NICE National Institute for Health and Care Excellence

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

Lead team presentation

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Disease background

- Systemic lupus erythematosus (SLE) is a chronic autoimmune condition that causes inflammation in the body's tissues. SLE manifestations can affect the whole body.
- Active SLE involves frequent flares and more severe symptoms.
- Persistent disease activity and side effects from cumulative dose of corticosteroids contribute significantly to the accrual of irreversible long-term organ damage.
- The aim of current treatments is to control and ease symptoms, prevent organ damage and long-term complications. Standard therapy currently includes using:
  - non-steroidal anti-inflammatory drugs (NSAIDs)
  - corticosteroids (e.g. **prednisolone**)
  - conventional disease-modifying anti-rheumatic drugs (DMARDs) such as antimalarials (e.g. **hydroxychloroquine**) or immunosuppressive agents (e.g. cyclophosphamide, **azathioprine**, methotrexate and mycophenolate mofetil)
  - biological DMARDs (rituximab and **belimumab**).

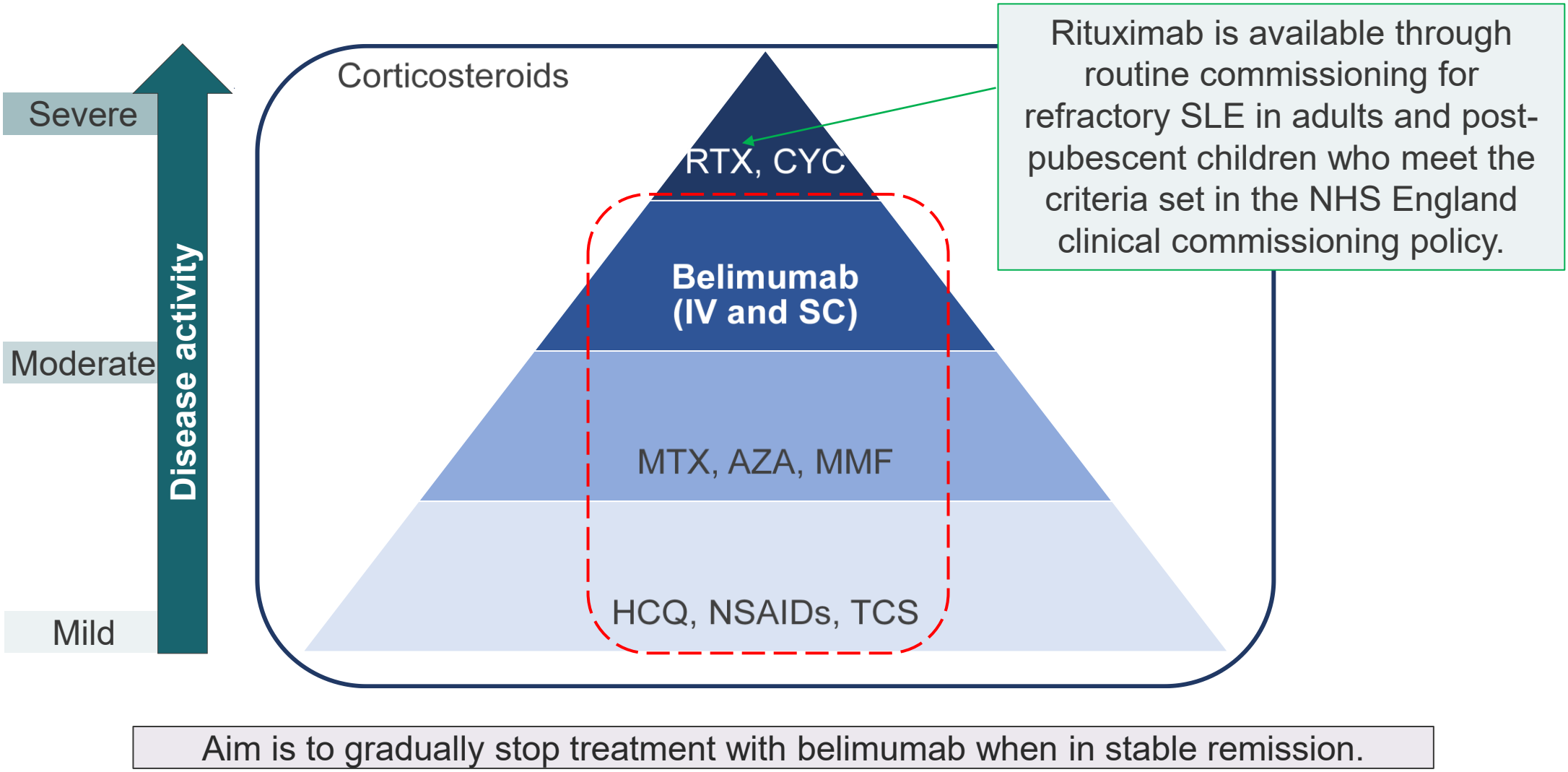
Drugs in bold are currently licensed for use in adults with SLE
Source: Final scope ID1591

Belimumab (Benlysta, GSK)

Marketing authorisation	Benlysta is indicated as add-on therapy in patients aged 5 years and older 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 **adult patients 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).

- **Results are presented for the licensed dose of IV belimumab (10 mg/kg)**
- **SmPC states that discontinuation of treatment should be considered if there is no improvement in disease control after 6 months of treatment.**

Company's proposed positioning of belimumab for SLE



Aim is to gradually stop treatment with belimumab when in stable remission.

