

7.01 BELIMUMAB, Injection 200 mg in 1 mL pre-filled pen, Benlysta[®], GlaxoSmithKline Australia Pty Ltd

1 Purpose of Application

- 1.1 The resubmission requested a Section 100 Highly Specialised Drugs Program (S100 HSDP) Authority Required listing for belimumab as add-on therapy for the treatment of active auto-antibody positive systemic lupus erythematosus (SLE) with a high degree of disease activity, despite defined ongoing standard of care (SOC).
- 1.2 This is the second consideration of belimumab by the PBAC. The PBAC previously considered belimumab in November 2019. Data previously considered by the PBAC is highlighted in blue throughout the document.
- 1.3 The basis for the requested listing was cost-utility analyses versus SOC (Table 1).

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Adult patients with active SLE with a high degree of disease activity despite standard therapy
Intervention	Belimumab 200 mg subcutaneous injection once weekly
Comparator	Placebo
Outcomes	SLE Responder Index (SRI) (a composite outcome consisting of SELENA-SLEDAI, PGA, BILAG), SFI flare, Prednisone use, SDI, HRQoL (FACIT Fatigue), Adverse events
Clinical claim	Superior effectiveness Inferior safety

Abbreviations: BILAG, British Isles Lupus Assessment Group; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; PGA, Physician Global Assessment; SC, subcutaneous; SDI, Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index. SFI, SLE Flare Index; SLE, systemic lupus erythematosus; SoC, standard of care; SRI, Systemic Lupus Erythematosus Responder Index

Source: Table 8, p3 of the resubmission.

2 Background

Registration status

- 2.1 Belimumab is TGA registered both as a powder for IV infusion (120 mg in 5 mL vial; 400 mg in 20 mL vial) and as a solution for subcutaneous (SC) injection (200 mg in 1 mL) via a pre-filled syringe or auto-injector. The approved TGA indication is:

“(Belimumab) is indicated as add-on therapy for reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. ANA titre \geq 1:80 and/or anti-dsDNA titre

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≥30 IU/mL) despite standard therapy. The safety and efficacy of (belimumab) have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.”

Previous PBAC consideration

2.2 In November 2019, the PBAC did not recommend belimumab. The PBAC considered that the evidence demonstrated a modest clinical benefit and that the economic model presented in the submission did not provide a reliable basis for estimating cost-effectiveness.

2.3 Table 2 summarises key issues identified by the PBAC in the previous submission and how this resubmission addressed them.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical evaluation		
Restriction	Wording of the required diagnostic criteria, disease activity level, concomitant therapy, excluded patients, prescribers and continuation criteria.	The resubmission’s proposed restriction reflects the PBAC’s comments.
Clinical benefit	The PBAC considered that belimumab demonstrated a modest clinical benefit compared with placebo, and noted that the SRI response at Week 52 was not statistically significant in the EMBRACE trial (conducted in patients of African American, Native American and African descent). SLE is more common and more severe in Indigenous Australians and the applicability of the pivotal trial (BLISS-SC) to these patients is uncertain (para 7.7 – 7.8, Nov 2019 Public Summary Document (PSD)).	There are no new clinical trial data available.
SDI progression	The economic model was based on organ damage (SDI progression), however the PBAC considered that the benefit of belimumab in reducing SDI progression was not adequately supported (para 7.9, Nov 2019 PSD).	The resubmission presented additional analyses at Week 52 in the trials, on the proportion of patients free from SDI progression, LS mean change from baseline in SDI score and the percentage of patients with SDI worsening.
Clinical claim	The PBAC considered that, given the potential severity of psychiatric adverse events, belimumab had inferior safety versus SOC alone (para 7.10, Nov 2019 PSD).	The resubmission revised the clinical claim to inferior safety of belimumab compared to placebo.
Economic evaluation		
Model structure	The model did not differentiate between responders and non-responders in the SOC arms.	The resubmission restructured the SOC arm to split the responders and non-responders.
SDI progression	The model assumed that treatment with belimumab reduced the rate of SDI progression and consequently reduced mortality. The PBAC considered that the submission had not adequately demonstrated an improvement in SDI progression (para 6.23, Nov 2019 PSD). Transition probabilities for SDI progression for the BEL arm were informed by Urowitz et al 2018. The PBAC considered that Urowitz et al 2018 was not reliable due to a high risk of unmeasured confounders (para 7.9, Nov 2019 PSD).	The resubmission continued to assume that belimumab would reduce the rate of SDI progression. The resubmission maintained that SLE disease activity and damage is overall associated with increased organ damage accrual and mortality. The resubmission used the odds ratio of patients with SDI worsening at Week 52 compared with baseline from BLISS-SC.

