NICE National Institute for Health and Care Excellence

Slides for the projector and public - no confidential information

Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (review of TA397)

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Company: GlaxoSmithKline (GSK)
ACM2: 16 September 2021

Key issues for consideration

Key issues	
1. PSM analysis applied as a calibration factor	• Has the committee seen any evidence to change its conclusion that the results of the PSM is biased in favour of belimumab? • Has the committee seen any evidence to change its conclusion that the application of the calibration factor is not suitable for decision-making?
2. 24-week response and treatment continuation	Is the company's modelling of 24-week response and treatment continuation in line with the BLISS trials and clinical practice?
3. Non-responder disease activity	Does the committee still consider that disease activity for belimumab non-responders should be based on the BLISS trials for the first 52 weeks?
4. Violation in utility estimation	Is the committee satisfied that the error in utility estimation is not likely to have a significant impact on the cost effectiveness results?
5. Comparison with rituximab	Has the committee seen any evidence to change its preference for an indirect treatment comparison between belimumab and rituximab?

Belimumab (Benlysta, GSK)

Marketing authorisation	Benlysta is indicated as add-on therapy in people aged **5 years and older** (previously adults only in TA397) with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy. Note: Subcutaneous formulation of belimumab is indicated in **adults only.**
Administration	2 formulations: intravenous (IV) and subcutaneous (SC) injection
Mechanism of action	Human monoclonal antibody that inhibits the activity of B-lymphocyte stimulator (BLyS).
Price	The list price for the IV formulation is £405.00 for the 400mg vial and £121.50 for the 120mg vial (excluding VAT). The list price for the SC formulation is [redacted] per 200mg pre-filled pen (excluding VAT). The company has a confidential commercial arrangement (simple discount patient access scheme - updated post ACM1).

- **SmPC states that discontinuation of treatment should be considered if there is no improvement in disease control after 6 months of treatment.**
- **Belimumab is now licensed for adults with lupus nephritis but this indication is outside of the scope of this appraisal (as outlined in the company submission).**

Appraisal history

- Belimumab is currently recommended in NICE technology appraisal (TA) 397 as an add-on treatment option for adults with systemic lupus erythematosus (SLE) within a managed access agreement (MAA).
- The MAA aimed to collect data on belimumab using the British Isles Lupus Assessment Group-Biologics Registry (BILAG-BR) to resolve the uncertainties identified by the committee.
- This appraisal is a review of TA397 now that the data collection period has ended.
- Company considers that the data captured from the BILAG-BR was limited because the high disease activity population (HDA-1) recommended in TA397 was too restrictive in clinical practice.
- Company has defined a broader high disease activity target population (HDA-2) in this appraisal that would allow more patients access to belimumab.
- The committee concluded that the company's updated population was appropriate for decision-making.

  - HDA-1: Patients with a SELENA SLEDAI score ≥10 AND low complement AND positive anti-dsDNA **(TA397)**
  - HDA-2: Patients with a SELENA-SLEDAI score ≥10 AND low complement OR positive anti-dsDNA **(company base case)**

Appraisal history

Belimumab is not recommended, within its marketing authorisation, as an add-on therapy for active autoantibody-positive systemic lupus erythematosus in people 5 years and older when there is a high degree of disease activity (for example, positive anti-double-stranded DNA, low complement) and despite standard therapy.

May 2021	June 2021	June – July 2021	Sept 2021
ACM1	ACD released	Consultation comments received	ACM2

Comparators

- The comparators in the final scope for this appraisal include:
    - **Standard therapy alone**

  For people in whom it is considered appropriate:
    - **Rituximab plus standard therapy**
    - **Cyclophosphamide plus standard therapy.**
- Standard therapy for treating SLE is likely to consist of non-steroidal anti-inflammatory drugs, corticosteroids, antimalarials and immunosuppressants (some are used off label in clinical practice).
- Rituximab is not licensed for SLE but available through routine commissioning for refractory SLE in adults and post-pubescent children who meet the criteria set in the NHS England clinical commissioning policy (updated July 2020).[a]
- The committee understood that, if belimumab is not recommended for routine commissioning, more people would potentially have treatment with rituximab in its absence.

- **The committee concluded that:**
    - **standard therapy and rituximab were relevant comparators**
    - **cyclophosphamide was not a relevant comparator for the population being considered in this appraisal.**

[a] People with moderate or severe refractory SLE with active disease, who have failed to respond or have had adverse events to 2 or more immunosuppressive therapies and have: EITHER disease activity with at least one BILAG A and/or two B scores or a SLEDAI-2K score ≥6; OR require unacceptably high levels of oral glucocorticoids to maintain a lower disease activity state. People must also have been assessed as not eligible for clinical trials or belimumab.