Source: modified from Figure 1 in company submission.
Red dashed line indicates intervention and comparators included in the model (includes corticosteroids).
AZA = azathioprine; CYC = cyclophosphamide; HCQ = hydroxychloroquine; IV = intravenous; MMF = mycophenolate mofetil; NSAIDs = non-steroidal anti-inflammatory drugs; MTX = methotrexate; RTX = rituximab; SC = subcutaneous; TCS = topical corticosteroids

Patient expert perspectives

- Systemic lupus erythematosus (SLE) can cause daily issues with fatigue, mental acuity, joint pain and headaches.
- SLE affects the ability to work, everyday activities and being able to socialise with others.
- There are limited treatment options for lupus and it can take a number of years to find the right treatment regime, often resulting in poor quality of life during this period.
- Belimumab is likely to be steroid-sparing and may help to improve lupus symptoms and quality of life.
- The availability of two formulations of belimumab gives patients and clinicians choices for treatment.

"Whilst lupus does see people with periods of more significant disease (flares) it is a condition that has an impact on your daily life, it just gets more challenging when you are flaring."

"A child with lupus can have belimumab and this can seriously improve their outcomes and hopefully reduce their [chances] of ill health being a life long burden in their lives and the lives of their families."

Clinical expert perspectives

- SLE is a complex and heterogenous disease. It can be difficult to treat and can be organ and life-threatening.
- There are limited treatments for severe disease. This often results in high doses of corticosteroids with side-effects or the use of cyclophosphamide with potentially permanent effects on fertility.
- Belimumab was a step-change in treatment when introduced as the only biological therapy currently licensed for SLE. It is a disease-personalised treatment.
- The pathway of care would also be improved further with access to the subcutaneous formulation of belimumab and reduce infection risk and NHS resource use.

"Changing the eligibility for belimumab to include people with either anti-dsDNA antibodies or low C3/C4 complement makes very good clinical and biologic sense here and would improve the ability of the technology to improve patient care."

"For the last 50 years drugs for patients with lupus have been borrowed from other conditions….Being able to tell patients that this drug is specific for their condition is very important."

Patient and professional organisation comments

- Many people still have ongoing symptoms (particularly fatigue) despite reasonable doses of steroids and other agents.
- People with SLE often experience depression, anxiety and loss of confidence/self-esteem.
- The impact of caring for someone with lupus can be significant.
- Belimumab is already showing benefits to patients by reduced steroid use and pill burden, and improved quality of life.
- In clinical practice, people with exceptionally active lupus miss out on treatment because of the current criteria for belimumab. Treatment should be available if there is either positive dsDNA antibodies or low complement with high disease activity by SELENA-SLEDAI.
- The adoption of subcutaneous belimumab for lupus will help to improve access to treatment and will be beneficial for adherent patients requiring more autonomy.

We would like to thank the Renal Association and British Society for Rheumatology, LUPUS UK, patient and clinical experts for their submissions.

NICE technology appraisal (TA) 397

Belimumab is recommended as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus in adults only if all the following apply:

- There is evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10 despite standard treatment.
- Treatment with belimumab is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more.

Key uncertainties identified by committee

- Standard of care in key trials (BLISS) and if this represents UK clinical practice
- Treatment effect of belimumab on the full range of SLE manifestations
- Steroid-sparing effect of belimumab and impact on quality of life
- Treatment duration and annual discontinuation rate with belimumab
- Stopping rule adherence and maintenance of belimumab treatment effect over time
- Development of organ damage whilst on treatment and safety data
- Clinical and cost-effectiveness of belimumab in comparison with rituximab

The committee agreed that, because of the considerable uncertainty that remained in the economic modelling, it was unable to conclude the true value of the ICER

TA397 recommendations for data collection

The committee instructed that data should be collected using the British Isles Lupus Assessment Group- Biologics Registry (BILAG-BR) to resolve uncertainties in a future review:

Efficacy data:

- comparison with rituximab
- clinical response measured by BILAG Index 2004 and SLEDAI-2K
- organ damage accrual using the SLICC Damage Index and BILAG Index 2004
- use of corticosteroids.

Safety data:

- incidence of serious adverse events, hospitalisation for infection, malignancy and death, other serious adverse events.

Patient-reported outcomes:

- EQ-5D, SF-36, LupusQoL.

Other data:

- such as previous and concomitant treatment, belimumab treatment details, demographics, clinical serology, laboratory parameters, comorbidities.

Updates since TA397

- The marketing authorisation for intravenous belimumab now includes people aged 5 years and older (previously adults only).
- Committee for Medicinal Products for Human Use has recommended the use of belimumab (in combination with background immunosuppressive therapies) for the treatment of active lupus nephritis in adults (indication extension).
- A subcutaneous formulation of belimumab is available (for adults only) in addition to the intravenous formulation previously considered.
- Company has defined a new high disease activity target population (next slide).
- Updated PAS for belimumab IV and SC formulations (size of discount is confidential).
- Updated NHS England clinical commissioning policy for rituximab (July 2020) recommends that belimumab should be considered prior to rituximab.

