an open-label, Phase II extension study (Study LBSL99).[2] This extension study suggests an annual discontinuation rate of around 12-13%, however there remain questions regarding the representativeness of the population recruited into this study.

There is no other empirical evidence relating to the long-term discontinuation rates for belimumab treatment in patients with SLE.

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PLEASE READ THE GUIDANCE IN THE NEXT SECTION BEFORE COMPLETING THE QUESTIONNAIRE

3. GUIDANCE ON COMPLETING THIS QUESTIONNAIRE

When answering each question, please carefully consider the following:

(i) Reasons for discontinuation

We are interested only in the continuous use of belimumab (Benlysta®) **in line with its marketing authorisation** – please **do not** include discontinuation due to treatment response or stabilisation in your responses.

When completing the questionnaire, please consider the following reasons for discontinuation:

1. **Loss of efficacy** – patients who discontinue treatment due to a lack of response to belimumab.
2. **Adverse events** – patients who discontinue treatment due to the incidence of side effects, complications or inability to tolerate treatment.
3. **Other patient-related causes for discontinuation** – patients who discontinue treatment for other non-clinical reasons, for example patient choice or migration.

(ii) Type of information requested

The majority of the questions in this questionnaire are presented in the same format. The information we would like to request concern:

(a) **The expected mean discontinuation rate** – Your subjective belief about the mean percentage of patients that would discontinue belimumab treatment within a particular time period.

(b) **The 95% credible interval** – This is the interval within which you are 95% certain that the true mean discontinuation rate lies. The width of the credible interval will give us some idea about how uncertain you are about your stated discontinuation rate. The wider the interval, the more uncertain you are. Suppose your mean estimate is 20% for a given 12 month period - a credible interval of 5% to 35% implies more uncertainty than a credible interval of 18% to 22%. Note that this credible interval does not need to be symmetrical but must include the mean.

(c) **The number of imaginary patients that reflects your uncertainty** – This is another measure of your uncertainty. A smaller sample size (for example *n*=10 patients) would imply more uncertainty around your expressed belief, whilst a larger sample size (for example *n*=1,000 patients), would imply that you are more certain about your expressed belief.

PLEASE COMPLETE ALL QUESTIONS HIGHLIGHTED IN YELLOW

4. PERSONAL INFORMATION

Please note: Your personal information will be held as strictly confidential by NICE and the DSU and will not be shared with any other party.

(i) Your name

PLEASE STATE

(ii) Your institution

PLEASE STATE

(iii) Your professional role

PLEASE STATE

(iv) Have you had experience treating lupus patients?

PLEASE MARK (X) **YES** **NO**

(v) Have you had experience treating lupus patients with belimumab?

PLEASE MARK (X) **YES** **NO**

5. SURVEY QUESTIONNAIRE

QUESTION 1 – BELIMUMAB DISCONTINUATION BETWEEN 6 MONTHS AND 18 MONTHS

Imagine that you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment. We would like you to consider the likely discontinuation rates during the period 6 months to 18 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 1

Discontinuations between 6 and 18 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 2 – LONGER-TERM DISCONTINUATION RATES

Do you believe that the discontinuation rate between 6 months and 18 months would be the same for each subsequent 12 month treatment period? Or alternatively, would the rate increase or decrease? Please also provide a reason for your answer.

Response 2

	PLEASE MARK (X)	**PLEASE PROVIDE A REASON FOR YOUR ANSWER**
(i) Same dropout rate over time		
(ii) Dropout rate increases over time		
(iii) Dropout rate decreases over time		

IF YOU BELIEVE THAT THE DISCONTINUATION RATE IS CONSTANT DURING EACH 12-MONTH INTERVAL, THE QUESTIONNAIRE IS COMPLETE. IF YOU BELIEVE THAT THE RATE DIFFERS FROM YEAR TO YEAR, PLEASE PROCEED TO QUESTION 3.

QUESTION 3 - BELIMUMAB DISCONTINUATION BETWEEN 18 MONTHS AND 30 MONTHS

Imagine that you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 18 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 18 months. We would like you to consider the likely discontinuation rates for the period 18 months to 30 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 3

Discontinuations between 18 and 30 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 4 - BELIMUMAB DISCONTINUATION BETWEEN 30 MONTHS AND 42 MONTHS

Imagine you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 30 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 30 months. We would like you to consider the likely discontinuation rates for the period 30 to 42 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 4

Discontinuations between 30 and 42 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 5 – BELIMUMAB DISCONTINUATION BETWEEN 42 MONTHS AND 54 MONTHS

Imagine you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 42 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab treatment after 42 months. We would like you to consider the likely discontinuation rates for the period 42 months to 54 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 5

Discontinuations between 42 and 54 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 6 – BELIMUMAB DISCONTINUATION BETWEEN 54 MONTHS AND 66 MONTHS

Imagine you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 54 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 54 months. We would like you to consider the likely discontinuation rates for the period 54 months to 66 months. What percentage of patients in each cohort would you expect to discontinue belimumab treatment during this period? Please also provide a 95% credible interval.

Response 6

Discontinuations between 54 and 66 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

QUESTION 7 – BELIMUMAB DISCONTINUATION AFTER 66 MONTHS

Imagine you have two cohorts of lupus patients. The first cohort had a response of ≥4 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 66 months. The second cohort had a response of ≥6 SELENA-SLEDAI points after 6 months of belimumab treatment and are still receiving belimumab after 66 months. We would like you to consider the percentage of patients who are likely to discontinue treatment each year after 66 months. Please also provide a 95% credible interval.

Response 7

Annual discontinuations after 66 months	**Subgroup with 6-month response ≥4 SELENA-SLEDAI points**	**Subgroup with 6-month response ≥6 SELENA-SLEDAI points**
	RESPONSE (STATE NUMBER)	**RESPONSE (STATE NUMBER)**
Mean percentage of patients discontinuing treatment		
Upper 95% credible interval		
Lower 95% credible interval		
Given your uncertainty, how many imaginary patients is your estimate based on?		

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE. PLEASE EMAIL THE COMPLETED QUESTIONNAIRE TO [redacted]