Background – pivotal BLISS RCTs

RECAP

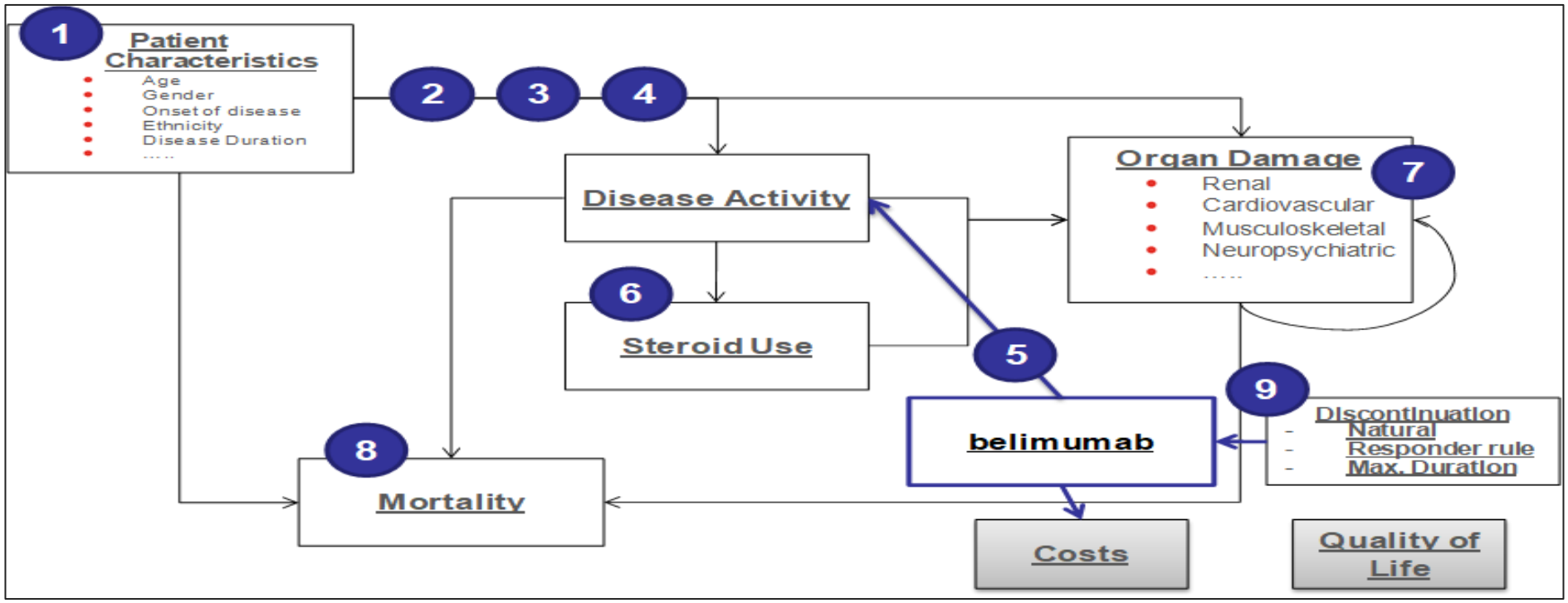
	BLISS-52 (n=865)	BLISS-76 (n=819)	BLISS-SC (n=836)
Considered in TA397?	Yes (only pooled ITT and HDA-1 populations)		No
Population	Adults with a clinical diagnosis of SLE and clinically active SLE disease		
Intervention	Belimumab 10 mg/kg (n=290) administered by IV infusion + standard therapy (ST)	Belimumab 10 mg/kg (n=273) administered by IV infusion + standard therapy (ST)	Belimumab 200 mg (n=556) administered by SC injection + standard therapy (ST)
Comparator	Matched placebo + ST (n=287)	Matched placebo + ST (n=275)	Matched placebo + ST (n=280)
Duration of study	52-weeks	76-weeks	52-weeks
Primary outcome	**SRI-4 (SLE responder index-4) response rate at week 52**		
ITT Results (OR vs placebo)	**Pooled**: 1.68 (95% CI: 1.3 to 2.2)		1.68 (95% CI: 1.25 to 2.25)
HDA-2 population (OR vs placebo)	**Pooled:** 2.29 (95% CI: 1.61 to 3.26)		1.79 (95% CI: 1.17 to 2.74)

Results are presented for the licensed dose of IV belimumab (10 mg/kg)

3 long term extension (LTE) studies: BLISS-76 US LTE, BLISS-52/76 non-US LTE, BLISS-SC LTE included people who completed the BLISS RCTs:

- LTEs were not considered in TA397 and include ITT population (not HDA subgroups)
- Participants in placebo group switched to belimumab in all trials (no comparator arms)
- Only BLISS-76 US LTE was used to inform the economic model

Model structure



Microsimulation cost-utility model:

- Structure remains unchanged from TA397 and incorporates the interaction between patient characteristics, disease activity, medication (corticosteroid use), risk of organ damage development (in 12 different organ systems) and mortality.
- Cycle length of 1 year (no half cycle correction) over a lifetime time horizon
- Separate models were presented for each formulation of belimumab (IV and SC)
- Committee concluded that as the model structure remains unchanged, it is suitable for decision making.