*** Note slide has been updated since committee meeting to correct factual inaccuracies**

Company's updated population

- Based on the data collected through the BILAG-BR, the company consider that the high disease activity (HDA)-1 population was too restrictive in clinical practice because:
  - patients will often experience high levels of disease activity but only have one defined serological biomarkers (low complement or positive anti-dsDNA)
  - 1 of the serological biomarkers may normalise with standard therapy but patients continue to experience high-disease activity due to a suboptimal treatment response
  - some patients may have an underlying complement deficiency but have high disease activity.
- The company have presented a broader high disease activity population (HDA-2) to be considered in this appraisal that would allow more patients access to belimumab.

- 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)**

Is the HDA-2 subgroup relevant to clinical practice?

Measure of disease activity in BLISS RCTs: SRI-4

SELENA SLEDAI

- Evaluates SLE disease activity over last 10 days using 24 items.
- A score of 6 or more is consistent with significant disease activity.

BILAG index

- Evaluates SLE disease activity and assesses flare and response to treatment using 97 items in 9 organ systems.
- Scores can range from A = severe disease activity to E = no disease activity ever in an organ system.

Physicians Global Assessment (PGA)

- A visual analogue score based on a clinician's assessment of SLE disease activity.
- Scores can range between 0 = no disease to 3 = severe disease.

BLISS trials

Primary end point of SRI-4 (SLE responder index-4) response rate at Week 52:

- ≥4-point reduction from baseline in SELENA-SLEDAI score, AND:
- No worsening (increase of <0.30 points from baseline) in PGA, AND:
- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline, at the time of assessment.

Results for pivotal BLISS RCTs

	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 + ST	Belimumab 10 mg/kg (n=273) administered by IV infusion + ST	Belimumab 200 mg (n=556) administered by SC injection + 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 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 results (OR vs placebo)	**Pooled:** [redacted] (95% CI: [redacted])		[redacted] (95% CI: [redacted])
EQ-5D score change from baseline	**Pooled treatment difference (vs placebo):** HDA-2: [redacted] (95% CI: [redacted]), p-value [redacted]		Not collected

ST= Standard therapy (alone or in combination) included antimalarials, NSAIDs, corticosteroids and immunosuppressants.

Results for BLISS long-term extension (LTE) studies

	BLISS-76 US LTE (n=268)	BLISS-52/76 non-US LTE (n=735)	BLISS-SC LTE (n=662)
Considered in TA397?	No	No	No
Description	US patients who completed BLISS-76	Non-US patients who completed either BLISS-52 or BLISS-76	Patients who completed BLISS-SC
Intervention	Belimumab 10 mg/kg IV every 28-days + ST (n=177, placebo to belimumab n=91)	Belimumab 10 mg/kg IV every 28-days + ST (n=503, placebo to belimumab n=232)	Belimumab 200 mg SC weekly + ST (n=456, placebo to belimumab n=206)
Duration of follow-up	7-years	8-years	6-months
Primary outcomes at follow-up: • **Placebo to belimumab** • **Belimumab** • **Total**	SRI-4 responder: • n=6/7, 85.7% • n=84/112, 75.0% • **n=90/119, 75.6%**	SDI change from baseline: • mean 0.0, SD 0.00 • mean 0.2, SD 0.58 • **mean 0.2, SD 0.56**	SRI-4 responder: • n=23/143, 16.1% • n=332/435, 76.3% • **n=355/578, 61.4%**

SD = standard deviation; SDI = Systemic Lupus International Collaborating Clinics (SLICC)/ ACR Damage Index

- LTEs include ITT population (not HDA subgroups)
- Patients in placebo group switched to belimumab in all trials
- Only BLISS-76 US LTE was used to inform the economic model

BILAG-BR sub-study

- Sub-study collected same data as main BILAG-BR cohort study but aimed to fulfil the requirements of the managed access agreement in TA397.
- Collected real-world data for patients prescribed belimumab meeting HDA-1 criteria and included 3 cohorts: belimumab IV (n=[redacted]), rituximab (n=[redacted]) or non-biologic (n=[redacted]).