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Component	Matter of concern	How the resubmission addresses it
	The ESC and the PBAC previously considered that the reliability and applicability of the Bruce et al 2015 model predictions were unclear. The description of the method was vague and the impact of other simplifying assumptions was unknown (paragraph 6.26, Nov 2019 PSD).	This was unchanged in the resubmission and favours belimumab.
Approach to modelling utility	The model estimated considerable quality of life gains, which were driven by time on belimumab treatment, rather than time in the SDI health states. The evaluation and the ESC considered that EQ-5D estimates by SDI health state in Aggarwal et al 2009 were more applicable to the requested PBS population than those in Wang et al 2014 (para 6.56, Nov 2019 PSD).	This was unchanged in the resubmission. The use of utility values from Wang et al 2014 was unchanged from the previous submission and favours belimumab.
Financial estimates		
Analytical approach	A mixed prevalence and incidence approach was used, which the DUSC advised was not appropriate.	A prevalence only approach was adopted.
Parameter values	SLE prevalence rate: the DUSC and the PBAC considered this uncertain. The PBAC considered the proportion of SLE patients assumed to meet the proposed PBS criteria likely overestimated (para 7.12, Nov 2019 PSD). The DUSC considered that the proportion of patients continuing treatment was likely overestimated, and the PBAC considered that the continuation rates were uncertain (para 6.66, Nov 2019 PSD). The submission assumed a compliance rate of 100%. The compliance rate in BLISS-SC was 96%. However, the DUSC considered that compliance in the PBS setting is anticipated to be lower than in the clinical trial setting (para 6.67, Nov 2019 PSD).	This was unchanged in the resubmission. This was unchanged in the resubmission, despite a tighter PBS restriction, which would reduce the proportion of SLE patients able to meet PBS eligibility criteria. This was unchanged in the resubmission. This was unchanged in the resubmission.
Uptake rate	The PBAC considered the uptake rates (15-40%) are highly uncertain. Further, the PBAC considered that the treatment effect is modest and use may be associated with potentially severe adverse events, which may temper uptake (para 6.64, Nov 2019 PSD).	The resubmission increased the uptake rates to 20% - 50% over Year 1 – Year 6.

Source: compiled during the evaluation

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 The PBS listing requested by the submission is outlined below. Suggestions and additions proposed by the PBAC Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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Name, manner of admin, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
Belimumab Single-dose pre-filled autoinjector contains 200 mg	1	4	5	BENLYSTA® SC GlaxoSmithKline

Requested restriction – initial treatment

Category/program: Highly Specialised Drugs Program (S100) GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Condition: Systemic lupus erythematosus
PBS indication: Active Systemic lupus erythematosus
Treatment phase: Initial
Restriction: <input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist; or
Must be treated by a nephrologist
AND
Clinical criteria:
Adult Patient must have a confirmed and documented diagnosis of systemic lupus erythematosus (SLE) (according to the ACR/EULAR SLE Classification Criteria 2019),
AND
Clinical criteria:
Patient must have laboratory evidence of disease activity with an elevated anti-double stranded deoxyribonucleic acid (anti-dsDNA) titre despite standard therapy; or
Patient must have <i>below the lower limits of normal</i> complement (C3 or C4) levels despite standard therapy
AND
Clinical criteria:
Patient must have Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of at least 10 points
AND
Clinical criteria:
Patient must be currently receiving hydroxychloroquine and must have received this for at least three months 12 weeks
AND
Clinical criteria:
Patient must be currently receiving immunosuppressant medication and must have received this for at least 12 weeks three months (minimum dose of methotrexate 20mg per week, azathioprine 100 mg per day, or mycophenolate 1,000 mg per day)
AND
Clinical criteria:
Patient must be currently receiving prednisolone or equivalent ≥ 7.5 mg per day and must have received this for at least 4 weeks one month
AND
Clinical criteria:
Patient must not have severe renal active lupus nephritis or severe active central nervous system systemic lupus erythematosus
AND
Clinical criteria:
Patient must not have previously received PBS-subsidised treatment with this drug for this condition.

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<p>Prescribing instructions: The authority application must be made in writing and must include: a) a completed authority prescription form; and b) details of current therapy used (dosage, date of commencement and duration of therapy) c) a completed SLEDAI-2K score sheet, including the date of assessment, and d) a copy of the pathology report showing low complement (C3 or C4) and/or <i>elevated</i> anti-dsDNA, including the testing laboratory's reference range.</p>
<p>Prescribing instructions: The name of the specialist consulted must be provided at the time of application for initial supply</p>
<p>Prescribing instructions: The date of the pathology report and name of the Approved Pathology Authority must be provided at the time of application.</p>
<p>Prescribing instructions: History of systemic lupus erythematosus medication therapy should be based on documented use of treatment prescribed by a physician.</p>
<p>Prescribing instructions: Standard of care for this condition is a combination of an antimalarial medicine, a corticosteroid (at least 7.5 mg per day prednisolone or equivalent) and a systemic immunosuppressive medicine.</p>
<p>Prescribing instructions: Where intolerance to standard of care of a severity necessitating permanent treatment withdrawal has occurred or is expected to occur, details of the degree of this toxicity must be provided at the time of application.</p>
<p>Prescribing instructions: If treatment with standard of care therapy is contraindicated according to the relevant TGA approved Product Information, details of the contraindication must be provided at the time of application.</p>
<p>Prescribing instructions: If fewer than the maximum stated repeats in the relevant treatment phase are requested at the time of the application, authority approvals for sufficient repeats to complete the balance of the stated repeats in the relevant treatment phase may be requested by telephone by contacting the Department of Human Services <i>Australia</i> and applying through the Balance of Supply restriction. Under no circumstances will telephone approvals be granted for treatment that would otherwise extend the relevant treatment phase.</p>
<p>Administrative advice: Special Pricing Arrangements apply.</p>
<p>Administrative advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7004 <i>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826</i></p>