Committee's considerations in ACD

Issue	Brief recap	Committee's conclusion
PSM analysis applied as a calibration factor (1)	• BLISS long term extension (LTE) studies did not have comparator arms. • So, the company conducted a propensity score-matched (PSM) analysis to match people who had belimumab plus standard therapy (ST) in the BLISS-76 US LTE with people from an external Toronto Lupus Cohort treated with ST. • The primary endpoint of the PSM was to compare organ damage progression (mean change in SDI score) from baseline to year 5 in people treated with belimumab or ST with ≥5 years of follow-up. • Several important variables were not included in the matching and there were differences between the cohorts before matching. • Most people withdrew from the BLISS 76 US LTE before 5 years, therefore people who continued on belimumab at 5 years are likely to have progressed less or responded better than people who had belimumab for 1-4 years before stopping.	The results of the propensity score-matched analysis is biased in favour of belimumab.

SLICC/ACR Damage Index (SDI) is a measure of organ damage and contains 41 damage items in 12 systems that are specific comorbidities associated with SLE or damage due to toxicity of SLE treatment. Scores range from 0 to 47 and items remain marked as damage is irreversible.

Committee's considerations in ACD

Issue	Brief recap	Committee's conclusion
PSM analysis applied as a calibration factor (2)	• The company considered that, compared with results from the PSM analysis, its model overestimated organ damage progression in the belimumab arm but underestimated progression in the standard therapy arm. • Therefore, the company simulated its model using several calibration factors until the results matched the observed results from the PSM analysis. • The chosen calibration factor was then applied annually for belimumab responders only for up to 6 years. This meant that the annual risk of organ damage for belimumab was adjusted downwards by 50.9%. • The main issue with applying the calibration factor was that the PSM analysis it was based on had methodological issues. • The uncalibrated model already assumes a constant treatment effect of belimumab on disease activity reduction after 1 year (based on trial data). Adding the calibration factor is likely to further increase the treatment benefit with belimumab.	Using a calibration factor to adjust for long-term organ damage is not suitable for decision making.

New evidence submitted

RECAP

Committee's considerations in ACD

Issue	Brief recap	Committee's conclusion
24-week response and treatment continuation	• In the model, people on belimumab with a SELENA-SLEDAI (SS) score reduction of ≥4 points at week 24 were classified as responders. • Actual SS scores are estimated based on a regression model, given that a 24-week time point does not exist in the model. • At 24 weeks, 34.1% of people from the HDA-2 subgroup were classified as non-responders and stopped treatment with belimumab, receiving standard therapy (ST) alone. • The committee did not think it was clinically plausible that nearly half of these non-responders would have gone on to have an SS score reduction of ≥4 points at 52 weeks on ST alone. • Clinical experts considered that non responders to belimumab would have their ST adjusted which may improve disease activity for some people. • The ERG was unable to validate whether the company's assumption was in line with the BLISS trials.	The committee concluded that it was unclear whether the modelled response to treatment for belimumab non-responders was consistent with the BLISS trials.

New evidence submitted

Committee's considerations in ACD

Issue	Brief recap	Committee's conclusion
Non-responder disease activity	• The ERG suggested an error in the company's model because non-responders in the belimumab arm had the same reduction in disease activity as people having standard therapy at 52 weeks. • BLISS trials showed that non-responders had a smaller reduction in disease activity than people having standard therapy in the first 52 weeks. • The company considered that this was not an error but an assumption that non-responders take the average standard therapy score from week 52 onwards. • The ERG explained that, because the model has an annual cycle, this assumption did not capture any disadvantage that non-responders may have in the first 52 weeks and was not in line with BLISS trials. • ERG base case uses the BLISS evidence to incorporate the difference between belimumab non-responders and people having standard therapy in the first 52 weeks.	Disease activity for people whose condition has not responded to belimumab should be based on the BLISS trials for the first 52 weeks.