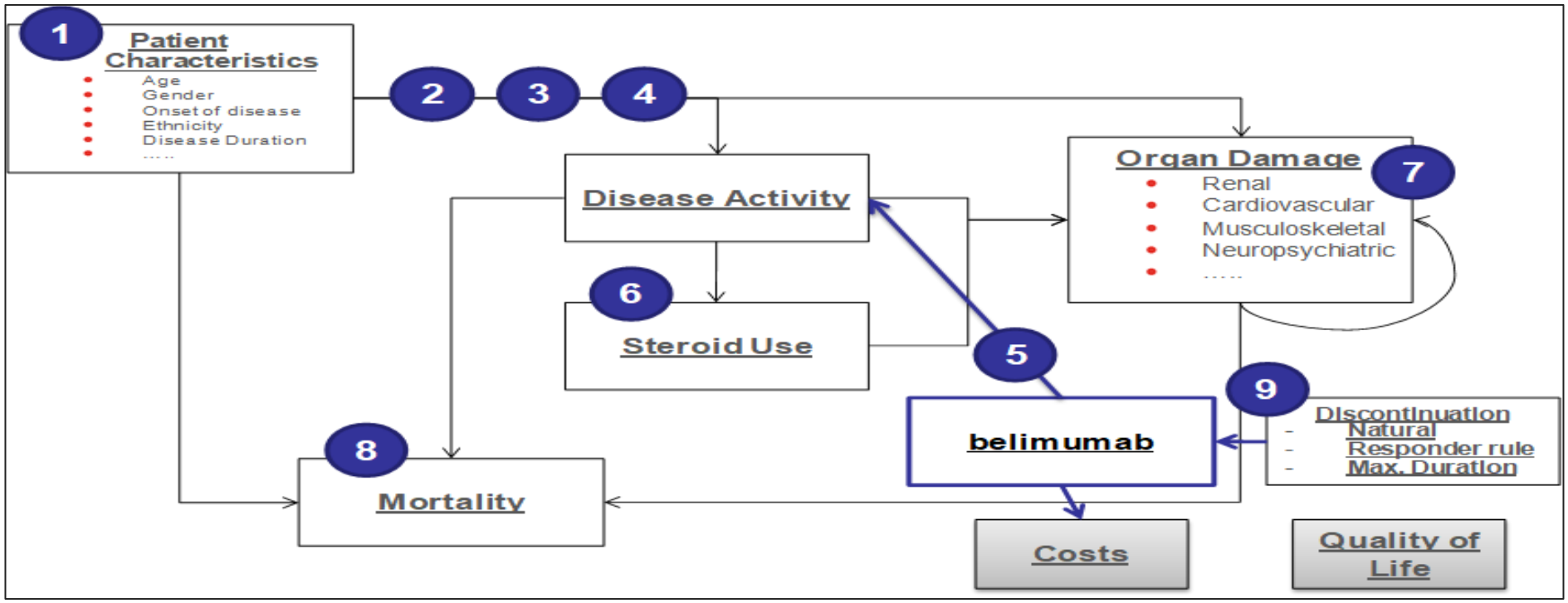
Disease activity, quality of life and steroid use in belimumab group

- At 12 months, average within-person change was [redacted] points for BILAG, [redacted] points for SLEDAI-2K and [redacted] for mean SDI score (n=[redacted]).
- [redacted] were seen for [redacted] domains of SF-36 and LupusQoL and EQ-5D health status but [redacted] number of responses at [redacted] (n= [redacted]).
- [redacted] in regular steroid dose at 3 and 12 months, but average dose reported at 6-months was [redacted].

Comparison of belimumab with rituximab

- Regression analysis comparing belimumab (n=[redacted]) to rituximab (n=[redacted]) showed [redacted] in SLEDAI-2K at 12 months follow-up and [redacted] in BILAG total score.
- Company consider that there is a high likelihood of confounding and selection bias so that these data are not appropriate for comparing treatment efficacy.

Model structure from company submission



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).

Key inputs/assumptions used in company models (1)

(new) = update to approach in TA397

	Base-case assumption
Population	HDA-2 subgroup *(new)*
Comparator	Standard therapy includes the use of antimalarials, NSAIDs, corticosteroids and immunosuppressants
Patient baseline characteristics	• HDA-2 subgroup based on pooled BLISS-52/76 or BLISS-SC *(new)* • Patient weight for IV model from BILAG-BR *(new)*
Year 1 treatment effects	BLISS trials (pooled for IV): • SELENA-SLEDAI (SS) response at week 24 • Change in SS at week 52 from baseline (using regression model)
Long-term treatment effectiveness	Johns Hopkins lupus cohort used to develop a natural history model to predict beyond 52 weeks: ○ change in adjusted mean SLEDAI (AMS) score (as a proxy for SS) ○ average corticosteroid dose per year ○ risk of organ damage ○ Weibull survival model developed for risk of death (based on AMS) adjusted by standardised mortality ratios from literature.
Treatment discontinuation	HDA-2 year 1: Pooled BLISS-52/76 ([redacted]) or BLISS SC ([redacted]) *(new)* HDA-2 year 2+: Phase 2 LBSL02 study + BLISS-52/76 LTEs ([redacted]) *(new)*

Key inputs/assumptions used in company models (2)

	Base-case assumption
Utility values	• A regression equation (which accounted for age, ethnicity and SS score), to calculate baseline HRQoL using EQ-5D captured from BLISS-52 and BLISS-76 for both IV and SC analyses. • Utility multipliers incorporate dis-utility from the organ damage sustained.
Drug wastage	Drug wastage assumed for belimumab IV
Treatment duration	Lifetime
Treatment effect	Lifetime
Treatment waning	Not applied
Calibration factor	A propensity score matched (PSM) analysis is applied as a calibration factor to the natural history model for long term organ damage and only to belimumab ***(new)***
Treatment continuation	• Responder rule = a SS score decrease of ≥ 4 at week 24 to continue treatment with belimumab. • Non-responders receive standard therapy (ST) and assume the average ST level of disease activity for remainder of model horizon.
Adverse events and disease flares	Not included in model

Data from the literature were used to inform the standardised mortality rate for a given SS score, and quality-of-life and cost impacts of long-term damage to each organ system (values updated where relevant in current model).