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HOBART TAS 7001

Cautions:

It is recommended that the first subcutaneous injection of belimumab be under the supervision of a healthcare professional in a setting that is sufficiently equipped to manage hypersensitivity reactions.

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Requested restriction – continuing treatment

Category/program: Highly Specialised Drugs Program (S100) GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Condition: Systemic lupus erythematosus
PBS indication: Systemic lupus erythematosus
Treatment phase: Continuing
Restriction: <input checked="" type="checkbox"/> Authority Required – by telephone
Treatment criteria:
Must be treated by a rheumatologist; or Must be treated by a clinical immunologist; or Must be treated by a nephrologist.
AND
Clinical criteria:
Patient must have previously been issued with an authority prescription for this drug for this condition.
AND
Clinical criteria:
Patient must have demonstrated or maintained at least a 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, compared to the baseline assessment; OR Patient must have demonstrated or maintained at least a 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, compared to the baseline assessment prior to having a treatment break for clinical reasons.
Prescriber instructions:
If fewer than the maximum stated repeats in the relevant treatment phase are requested at the time of the application, authority approvals for sufficient repeats to complete the balance of the stated repeats in the relevant treatment phase may be requested by telephone by contacting the Services Australia and applying through the Balance of Supply restriction. Under no circumstances will telephone approvals be granted for treatment that would otherwise extend the relevant treatment phase
Administrative advice:
Special Pricing Arrangements apply.
Administrative advice:
Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
<i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i>

- 3.2 The proposed effective price was unchanged compared to the previous submission.
- 3.3 The proposed PBS restriction largely mirrors the wording proposed by the PBAC in November 2019. As such, the target population in the resubmission is a more severe subgroup of SLE patients compared to the November 2019 submission.
- 3.4 In December 2019, the Sponsor announced positive headline results for BLISS-LN, a randomised controlled trial of IV belimumab versus placebo for lupus nephritis. Therefore, increased use of belimumab for renal patients may occur, due to the following factors:
- Although the proposed PBS restriction specifies that patients must not have severe renal SLE, this does not limit use in patients with mild to moderate lupus

nephritis. The ESC noted that 11.8% of patients enrolled in BLISS-SC had renal involvement at baseline; and that the BLISS-SC trial only excluded patients with severe lupus kidney disease (defined by proteinuria > 6 g/24 hour or serum creatinine > 2.5 mg/dL, or who had severe active nephritis requiring acute therapy not permitted by the protocol).

- Furthermore, the limitation on patients with severe active lupus nephritis is largely reflective of regulatory guidelines, which include this statement because belimumab had not been previously trialled in these patients. The sponsor indicated in the pre-PBAC response that a regulatory submission based on the results of the BLISS-LN study is progressing.
- The requested PBS restriction specifies nephrologists as one of only three specialist physician groups who can prescribe belimumab. The PBAC considered that belimumab should not be prescribed by a nephrologist, only a rheumatologist or immunologist.
- Renal SLE patients have no other options on the PBS and access through hospitals for the IV formulation is a difficult and lengthy process.

This may have implications for increasing the risk of leakage in severe lupus nephritis and any Risk Sharing Arrangements (RSA).

- 3.5 The submission requested in the initial restriction that a patient must be currently receiving immunosuppressant medication (methotrexate 20mg per week, azathioprine 100 mg per day, or mycophenolate). The PBAC considered that the restriction should be more specific and that the requirement for prior immunosuppressant medication should specify that patients must be currently receiving at least one of the following medications for at least 12 weeks: methotrexate 20 mg/week, azathioprine 100 mg daily, mycophenolate 1,000 mg daily. The restriction should clarify that the aforementioned doses are the minimum doses that meet the requirement for prior immunosuppressant medication.
- 3.6 The resubmission requested that patients with severe renal or CNS SLE be excluded, in line with clinical trial evidence. This was updated from the November 2019 submission and is consistent with the previous recommendation from the PBAC (paragraph 7.5, belimumab PSD, November 2019). The PBAC considered that “severe renal or central nervous system” SLE should be changed to “severe active lupus nephritis or severe active central nervous system” SLE to more closely align with the TGA-approved indication, which includes the statement “The safety and efficacy of BENLYSTA have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.” Furthermore, since the exclusion of patients in the BLISS-SC trial was based on patients having a particular thresholds of proteinuria or serum creatinine (definitions shown in paragraph 3.4), the PBAC considered these criteria should be also be specified in the restriction.