New evidence submitted

Committee's considerations in ACD

Issue	Brief recap	Committee's conclusion
Violation in utility estimation	• The company's utility regression model used to estimate utility values excluded key organ damage coefficients without re-estimating the remaining coefficients used in the regression equation. • The company agreed that this was an error but were unable to provide a re-estimated model during technical engagement.	The committee concluded that it would have preferred the company to provide a re-estimated model to resolve the uncertainty in the cost-effectiveness results.

The committee agreed that it would like to see analyses that include:

- an indirect comparison with rituximab
- removal of the calibration factor
- the regression analysis that informs response to treatment at 24 weeks
- disease activity at 52 weeks in people whose condition has not responded to belimumab that matches the BLISS trials
- a re-estimated utility regression model.

The company did not provide any of the analyses requested by the committee.

ACD consultation responses

Consultation comments

- GSK (company) – **new evidence**
- British Society for Rheumatology
- LUPUS UK

Web comments

- 1 public response from British Isles Lupus Activity Group (BILAG)
- 8 other public responses

All consultation comments disagreed with the ACD outcome. Key themes have been summarised over the next few slides.

Summary of consultation comments from British Society for Rheumatology

Clinical and cost effectiveness evidence

- People currently receiving belimumab in England have a higher level of disease activity and more refractory disease compared with the BLISS clinical trial populations.
- The Toronto Lupus Cohort used in the PSM may not be an appropriate comparator because it was difficult to match on patients with high disease activity and it included a large cohort of patients managed in a different country up to 30 years ago:
    - changes in medical care have taken place over this time frame which may influence the development of organ damage and associated costs.
- There is significant risk that the evidence, assumptions and extrapolations required to assess cost effectiveness is subject to considerable uncertainty and risk of inaccuracy.

Unmet need and impact of a negative recommendation

- Further consideration needs to be given to the decision to decline usage of 1 of only 3 licensed therapies for this condition.
- “We are also concerned about the fate of the existing patients receiving belimumab. The prospect of stopping treatment and ‘transitioning’ them on to an alternative therapy, when most of these patients have already failed on these alternative therapies is unrealistic and will be devastating for these patients.”

Summary of consultation comments from LUPUS UK

Unmet need and impact of a negative recommendation

- Belimumab is currently reserved for severe and/or refractory lupus for which standard therapy alone has proved ineffective or insufficient.
- Withdrawing belimumab would leave only rituximab as a possible addition/alternative to standard therapy and it is not effective in many people.
- This will result in increased dependence on corticosteroids, worsened quality of life and increased flares requiring hospitalisation.

Quality of data and vaccinations

- The appraisal has not given appropriate consideration to the challenges of obtaining sufficient quality data in SLE because of the heterogeneous, fluctuating nature of the disease.
- “The COVID-19 pandemic has introduced additional need for vaccinations and, as a B-cell depleter, rituximab can present challenges for important vaccinations… The potential increased vulnerability to COVID-19 infection needs to be carefully considered if comparing rituximab and belimumab.”

Summary of public comments from BILAG

Clinical evidence

- "Belimumab is central to European (EULAR) guidelines for treatment of refractory SLE if refractory to methotrexate or azathioprine, as well as BSR guidelines. The UK would be deviating from internationally agreed treatment pathways if belimumab were not available."

Unmet need and impact of a negative recommendation

- "Patients with SLE require markedly greater use of medical resource than most other rheumatic conditions… Yet, treatments options are fewer that other autoimmune rheumatic diseases such as rheumatoid arthritis"
- "If belimumab is not available as a treatment option, patients who are refractory to other therapies, and suffer from persistently active disease are likely to be treated with high dose steroids, with all the associated adverse effects"
- "…patients who are currently receiving belimumab and are responding well will need to stop therapy within 12 months of this negative decision…most of these patients have already failed other options and would be forced back into severely active disease if their treatment were withdrawn…we consider this to be unethical when there is a licensed therapy that can prevent such an outcome."

People receiving belimumab as part of the MAA were informed that they would have to stop treatment if the final review recommendation is negative.

Summary of other public comments

Benefits of belimumab

- “Since starting Belimumab I have felt so much better. No further hospital admissions. My symptoms have improved greatly and I have been able to reduce my steroid dose.”
- “This drug has made such a difference to my life where there was no response to other medication that had been tried over many years.”
- “Subcutaneous belimumab has been of significant benefit to patients with fewer hospital attendances during the COVID-19 pandemic and less time off work”

Unmet need and impact of a negative recommendation

- “Belimumab is the first and only drug licensed for the treatment of lupus in 50 years.”
- “Discontinuing the use of Belimumab as a treatment for lupus will have a devastating impact on many patient's mental and physical wellbeing impacting on the ability to work and maintain an independent life.”
- “It is likely that healthcare costs of patients who are currently being treated with belimumab or are currently eligible for this will increase significantly if this drug is withdrawn. Patients will require increased hospital admissions, requirement for high dose steroids (with associated risks…) and potential need for organ support..”