Summary of ERG's key issues considered at technical engagement		Status
1a.	No evidence for belimumab in people with severe active CNS lupus.	Resolved
1b.	Population focuses on adult population only	Unresolved
2a.	Comparators – cyclophosphamide	Resolved
2b, 5 & 6.	Comparators – rituximab	Unresolved
3.	Long-term comparative data for pivotal belimumab trials	Unresolved
4 & 8	PSM analysis is applied to the model (as a calibration factor) • Is the application of a calibration factor to adjust the long-term effects of belimumab on organ damage appropriate?	For discussion
7	IV and SC formulations of belimumab are not compared with each other.	Resolved
9	24-week response and treatment continuation in the model • Is the modelling of 24-week response and treatment continuation in line with the BLISS trials and clinical practice?	For discussion
10	Belimumab non-responder disease activity at 52 weeks • Should belimumab non-responders in the model have the same reduction in disease activity as ST patients in the first 52 weeks?	For discussion
11	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?	For discussion
12	Organ damage utility multipliers	Unresolved
13	Sampling of organ damage and death	Unresolved

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in base case?
1a	The pivotal BLISS trials excluded people with severe active CNS lupus.	The company do not anticipate NICE to issue guidance on the use of belimumab in this population, because it is not currently included in the marketing authorisation (MA) for both formulations.	Belimumab can only be recommended for use within its MA.	Not applicable
2a	The company have not included cyclophosphamide plus ST as a comparator.	Clinical experts and stakeholders agreed that cyclophosphamide is largely used for treating lupus nephritis or CNS lupus, which are both outside of the current MA for belimumab.	Cyclophosphamide is not a relevant comparator.	Not applicable
7	The IV and SC formulations of belimumab are not compared with each other in the same model, to allow a fully incremental analysis.	Company and clinical experts consider that there would be similar efficacy between formulations.	It is likely that IV and SC belimumab formulations are comparable.	Not applicable

Issues unresolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in base case?
1b	Belimumab IV is indicated in people aged 5 years and older. Submission and model focus on adult SLE population. Company presents PLUTO RCT comparing belimumab IV + ST with placebo in people aged 5-17 years. Results for SRI-4 response at week-52 for full trial population (n=93) and the HDA-2 subgroup (n=48) were not statistically significant.	Company consider PLUTO was not statistically powered to show a difference between treatments. There is sufficient clinical and safety data for belimumab IV to support its use in children (based on the EPAR). Other stakeholders commented: • the onset of lupus is rarer in children, so trial numbers will be small • data from the PLUTO study are consistent with data from trials in adults • belimumab IV is being used in children in England if they meet the criteria for use.	There is unresolvable uncertainty in the cost-effectiveness of belimumab in people aged 5-17.	Not applicable

Issues unresolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in base case?
2b, 5 & 6	Rituximab plus ST has not been included as a comparator. Data from the BILAG-BR registry are not suitable for a comparison because of the different eligibility criteria for treatment, cohort sizes and follow-up period.	• EXPLORER trial did not meet its primary endpoint and there are differences between trial populations and end points. • Patients who meet the HDA-1 criteria could be identified from BILAG-BR and the data compared, but numbers will be small. • The NHSE guidance for rituximab suggests to use belimumab first so a different group of patients would be being compared.	There is uncertainty on the clinical and cost-effectiveness of belimumab compared with rituximab.	Not applicable

- No new studies were identified that directly compared belimumab with rituximab.
- EXPLORER trial reported no statistically significant differences in major or partial clinical responses between rituximab and placebo in people with moderate to severe SLE.

Is rituximab a relevant comparator?

Issues unresolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in base case?
3	There is lack of reliable long term comparative data for belimumab compared with ST (beyond 76 weeks).	• Follow-up length in the BLISS trials is the standard duration for a lupus RCT. • LTEs provide longer term efficacy and safety data for belimumab.	Uncertainty remains on the long-term effectiveness of belimumab compared with ST.	Not applicable
12	Uncertainty on organ damage utility multipliers which may overestimate the impact of organ damage on HRQoL	Company scenario analyses explored changes to weightings of particular organ damage utility multipliers in line with clinical expert feedback.	Uncertainty remains, about impact of organ damage on HRQoL, but company's scenarios had a minimal impact on the ICER.	✓
13	In the model, organ damage and death are sampled after patients are allocated to a treatment arm, which makes model validation difficult.	• Sampling error minimised by simulating large number of patients. Order does not affect validity of model results. • ERG prefers patient characteristics to be sampled before treatment allocation to minimise sampling error.	Uncertainty remains, but the impact of sampling order is likely to have a minimal impact on the ICER.	✓

Outstanding issues after technical engagement

- **Issues 4 and 8:** PSM analysis to calibrate the model 
- **Issue 9:** 24-week response and treatment continuation 
- **Issue 10:** Belimumab non-responder disease activity 
- **Issue 11:** Violation in utility estimation 

 **Model driver**

 **Small impact**

 **Unknown impact**

Organ damage reduction on belimumab

- In TA397, long-term effects on disease progression were simulated using the natural disease history model based on Johns Hopkins (JH) cohort.
- In this appraisal, the BLISS long-term extension studies (LTE) were used to extrapolate long-term effects on disease progression.
- However, as the long-term extension studies did not have comparator arms:
    - The company conducted a propensity score matched (PSM) primary analysis to match patients who had **belimumab plus standard treatment** in the **BLISS-76 US LTE** with patients from an external **Toronto Lupus Cohort** treated with **standard therapy** (n=99 in each cohort).
    - The primary endpoint of the PSM was to compare organ damage progression (mean change in SDI score) from baseline to Year 5 in patients treated with belimumab or standard therapy with ≥5 years of follow-up.
    - Company considers that PSM analysis provided the opportunity to validate and calibrate organ damage model results using observed long-term evidence.

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.