- 3.7 The majority of biological medicines are S100 HSDP listings, but some (usually the self-administered injections) have at least a dual General Schedule/S100 listing in recognition that continuing treatment can often be administered to the patient outside of an institution. The Secretariat questioned whether designation of belimumab as a S100 HSDP listing is warranted, given that it can be self-administered with appropriate training at commencement of treatment. Listing as a non-S100 item would have implications for estimates of the cost of treatment as there are differences in pharmacy mark-ups and dispensing fees between General Schedule and S100 items.
- 3.8 The Secretariat noted that in any future resubmission, if reference to proprietary measures/indices of disease activity/severity are made in the PBS restriction, instructions to doctors should be provided in the restriction as to where to find/how to use such indices. A statement declaring the copyright holder and any need for a licence to reproduce the index/measure (by Services Australia, the Department or a prescriber) or to use it in clinical practice should either feature in the submission, the proposed PBS restriction or both.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 SLE is a chronic autoimmune, relapsing, remitting disease, which typically affects multiple organ systems without a predictable pattern, even in the same patient. Patients present with variable expression and severity of clinical features, ranging from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement. Constitutional symptoms such as fatigue, fever, and weight loss are present in most SLE patients at some point during the course of the disease. Immunologic abnormalities, such as the production of a number of antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) are highly associated with the disease. SLE occurs more commonly in women of childbearing age (20 – 40 years old) and in certain ethnic groups. In Australia, SLE is more common and more severe in Indigenous Australians and descendants from South-East Asia.^{1,2}
- 4.2 The goals of therapy are to ensure long-term survival, achieve the lowest possible disease activity, prevent organ damage, minimise drug toxicity, improve quality of life, and educate patients about their role in disease management. The four main groups of drugs that are used to treat SLE are non-steroidal anti-inflammatory drugs (NSAIDs), anti-malarial drugs, corticosteroids, and immunosuppressants. Corticosteroids are

¹ Connelly K, Morand EF, Hoi AY. Asian ethnicity in systemic lupus erythematosus: an Australian perspective. *Intern Med J* 2013;43:618–24.

² Vincent FB, Bourke P, Morand EF, Mackay F, Bossingham D. Focus on systemic lupus erythematosus in Indigenous Australians: towards a better understanding of autoimmune diseases. *Intern Med* 2013;43:227–34.

tapered once disease flares are under control, with the overarching goal to use minimum medication to maintain disease control. The increasing cumulative dose of low-dose maintenance or higher-dose pulsatile corticosteroid treatment contributes to organ damage in SLE patients, for example osteoporosis, diabetes and cataracts.

- 4.3 Measuring disease activity or response to treatment is challenging given the complex multi-system nature of SLE, the variability of manifestations both between patients and within the same patient over time, the different co-morbidities and cumulative organ damage between patients, and individualised background polypharmacy. There is no gold standard instrument or endpoint to assess SLE disease activity or response to treatment. There have also been variations in defining what constitutes a clinically meaningful benefit using different disease activity indexes (DAIs).
- 4.4 The main instrument presented by the resubmission was the SLE responder index (SRI), a composite index consisting of three individual DAIs (see Table 3 below):
- the Safety of Estrogen in Lupus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI),
 - the British Isles Lupus Assessment Group of SLE Clinics (BILAG) index, and
 - the Physician’s Global Assessment (PGA).

Of note, there is high inter-rater variability in the assessment of disease activity, even among trained and experienced clinicians³.

- 4.5 The SRI was developed by the belimumab investigators following retrospective exploratory analyses of a Phase II belimumab RCT⁴. Other relevant disease indexes reported in the trials and presented in the resubmission included the SLE flare index (SFI) and the SLICC/ACR damage index (SDI). The health states in the resubmission’s economic model are defined in part by the SDI.

³ Mikdashi, J., & Nived, O. (2015). Measuring disease activity in adults with systemic lupus erythematosus: the challenges of administrative burden and responsiveness to patient concerns in clinical research. *Arthritis research & therapy*, 17(1), 183. doi:10.1186/s13075-015-0702-6

⁴ Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, et al. A phase II, randomized, double-blind, placebo controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 2009; 61:1168–78.