PSM and calibration factor (1)

New evidence

RECAP:

- The committee concluded that the results of the PSM analysis is biased in favour of belimumab

Company consultation comments on PSM

- The company disagrees that the results of the PSM analysis is biased in favour of belimumab or that clinically important variables were not matched on.
- It considers that is not suitable to match on variables such as disease progression and disease activity over time due to potential confounding.
- Household income and educational attainment were matched variables and will in some way act as a proxy for social deprivation.
- There are some differences in the baseline characteristics between the cohorts before and after matching. Once the cohorts were matched, the samples of participants were well balanced with a bias of less than 10% for all variables and 0% bias for the smoking variable.
- Only 75/268 (28%) participants entering the US long-term extension study withdrew by the end of Year 5, of which n= 64 withdrew due to reasons other than lack of efficacy.
- "…it is conceivable that many of the patients who withdrew due to a reason other than lack of efficacy could have potentially continued to receive the benefits of belimumab until year 5 if they were to continue treatment".

This slide has been updated after the committee meeting to correct factual inaccuracies

PSM and calibration factor (2)

New evidence

ERG comments on PSM

- The PSM analysis did not match on important, clinically relevant variables including disease activity over time, household income and educational attainment (so social deprivation was not accounted for through these proxy variables).
- Whilst disease progression and disease activity over time are potential confounders, they are important prognostic factors. In a PSM analysis, all effect modifiers and prognostic factors need to be adjusted for to give an unbiased treatment comparison.
- The degree of differences in the baseline characteristics in the BLISS-76 US LTE study cohort and the Toronto Lupus Cohort are large (sample size in the US LTE study cohort reduced from n=195 to n=99 in the PSM analysis) and are likely to extend beyond the included variables to all unknown and unmeasured effect modifiers and prognostic factors.
- A large percentage of participants withdrew from belimumab in the BLISS-76 US LTE. While lack of efficacy was the stated reason in a minority of these withdrawals, it is possible that lack of efficacy could have been a factor in withdrawals for other stated reasons.
- “There is the potential of substantial bias in favour of belimumab from analysing only patients continuing to receive belimumab beyond 5 years.”

⊙ ***Has the committee seen any evidence to change its conclusion that the results of the PSM is biased in favour of belimumab?***

PSM and calibration factor (3)

New evidence

RECAP:
- Using a calibration factor to adjust for long-term organ damage is not suitable

Company consultation comments on calibration factor (CF)

- "It is inappropriate to completely dismiss the application of the PSM analysis results showing the positive benefit of belimumab on organ damage progression to the economic model."
- Company considers its approach is conservative and likely underestimates the benefit of belimumab in reducing long-term organ damage because:
  - The company's model was validated using a matched BLISS LTE ITT population. The target high disease activity population showed a greater benefit on disease activity.
  - The CF was applied to belimumab responders only and for up to 6 years despite belimumab being continued up to a lifetime in the model and clinical practice.
  - The CF was not applied to the standard therapy arm.

5-year SDI increase	Belimumab + ST	ST
Results from uncalibrated model (matched LTE ITT population)	0.568	0.611
Results from PSM analysis (applied to responders by CF = 0.491)	0.283	0.717

Compared with the PSM analysis, the company consider the model overestimated SDI progression in the belimumab arm and underestimated SDI progression in the ST arm.

PSM and calibration factor (4)

New evidence

Company consultation comments on calibration factor continued

- The model is likely to underestimate the benefits of belimumab treatment because disease flares are not fully captured and carer utilities have not been incorporated in the model.
- TA397 states that some of the benefits with delaying certain types of organ damage may have been underestimated in the model because cost data was from different sources.
- The company recognises the uncertainty in applying a constant calibration factor to belimumab responders who stopped treatment at years 2-4 in the model. This assumes that patients receive the full benefit proportional to the time spent in the model.