For discussion

Issues 4 and 8: PSM analysis to calibrate the model (1)

Background

- **Company**: model overestimated organ damage progression in the belimumab arm but underestimated progression in the standard treatment arm, compared with results from the PSM analysis.
- So, company derived a calibration factor by simulating the model until the results matched the observed results from the PSM.
- Application of the calibration factor at 5 years exposure to belimumab allowed adjustment of the existing natural history model in the cost effectiveness model.
- The model is calibrated using estimates from 1.5 to 6.5 years. The calibration factor is applied to both models only to patients who remain on belimumab for a maximum of 6 years.

ERG comments

1. Patients in both the Toronto Lupus Cohort (TLC) and the BLISS long term extension (LTE) studies have been highly selected into the PSM analysis and therefore are unlikely to be representative of SLE patients in the UK.
2. The key issue is application of the calibration factor derived at 5 years to the whole 5 years.
3. The calibration factor derived from the PSM comparative analysis (0.491) effectively doubles the effectiveness of belimumab for preventing organ damage, compared with the JH model
    - The pre-calibration Johns Hopkins model (TA397) was already adjusted to predict SS score of a patient treated with standard therapy after 1 year, onto which a constant treatment effect of belimumab on disease activity reduction was applied (based on the trial data).

For discussion

Issues 4 and 8: PSM analysis to calibrate the model (2)

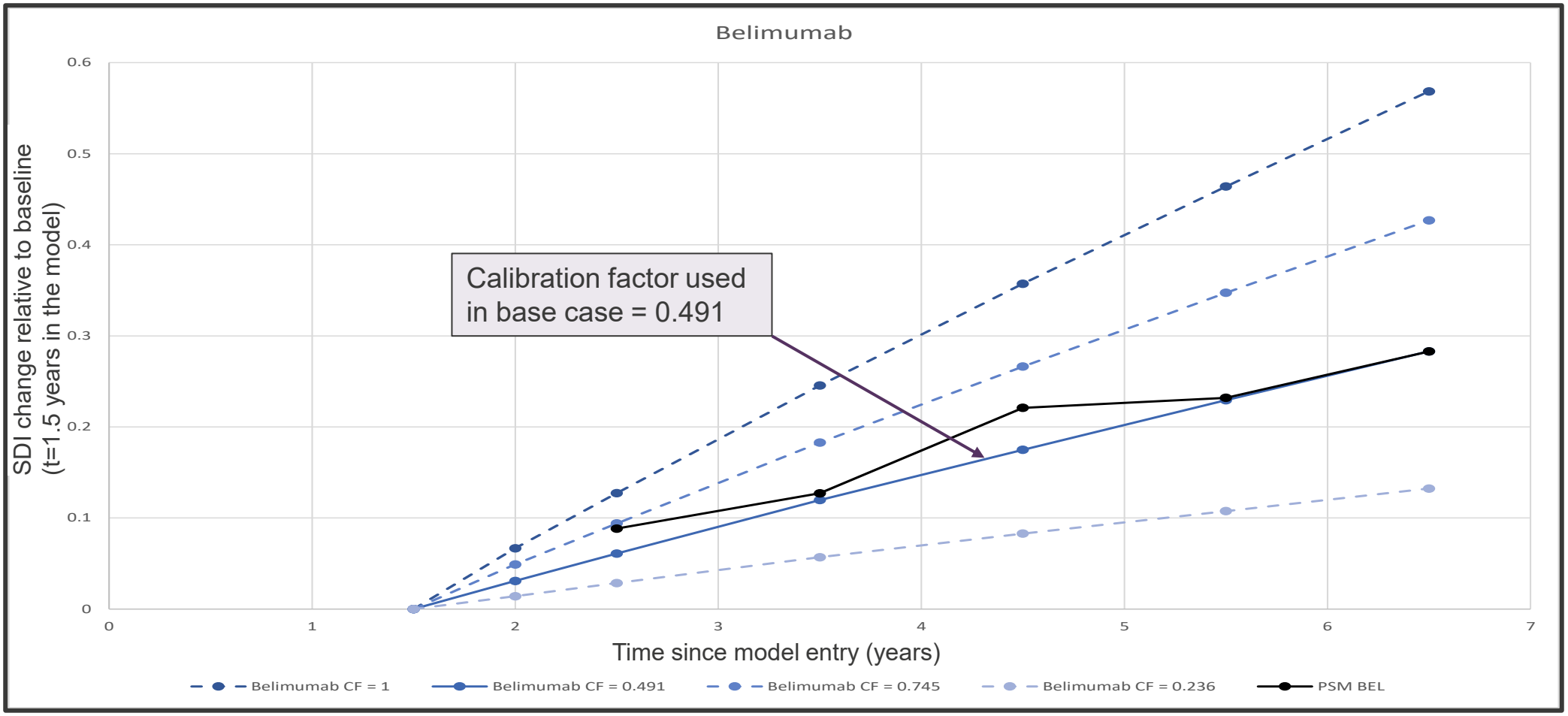
Company comments responding to ERG issues

1. Company clinical experts consider the BLISS-76 US LTE PS-matched cohort to be clinically reflective of the UK SLE population (based on a comparison of baseline characteristics of the matched cohort and BILAG-BR).
2. The company presented a plot (see next slide) estimating change in SDI from baseline using the PSM compared with using different calibration coefficients for years 1-5 in the model:
   - calibrated values do not show a systematic under- or over-estimation of SDI scores over the years, so the use of a single calibration factor value applied for each of the years in the model is appropriate.
   - it is unclear how the SDI increase after 5 years should be extrapolated beyond this point, so the calibration factor was conservatively applied for a maximum of 6 years.
3. In the belimumab arm in the model, non-responders at week 24 are not subject to the calibration factor:
   - belimumab responders will only have the calibration factor applied from 1 year until their time of withdrawal or to a maximum of 6 years (whichever occurs earliest).
   - calibration factor has not been applied to the standard therapy arm, which could further underestimate the benefit of belimumab.