Table 3: Summary of the single disease activity indexes relevant to the resubmission

Single disease activity indexes		
Original	Modified	Scoring system
BILAG or "classic BILAG"	BILAG-2004	Measures disease activity in individual organ systems Both versions score each organ/system on an ordinal scale representing level of disease severity and treatment required (A = severe disease requiring action; to E = disease has never been active). The revised BILAG-2004 distinguishes nine organs/systems instead of eight in the classic BILAG. Completing the BILAG is complex, time consuming and not routinely used in clinical practice due to the difficulty of use (physician training is critical for accurate use).
SLEDAI	SELENA-SLEDAI SLEDAI-2K	Global measures of disease activity All versions evaluate disease activity over the previous 10 days and scores (one to eight) 24 descriptor items on specific manifestations in nine organ systems. There are slight variations in descriptors across versions. A total score of zero indicates no disease activity and scores ≥ 20 indicates very high disease activity. Literature review conducted during the evaluation indicated that the SLEDAI-2K is a more commonly used and better validated tool than the SELENA-SLEDAI.
PGA		A visual analogue scale using three benchmarks for assessing disease activity over the last two weeks. Mild flare will score 1.0 point, moderate flares will score 2.0–2.5 points and severe flares will score a 3 on the 0–3 analogue scale.
Other relevant indexes		
SFI		An assessment of new or worsening disease activity, medication changes, and hospitalisations not captured by the SELENA-SLEDAI.
SDI		An assessment of accumulated non-reversible chronic organ damage in 12 organ systems since SLE diagnosis. However, organ damage does not need to be attributable to SLE.

Blue indicates components of the SRI

Abbreviations: BILAG, British Isles Lupus Assessment Group; PGA, Physician Global Assessment; SC, subcutaneous; SDI, Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index. SFI, SLE Flare Index; SLE, systemic lupus erythematosus.

- 4.6 Overall, important aspects when considering whether SLE treatment is successful are recognising that the disease has an unpredictable course, that there is no gold standard instrument to measure the disease severity or activity, and that the goals of treatment and measure of “success” are individualised based on patient manifestations of SLE.
- 4.7 The resubmission is specifically targeting the subgroup of patients with highly active disease and who are most likely to respond to therapy, as defined (in the proposed PBS restriction) by patients with elevated anti-dsDNA titre or low complement levels, a SLEDAI-2K score of at least ten points and taking triple therapy for at least three months (including ≥ 7.5 mg/day prednisone for at least one month) at baseline. The population targeted in the resubmission was consistent with the PBAC’s recommendations from November 2019.

For more detail on PBAC’s view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission appropriately nominated placebo/SOC as the main comparator based on the argument that there are currently no treatment options for patients with highly active disease despite taking triple therapy. The PBAC previously accepted standard of care as the appropriate comparator (paragraph 7.6, Belimumab PSD, November 2019 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (HCPs; 3) and organisations (3) via the Consumer Comments facility on the PBS website.
- 6.3 Four of the 7 comments from individuals were from people who are living with SLE; they stated that access and affordability are important for pain relief and improvements in quality of life.
- 6.4 Three HCPs working in the SLE therapeutic area supported the PBS listing of belimumab. One stated that there is good evidence that the drug has utility in SLE, and there are many patients who have suboptimal control who would benefit from this medication. Another indicated that SC belimumab might be a useful adjunct to reducing disease activity and steroid toxicity if reasonably priced, and current low use is likely due to need for monthly infusions and price considerations. The third HCP drew attention to the increased mortality associated with SLE. The HCP stressed that while not all patients respond to belimumab, when a patient does respond it can be marked and life-changing, and that a SLEDAI cut-off of 10 identifies a group who have failed available therapies and are particularly at need.
- 6.5 The 3 organisations who provided comments were Lupus WA, the National Aboriginal Community Controlled Health Organisation (NACCHO), and Pain Australia. Lupus WA, which is a patient run organisation, commented that belimumab offers lupus patients an alternative treatment option, with potentially fewer side effects and long term organ management benefits. NACCHO drew attention to the greater rates and severity of SLE in the Aboriginal and Torres Strait Islander populations compared to other Australians. Pain Australia provided comments from SLE patients describing

disruption to work and personal life, stigmatisation and misunderstanding, and side effects with current medications.

- 6.6 The PBAC also considered input from the Consumer Evidence and Engagement Unit within the Office of Health Technology Assessment. This input consisted of qualitative interviews conducted with Australian lupus patients (4) alongside a summary of published consumer organisation comments made to other international HTA bodies on the use of belimumab for systemic lupus erythematosus.

Clinical trials

- 6.7 The resubmission was based on the same trial evidence as the previous submission, five randomised controlled trials (RCTs) comparing belimumab + SOC to SOC alone:
- Pivotal trial: 1 RCT of the belimumab SC formulation (BLISS-SC); and
 - Supportive trials: 4 RCTs of the belimumab IV formulation (BLISS-52, BLISS-76, NE-Asia; EMBRACE).

No updated clinical evidence was available; however, additional analyses for SDI outcomes were presented to support the economic evaluation.

- 6.8 Details of the trials presented in the resubmission are provided in Table 4. These are unchanged from the previous submission.