ERG comments on calibration factor

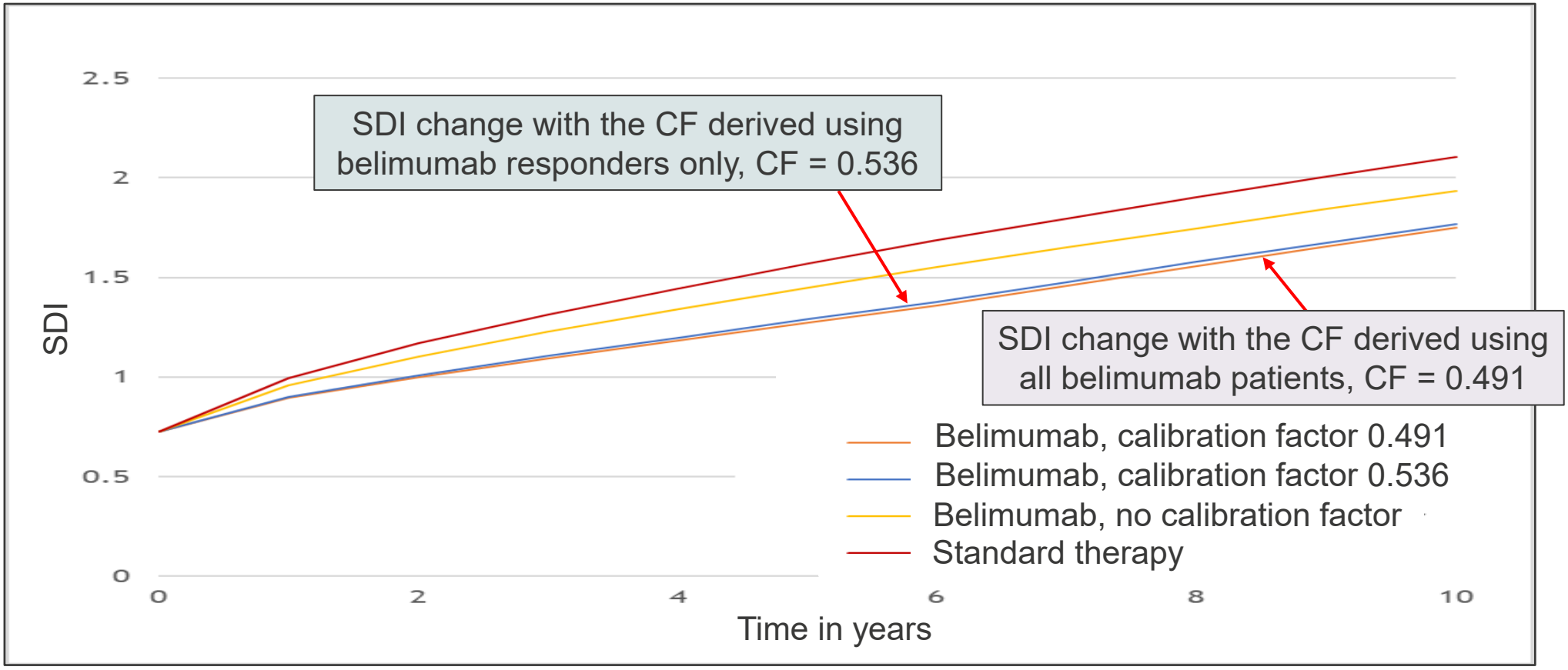
- The calibration factor was derived by calibrating the organ damage progression of the entire modelled belimumab cohort (responders and non-responders) to match that of the PSM.
- Using all belimumab patients biases the model outcomes in favour of belimumab as:
  - Modelled SDI change was significantly above PSM SDI change (indicating more organ damage in the modelled population than in the PSM)
  - This would be expected as organ damage progression from the PSM is based on responders who have continued treatment with belimumab
  - To calibrate the SDI of all modelled belimumab patients to match the PSM SDI, the proportional decrease in SDI change (as estimated by the calibration factor), would have likely been over-estimated. Therefore, only belimumab responders should be used.

PSM and calibration factor (5)

New evidence

- NICE requested the company to present an additional scenario analysis using belimumab responders only in the model to derive a calibration factor.
- Compared with the original calibration factor of 0.491, the scenario analysis resulted in a calibration factor of 0.536 (less favourable for belimumab as closer to 1 = no calibration) which had a small impact on the ICER (+£1,515 per QALY gained based on the IV model).

Change in SDI (organ damage) over time using different calibration factors



PSM and calibration factor (6)

New evidence

ERG comments on company's calibration factor scenario

- Difference between calibration factors smaller than expected – unclear why SDI progression of non-responders did not substantially affect SDI progression of all belimumab-treated patients at 5 years.
- SDI progression of belimumab non-responders may be under-estimated in the model (non-responders do better than they should).

Other ERG comments on calibration factor

- People who continue belimumab for 5 years are likely to have progressed less than people who took belimumab in the preceding years before discontinuing. Applying calibration factor estimated based on 5 years may underestimate SDI progression in years 2, 3 and 4.
- It remains unclear whether the calibration factor should be used, given the significant doubts over the appropriateness of the PSM for this purpose.
- If it is used, the ERG prefers the new calibration factor over the original one. However, this has not been fully validated and is likely to overestimate the impact belimumab has on the reduction of organ damage.