For discussion

Issues 4 and 8: PSM analysis to calibrate the model (3)

Change in SDI (organ damage) from baseline using the PSM (black line) compared with different calibration coefficients (blue lines) for years 1-5 in the model



Use of calibration factor in company base case indicates less organ damage progression compared with the PSM for first 3 years (post 1.5 years observed follow-up in BLISS studies).

For discussion

Issues 4 and 8: PSM analysis to calibrate the model (4)

ERG further comments

1. Disease severity differed between patients in the BILAG-BR and BLISS-76 US LTE PS-matched cohort (baseline SLEDAI scores of 8.5 in the PSM, [redacted] in BILAG-BR), so it is unclear if patients in the PSM analysis are generalisable to the UK SLE population.
2. It is unclear how the calibration coefficients have been estimated in the company's plot:
   - however, there would remain likely underestimation of progression at years 1 to 3 based on the calibration factor curve of 0.491 lying under the PSM curve for the first 3 years
   - the ERG is unsure whether the calibration factor has been derived from the whole modelled cohort but consider that only responders should be used.
3. Most patients withdrew from the BLISS US LTE before 5 years, therefore patients who continue on belimumab at 5 years are likely to have progressed less or responded better than patients who took belimumab for 1-4 years before discontinuing:
   - applying the calibration factor estimated based on 5 years to all time points up to 5 years probably overestimates the effectiveness of belimumab for the preceding years
   - the calibration factor lacks validity and should not be used.

Impact on ICER – Significant

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

Is the application of a calibration factor to adjust the long-term effects of belimumab on organ damage appropriate?

For discussion

Issue 9: 24-week response and treatment continuation (1)

Background

- In the model, the probability of being a responder is based on the baseline SELENA SLEDAI (SS) score, which is linked to the responder criteria applied to patients in the BLISS trials (patients with a reduction of ≥ 4 points in SS score at week 24).
- It is estimated at baseline and not directly linked to the actual improvement in SS score in the model. Actual SS scores are estimated based on a regression model, given that a 24-week time point does not exist in the model.
- This means that a large proportion of patients are classed as non-responders but experience >4 points reduction in SS at 52 weeks.
- If patients with response are classified as non-responders and therefore modelled to discontinue treatment with belimumab, this could lead to under-estimation of belimumab costs in the model compared to clinical practice.

Company comments

- The company disagrees that there is an issue with the implementation of the belimumab 24-week response and treatment continuation in the model.
- A 24-week responder rule has been implemented in the model only for patients on belimumab to reflect TA397 and the SmPC.

For discussion

Issue 9: 24-week response and treatment continuation (2)

Company comments continued

- Belimumab non-responders at week 24 could have an SS reduction of more than 4 points at 52 weeks compared to baseline.
- This observation does not mean that these patients were incorrectly classified in the model as non-responders due to the chronology of the measurements;
  - no patients that were modelled as non-responders had a SS-reduction of >=4 points at 24 weeks
  - In the IV HDA-2 subgroup 46.5% of all belimumab non-responders had a SS-reduction of >=4 points at 52 weeks
  - Clinical expert advice to the company was that all non responders at week 24 would cease belimumab treatment and receive alternate therapies
  - It is not unreasonable to assume a further improvement in SELENA-SLEDAI score in line with the average ST score by week 52 in a belimumab non-responder patient

ERG comments

- It is unclear whether the implementation of 24-week response and treatment continuation in the model is in line with the clinical trial evidence.

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

Issue 10: Non-responder disease activity (1)

For discussion

Background

- The ERG considers there to be an error in the model as belimumab non-responders have the same reduction in disease activity (SS score) as standard therapy (ST) patients at 52 weeks:
  - the ST group included both patients whose disease had responded and not responded to standard care
  - BLISS trials showed that belimumab non-responders have a smaller reduction in disease activity than ST patients in the first 52-weeks
  - this is likely to overestimate the benefit of belimumab.

Company comments

- This is not an error in the model, but an assumption that belimumab non-responders take the average ST score regression coefficient from week 52 onwards.
- Some belimumab non-responders may have experienced a reduction in SS score from 1-3 points, but stopped treatment due to the week-24 stopping criteria.
- Company clinical experts consider belimumab non-responders would likely receive alternative treatments (further optimised ST or other non-standard therapies) and aim for an improvement in disease activity within 3-6 months of changing treatments.
- Company scenario analysis assumed return to ST efficacy for belimumab non-responders after 1 full year of ST treatment alone (i.e. after week 76) which had a small impact on the ICER.