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Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Pivotal trial: SC formulation		
BLISS-SC	A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) Administered Subcutaneously (SC) to Subjects with Systemic Lupus Erythematosus (SLE). Stohl W, Schwarting A, Okada M et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus.	March 2016 <i>Arthritis & Rheumatology</i> 2017; 69 (5): 1016-1027.
Supportive trials: IV formulation		
BLISS-52	A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006, LymphoStat-B™), a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE). Navarra SV, Guzman RM, Gallacher AE et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial.	January 2010. <i>Lancet</i> 2011; 377: 721-731.
BLISS-76	A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 76-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006, LymphoStat-B™), a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE). Furie R, Petri M, Zamani O et al. A phase 3, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits BLyS< in patients with systemic lupus erythematosus.	March 2010 <i>Arthritis & Rheumatology</i> 2011; 63 (12): 3918-3930.
NE-Asia	GSK1550188. A 52 week study with belimumab versus placebo in the treatment of subjects with systemic lupus erythematosus (SLE) located in Northeast Asia – Double-Blind Endpoint Analysis. Zhang F, Bae S-C, Bass D et al. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea.	August 2017 <i>Annal Rheumatol Disease</i> 2018; 77: 355-363.
EMBRACE	A Phase 3/4, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Adult Subjects of Black Race with Systemic Lupus Erythematosus (SLE).	February 2019

Source: Table 21, pp32-33 of the November 2019 submission; pp38-39 of resubmission.

6.9 The key features of the direct randomised trials are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in economic model		
Belimumab SC formulation (pivotal trial)								
BLISS-SC	839	R, DB, MC, 52 wks	Low	Autoantibody positive; SELENA-SLEDAI score ≥ 8 at screening	Primary: SRI response (and components) at Wk 52 Secondary: time to 1 st severe flare; prednisone dose reduction $\geq 25\%$ from baseline to ≤ 7.5 mg/day during Wk 40 to 52; percent patients with ≥ 4 -point reduction from baseline in SELENA-SLEDAI score at Wk 52; mean change/percent change in PGA at Wk 24	Proportion achieving a ≥ 4 point reduction in the SELENA-SLEDAI at Week 24 from BLISS-SC; Rate of SLE flares from BLISS-SC.		
Belimumab IV formulation (supportive evidence)								
BLISS-52	867	R, DB, MC, 52 wks	Low	Autoantibody positive; SELENA-SLEDAI score ≥ 6 at screening				
BLISS-76	826	R, DB, MC, 76 wks	Low	Autoantibody positive; SELENA-SLEDAI score ≥ 6 at screening				
NE-Asia	707	R, DB, MC, 52 wks	Low	Autoantibody positive; SELENA-SLEDAI score ≥ 8 at screening; Asian race				
EMBRACE	503	R, DB, MC, 52 wks	Low	Autoantibody positive; SELENA-SLEDAI score ≥ 8 at screening; Black race				

Blue highlights indicate results previously seen by the PBAC.

Abbreviations: DB=double blind; MC=multicentre; PC=placebo controlled; R=randomised; PCS=physical component summary; SLE=Systemic lupus erythematosus; SLEDAI= SLE Disease Activity Index; SRI= SLE Response Index; wk=week.

Source: compiled during the evaluation from submitted trial and published reports.

- 6.10 BLISS-SC was the pivotal RCT that supported the use of belimumab SC formulation, at a dose consistent with the draft TGA PI, of 200 mg injected once a week. In the supportive trials, patients were randomised to receive belimumab IV 10 mg/kg or 1 mg/kg or placebo (in BLISS-52 and BLISS-76), and belimumab IV 10 mg/kg or placebo in NE-Asia and EMBRACE. Belimumab 10 mg/kg is the registered dose for the IV formulation.
- 6.11 All trials enrolled adults with a diagnosis of SLE according to ACR criteria, with unequivocally positive autoantibody test results defined as an ANA titer $\geq 1: 80$ and/or a positive anti-dsDNA (≥ 30 IU/mL) serum antibody test from two independent time points. BLISS-SC, NE-Asia and EMBRACE required patients to have a SELENA-SLEDAI score ≥ 8 at screening, compared to ≥ 6 in BLISS-52 and BLISS-76. Patients with severe active lupus nephritis, CNS lupus, treatment with prednisone >100 mg/day within three months prior to screening, and treatment with a B cell targeted therapy at any time were excluded in all trials.

Comparative effectiveness

6.12 The primary efficacy results are unchanged from the November 2019 submission and re-presented below. The primary efficacy outcome in the belimumab trials was the proportion of patients classified as responders, based on the SRI at Week 52. Table 6 presents the components of the SRI.

Table 6: Components of the primary outcome, SRI response at Week 52

Primary outcome across all trials: SRI response rate at Week 52		Comments
Components of the SRI (supportive/secondary analyses)	≥4-point reduction from baseline in SELENA-SLEDAI ^a	Considered as a clinically meaningful improvement
	No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment	The development of either ≥1 A or ≥2 B organ system scores represents an increase in disease activity sufficient to add new therapy (corticosteroids / immunosuppressant)
	No worsening (increase of <0.30 points from baseline) in PGA	To ensure that improvement in the SELENA–SLEDAI score was not achieved at the expense of worsening of the patient’s overall condition

Abbreviations: BILAG, British Isles Lupus Assessment Group; PGA, Physician Global Assessment; SC, subcutaneous; SDI, Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus.