Impact on ICER – Significant

- Removal of calibration factor increases the ICERs in both models (ERG base case)

⊙ ***Has the committee seen any evidence to change its conclusion that the application of the calibration factor is not suitable for decision-making?***

24-week response and treatment continuation

New evidence

RECAP:

- Nearly half of non-responders at week 24 become responders at 52 weeks on ST alone.
- The committee concluded that it was unclear whether the modelled response to treatment for belimumab non-responders was consistent with the BLISS trials.
- The model could have underestimated belimumab costs because people having a response to belimumab were classified as non-responders and therefore modelled to stop treatment.

Company consultation comments

- Company has presented a post-hoc analysis of the pooled BLISS-52/76 trial data to show the number of responders at week 24 compared to week 52 in the HDA-2 subgroup.
- Non-responders at week 24 could respond later and it is plausible that additional standard therapy medications are also likely to improve disease activity levels.

ERG comments

- Company previously stated that in the model, 46.5% of all belimumab non-responders had a ≥4 point reduction in SS score at week 52.
- Comparing this value to the pooled BLISS trial data (34.5%) indicates that the company's model overestimates the reduction in SS score of belimumab non-responders.

Pooled BLISS-52/76 trial data (HDA-2 subgroup)	Belimumab non-responder at week 24 (n=87)
Belimumab responder at week 52	30 (34.5%)
Belimumab non-responder at week 52	57 (65.5%)

⊙ ***Is the company's modelling of 24-week response and treatment continuation in line with the BLISS trials and clinical practice?***

Non-responder disease activity (1)

New evidence

RECAP:

- The ERG suggested an error in the model because non-responders have the same disease activity (measured by SS score) at 1 year as people having standard therapy.
- As the model has an annual cycle, this assumption does not capture any disadvantage that non-responders may have in the first 52 weeks and was not in line with BLISS trials.
- The committee concluded that disease activity for people whose condition has not responded to belimumab should be based on the BLISS trials for the first 52 weeks.

Company consultation comments

- Company considers there to be no error related to how SELENA-SLEDAI (SS) score is modelled.
- It acknowledges the ERG's concern that no detriment has been applied to the belimumab non-responders in the model if it is assumed that people take the average standard therapy (ST) disease activity score at week 52.
- Company conducted a new scenario analysis adding a cost of £600 to belimumab non-responders in year 1 in the model to cover costs relating to additional standard therapy medication and physician visits, which had a small impact on the ICER.
- Company scenario analysis presented in ACM1 which assumed return to ST efficacy for belimumab non-responders by week 76 instead of at 52 weeks (company base case) had a small impact on the ICER (including with revised PAS).

Non-responder disease activity (2)

New evidence

ERG comments

- Given the 24-week assessment point, a model cycle of 24 weeks would have been more appropriate as highlighted in the ACD.
- It is unclear what additional advantages can be derived from using an annual cycle length compared to a cycle length of 24-weeks even in a chronic disease (as highlighted by the company).
- ERG base case uses the BLISS evidence to incorporate the difference between belimumab non-responders and people having ST in the first 52 weeks.
- After 52-weeks belimumab non-responder disease activity is modelled to be the same as ST (in line with ERG clinical expert opinion).
- The ERG considers that it is unclear whether this modelling error had any impact on the derivation of the calibration factor.

Impact on ICER - Small

- First year corrected reductions in SS score for belimumab non-responders increases the ICER in both models (ERG base case)

⊙ ***Does the committee still consider that disease activity for belimumab non-responders should be based on the BLISS trials for the first 52 weeks?***

Violation in utility estimation

No comments received, no new evidence

RECAP:

- The committee concluded that it would have preferred the company to provide a re-estimated model to resolve the uncertainty in the cost-effectiveness results.

Company comments from ACM1

- The company agrees that there is an error in the utility regression equation but state that they were unable to fix the error within the time period of technical engagement.
- Instead the company presented scenario analyses to explore the impact of varying the regression utility coefficients (log of age, constant, SLEDAI score, black ethnicity) in the regression equation by 1 standard deviation in each direction.

ERG comments from ACM1

- Company's scenarios likely explore the full impact but ICERs increased or decreased up to around £3,000/QALY gained with only 1 of the coefficients varied (including with revised PAS).
- ICERs could increase or decrease further with combinations of coefficients varied.
- The ERG agrees that the variation by 1 standard deviation is likely substantial but considers that this potential uncertainty should be considered in decision-making.