Issue 10: Non-responder disease activity (2)

For discussion

ERG comments

- The model has a yearly cycle and so does not capture any disadvantage belimumab non-responders may experience in the first 52 weeks.
- The company's assumption is not in line with the BLISS trials and this discrepancy has not been explained.
- ERG were unable to validate company's scenario analysis (as they did not receive model file).
- ERG base case uses the BLISS evidence to incorporate the difference between belimumab non-responders and ST treated patients 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).

Impact on ICER - Small

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

Should belimumab non-responders in the model have the same reduction in disease activity as standard therapy patients in the first 52 weeks?

Issue 11: Violation in utility estimation

For discussion

Background

- In the model, the regression equation used to estimate utilities excludes key organ damage coefficients without re-estimating the remaining coefficients used in the equation.
- The ERG would have preferred the use of re-estimated coefficients after excluding the organ damage covariates.

Company comments

- 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 have 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

- 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.
- 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?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Baseline weight distribution was obtained from the BILAG-BR.	As BILAG-BR data was not used to assess long-term outcomes, the ERG is concerned that the patient baseline characteristics do not match the effectiveness data.	Using mean weight from the BLISS IV trials reduces the ICER.
Long-term corticosteroid sparing effect of belimumab remains unchanged from TA397.	The ERG considers that there is still uncertainty on whether the corticosteroid sparing effect and other benefits of belimumab would reduce the development of organ damage and translate into long-term benefit.	Impact on ICER unknown.
Lifetime treatment duration and effect for belimumab.	Company conducted a scenario analysis where both the treatment duration and effect of belimumab is restricted to 10 years.	The ICER reduces in both IV and SC models.

- In TA397 clinical experts considered that continuous use of belimumab for a long time would be very unlikely.
- In this appraisal, company reported flare rates from a non-randomised 52-week post-marketing treatment holiday study in adults who received IV belimumab for ≥6 months:
  - 2.1 for long-term belimumab discontinuation arm (n=39)
  - 1.0 for treatment holiday arm (24-week belimumab withdrawal, reintroduction for 28-weeks, n=12)
  - 0.6 in the continuous belimumab treatment arm (n=29).

Other issues for consideration

Innovation

- Company highlighted that disease flares and the potential benefit of reduced exposure to the cumulative effects of steroids have not been fully captured in the economic model.
- Technical team considers that all relevant benefits associated with the drug are adequately captured in the model.

Equality considerations

- Stakeholders commented that SLE is more common in women, particularly in those of child-bearing age.
- SLE is more common in people from African, Caribbean and Asian family origin, who are more likely to experience severe disease, co-morbidities and higher rates of premature mortality:
    - "*Double-stranded-DNA antibodies are less common in patients of African descent, so it could be perceived as discriminatory to stipulate dsDNA antibody positivity as a criterion and not consider other lupus-related antibodies*".
- Stakeholders highlighted that the current administration of intravenous belimumab within a specialist centre presents a barrier to access to treatment as a result of geography.
- Issues related to differences in the prevalence/incidence of a disease or the implementation of health care cannot be addressed in a technology appraisal.
- The committee will only make recommendations for belimumab in line with its marketing authorisation.

Cost effectiveness results – company base case

HDA-2 subgroup – ICERs include 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]	29,162
ST	160,470	16.90	9.81				

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]	30,808
ST			

Cost effectiveness results – ERG base case

HDA-2 subgroup – ICERs include belimumab PAS

IV formulation

Deterministic ICERs

Assumption	ICER (£/QALY)
Company base case	**29,162**
1. First year corrected reductions in SS score for belimumab non-responders (issue 10)	30,839
2. Calibration factor removed (issues 4 and 8)	49,202
ERG base case (1 + 2)	**51,817**

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Belimumab	[redacted]	[redacted]	53,910
ST			

NICE

Cost effectiveness results – company base case

HDA-2 subgroup – ICERs include 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]	30,566
ST	151,999	17.12	10.06				

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Belimumab	[redacted]	[redacted]	29,264
ST			

Cost effectiveness results – ERG base case

HDA-2 subgroup – ICERs include belimumab PAS

SC formulation

Deterministic ICERs

Assumption	ICER (£/QALY)
Company base case	**30,566**
1. First year corrected reductions in SS score for belimumab non-responders (issue 10)	32,617
2. Calibration factor removed (issues 4 and 8)	56,277
ERG base case (1 + 2)	**61,057**

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
ST	[redacted]	[redacted]	**62,367**
Belimumab			

NICE

Summary of ERG's key issues considered at technical engagement		Status
1a.	No evidence for belimumab in people with severe active CNS lupus.	Resolved
1b.	Population focuses on adult population only	Unresolved
2a.	Comparators – cyclophosphamide	Resolved
2b, 5 & 6.	Comparators – rituximab	Unresolved
3.	Long-term comparative data for pivotal belimumab trials	Unresolved
4 & 8	PSM analysis is applied to the model (as a calibration factor) • Is the application of a calibration factor to adjust the long-term effects of belimumab on organ damage appropriate?	For discussion
7	IV and SC formulations of belimumab are not compared with each other.	Resolved
9	24-week response and treatment continuation in the model • Is the modelling of 24-week response and treatment continuation in line with the BLISS trials and clinical practice?	For discussion
10	Belimumab non-responder disease activity at 52 weeks • Should belimumab non-responders in the model have the same reduction in disease activity as ST patients in the first 52 weeks?	For discussion
11	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?	For discussion
12	Organ damage utility multipliers	Unresolved
13	Sampling of organ damage and death	Unresolved