^a EMBRACE used SLEDAI-2K (S2K) rules instead of SELENA-SLEDAI (SS) rules when scoring for proteinuria for the primary SRI outcome. Source: p55 of the resubmission; Furie et al 2009

6.13 Table 7 presents the results of the primary outcome, response as measured by the composite index, SRI, and the results to the component indexes of the SRI (secondary outcomes), at Week 52 across all trials. Results for the adjusted odds ratio (OR’s) (from logistic regression models in the CSRs) and unadjusted risk difference (RD’s) are presented below.

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Table 7: Proportion with SRI response (primary outcome) and response to component indexes (secondary outcomes) across the trials

	BEL (200mg SC or 10mg/kg IV)	Placebo	Adjusted OR (95%CI)	Unadjusted RD (95%CI)
SRI response rate at Week 52				
BLISS-SC ^a	340/554 (61.4)	135/279 (48.4)	1.68 (1.25, 2.25)^b, p=0.0006	0.13 (0.06, 0.20), p=0.0004
BLISS-52	167/290 (57.6)	125/287 (43.6)	1.83 (1.30, 2.59)^e, p=0.0006	0.14 (0.06, 0.22), p=0.0007
BLISS-76	118/273 (43.2)	93/275 (33.8)	1.52 (1.07, 2.15)^e, p=0.0207	0.09 (0.01, 0.18), p=0.0231
NE-Asia	240/446 (53.8)	87/217 (40.1)	1.99 (1.40, 2.82)^f, p=0.0001	0.14 (0.06, 0.22), p=0.0008
EMBRACE (SS) ^g	146/298 (49.0)	62/149 (41.6)	1.42 (0.94, 2.15) ^h , p=0.0937	0.07 (-0.02, 0.17), p=0.1374
EMBRACE (S2K) ^g	145/298 (48.7)	62/149 (41.6)	1.40 (0.93, 2.11) ^h , p=0.1068	0.07 (-0.03, 0.17), p=0.16
Meta-analysis (including EMBRACE – SS results)			1.69 (1.45, 1.97), p<0.00001	0.12 (0.08, 0.15), p<0.00001
≥4 point reduction from baseline in SELENA-SLEDAI score at Week 52				
BLISS-SC ^a	345/554 (62.3)	137/279 (49.1)	1.69 (1.26, 2.27)^b, p=0.0005	0.13 (0.06, 0.20), p=0.0003
BLISS-52	169/290 (58.3)	132/287 (46.0)	1.71 (1.21, 2.41)^e, p=0.0024	0.12 (0.04, 0.20), p=0.0029
BLISS-76	128/273 (46.9)	98/275 (35.6)	1.63 (1.15, 2.32)^e, p=0.0062	0.11 (0.03, 0.19), p=0.0071
NE-Asia	249/446 (55.8)	91/217* (41.9)	2.01 (1.42, 2.86)^f, p<0.0001	0.14 (0.06, 0.22), p=0.0007
EMBRACE (S2K) ^g	149/298 (50.0)	63/149 (42.3)	1.46 (0.97, 2.20) ^h , p=0.0726	0.08 (-0.02, 0.17), p=0.1209
Meta-analysis			1.70 (1.46, 1.99), p<0.00001	0.12 (0.08, 0.16), p<0.00001
No worsening (increase of <0.30 points from baseline) in PGA by Week 52				
BLISS-SC ^a	450/554 (81.2)	203/279 (72.8)	1.61 (1.15, 2.27)^{b, c}, p=0.0061	0.08 (0.02, 0.15), p=0.0070
BLISS-52	231/290 (79.7)	199/287 (69.3)	1.74 (1.18, 2.55)^{e, c}, p=0.0048	0.10 (0.03, 0.17), p=0.0042
BLISS-76	189/273 (69.2)	173/275 (62.9)	1.32 (0.92, 1.90) ^{e, c} , p=0.1258	0.06 (-0.02, 0.14), p=0.1173
NE-Asia	345/446 (77.4)	149/217 (68.7)	1.57 (1.09, 2.27)^{f, c}, p=0.0149	0.09 (0.01, 0.16), p=0.0195
EMBRACE ^g	207/298 (69.5)	96/149 (64.4)	1.26 (0.82, 1.93) ^{h, c} , p=0.2856	0.05 (-0.04, 0.14), p=0.2886
Meta-analysis			1.50 (1.27, 1.77), p<0.00001	0.08 (0.05, 0.11), p<0.00001
No new 1A/2B BILAG domain scores at Week 52				
BLISS-SC ^a	448/554 (80.9)	207/279 (74.2)	1.46 (1.04, 2.07)^{b, d}, p=0.0305	0.07 (0.01, 0.13), p=0.0318
BLISS-52	236/290 (81.4)	210/287 (73.2)	1.62 (1.09, 2.42)^{e, d}, p=0.0181	0.08 (0.01, 0.15), p=0.0181
BLISS-76	189/273 (69.2)	179/275 (65.1)	1.20 (0.84, 1.73) ^{e, d} , p=0.3193	0.04 (-0.04, 0.12), p=0.3017
NE-Asia	358/446 (80.3)	148/217 (68.2)	1.91 (1.32, 2.77)^{f, d}, p=0.0007	0.12 (0.05, 0.19), p=0.0010
EMBRACE ^g	202/298 (67.8)	93/140 (62.4)	1.24 (0.81, 1.88) ^{h, d} , p=0.3218	0.01 (-0.08, 0.11), p=0.7785
Meta-analysis			1.47 (1.24, 1.74), p<0.0001	0.07 (0.04, 0.10), p<0.0001