⊙ **Is the committee satisfied that the error in utility estimation is not likely to have a significant impact on the cost effectiveness results?**

Comparison with rituximab

RECAP:

- An indirect treatment comparison (ITC) was not appropriate because the rituximab trial did not meet its primary endpoint and the trial population was different to the BLISS trials.
- Company considers the regression analysis using data from the BILAG-BR substudy comparing belimumab with rituximab was not appropriate for comparing treatment efficacy.
- Committee concluded that as rituximab is a relevant comparator, an ITC between belimumab and rituximab in the relevant population would have been preferred.

Company consultation comments

- BILAG-BR collected data for the HDA-1 population only, therefore an indirect treatment comparison between belimumab and rituximab in the HDA-2 population is not possible.
- Due to lack of positive and robust RCT and long-term effectiveness data for rituximab in people with SLE, a reliable and robust ITC cannot be conducted.

Consultation comments

- Rituximab is not a relevant comparator:
  - NHSE guidance outlines different eligibility criteria for both treatments and suggests to use belimumab first. So, a different group of people would be being compared.
  - Rituximab did not show efficacy in RCTs. It can rarely be given to induce control over years (due to low immunoglobulins or allergy) and is not licensed.

⊙ ***Has the committee seen any evidence to change its preference for an indirect treatment comparison between belimumab and rituximab?***

Other considerations: equality

RECAP:

- Committee concluded that there are no equality issues that can be addressed in this technology appraisal.

Comments received at consultation:

- SLE is more common in women, particularly in those of child-bearing age:
  - belimumab may be used in early stages of pregnancy due to lower likelihood of placental transfer in first trimester
  - the promotion of standard of care which can include gonadotoxic agents is potentially discriminatory
  - withdrawal of belimumab could disadvantage women of reproductive age
  - women tend to have more caregiving responsibilities therefore belimumab offers advantages with its shorter infusion time [compared with rituximab].
- SLE is more common in people from African, Caribbean and Asian family origin, who are more likely to experience severe disease.
- Withdrawal of subcutaneous belimumab may increase inequalities in access to treatment because rituximab is only available as an IV infusion administered at a specialist centre.
- Rituximab is currently commissioned for post-pubescent children, potentially discriminating against children aged 5 to 12 years who have no access to any funded biological agent [if belimumab is withdrawn].

⊙ ***Are there any additional equality issues that need to be considered?***

Cost effectiveness results – company base case

HDA-2 subgroup – ICERs include updated belimumab PAS

IV formulation

Deterministic ICER

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,952
ST	160,470	16.900	9.809				

ICER = incremental cost-effectiveness ratio; Inc = incremental; LYG = life years gained; ST = standard therapy; QALYs = quality-adjusted life years

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Belimumab	[redacted]	[redacted]	27,148
ST			

Cost effectiveness results – ERG base case

HDA-2 subgroup – ICERs include updated belimumab PAS

IV formulation

Deterministic ICERs

Assumption	ICER (£/QALY)
Company base case	**24,952**
1. First year corrected reductions in SS score for belimumab non-responders	26,539
2. Calibration factor removed	43,951
ERG base case (1 + 2) - includes committee's preferred assumptions from ACD	**46,428**

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Belimumab	[redacted]	[redacted]	**47,927**
ST			

NICE

Cost effectiveness results – company base case

HDA-2 subgroup – ICERs include updated belimumab PAS

SC formulation

Deterministic ICER

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Belimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,041
ST	151,999	17.122	10.056				

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Belimumab	[redacted]	[redacted]	24,110
ST			

Cost effectiveness results – ERG base case

HDA-2 subgroup – ICERs include updated belimumab PAS

SC formulation

Deterministic ICERs

Assumption	ICER (£/QALY)
Company base case	**25,041**
1. First year corrected reductions in SS score for belimumab non-responders	26,773
2. Calibration factor removed	48,913
ERG base case (1 + 2) - includes committee's preferred assumptions from ACD	**53,116**

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
ST	[redacted]	[redacted]	**51,442**
Belimumab			

NICE

Key issues for consideration

Key issues	
1. PSM analysis applied as a calibration factor	• Has the committee seen any evidence to change its conclusion that the results of the PSM is biased in favour of belimumab? • Has the committee seen any evidence to change its conclusion that the application of the calibration factor is not suitable for decision-making?
2. 24-week response and treatment continuation	Is the company's modelling of 24-week response and treatment continuation in line with the BLISS trials and clinical practice?
3. Non-responder disease activity	Does the committee still consider that disease activity for belimumab non-responders should be based on the BLISS trials for the first 52 weeks?
4. Violation in utility estimation	Is the committee satisfied that the error in utility estimation is not likely to have a significant impact on the cost effectiveness results?
5. Comparison with rituximab	Has the committee seen any evidence to change its preference for an indirect treatment comparison between belimumab and rituximab?