Bold typography indicates statistically significant results. Blue highlights indicate results previously seen by the PBAC.

Abbreviations: BEL=belimumab; CI=confidence interval; IV=intravenous; OR=odds ratio; RD=risk difference; S2K= the primary efficacy endpoint was SRI response rate with the SLEDAI-2K scoring rules for proteinuria; SC=subcutaneous; SRI=SLE responder index; SS= the secondary efficacy endpoint was SRI response rate using SELENA-SLEDAI scoring rules for proteinuria

* The submission (Figure 44, p113) erroneously used N=249 instead of 219 in its RevMan analyses. This and the corresponding ORs and RDs was corrected during evaluation.

^a Three ITT subjects did not have a baseline PGA assessment and, therefore, do not contribute to SRI/component analyses.

^b Logistic regression model with covariates treatment group, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

^c Baseline PGA was also included in the model.

^d Baseline BILAG domain involvement (at least 1A/2B vs. at most 1B) was also included in the model.

^e Logistic regression model with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

^f Logistic regression model with independent variables treatment group, country, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10) and complement levels (low C3 and/or C4 vs. no low C3 or C4).

^g One subject in the mITT population did not have a screening or baseline PGA assessment; therefore, this subject did not contribute to the SRI/component analysis.

^h Logistic regression model with covariates treatment group, baseline SS-S2K score (≤ 9 vs ≥ 10), baseline complement levels (at least 1 low C3 and/or C4 vs. NO low C3 or C4), and region (US/Canada vs. other).

Source: Tables 31-34, p87-92 and Tables 49-52, p119-123 of the resubmission; Tables 15-16, p78-79 of BLISS-SC CSR; Tables 7-1, 7-2 p80-81 of BLISS-52 CSR; Tables 7-1, 7-2 p86-87 of BLISS-76 CSR; Tables 16-17, p64-65 of NE-Asia CSR; Tables 19-20, 28, p59-60, p81 of EMBRACE CSR.

- 6.14 BLISS-SC demonstrated that belimumab 200 mg SC in addition to SOC achieved a greater proportion of SRI responders at Week 52 compared to placebo plus SOC (RD; 95% confidence interval [CI] = 0.13; 0.06, 0.20). The results of BLISS-SC were similar to the results from the pooled trials (RD; 95% CI = 0.12; 0.08, 0.15).
- 6.15 The sponsor noted in the pre-PBAC response that the treatment effect was greater in the sub-group of patients receiving triple therapy at baseline, and stated that the economic model uses the more conservative ITT results, rather than subgroup results based on patients with characteristics similar to the PBS population. In BLISS-SC the risk difference for SRI responders at Week 52 for the subgroup of patients receiving triple therapy at baseline was 0.19 (95% CI: 0.05, 0.34).
- 6.16 At its November 2019 meeting, the PBAC considered that belimumab demonstrated a modest clinical benefit compared with placebo. The response rate in the placebo arms of the trials were high, which the PBAC considered was likely due to a combination of reasons including optimisation and adherence to SOC in the clinical trial setting, as well as regression to the mean as some patients may have commenced therapy during a disease flare (paragraph 7.7, Belimumab PSD November 2019 PBAC meeting).
- 6.17 The PBAC also previously noted that SRI response at Week 52 was not statistically significant in the EMBRACE trial, which was conducted in patients of African American, Native American and African descent. SLE is more common and more severe in Indigenous Australians and the applicability of the pivotal trial, BLISS-SC, to these patients is uncertain (paragraph 7.8, Belimumab PSD November 2019 PBAC meeting).
- 6.18 The ESC noted that while the efficacy claim was based on response as measured by SRI at Week 52 (adjusted OR; 95% CI = 1.68; 1.25, 2.25 in BLISS-SC), which is not used in clinical practice, a similar response was obtained in the SLEDAI-based assessment (≥ 4 point reduction from baseline in SELENA-SLEDAI score at Week 52: adjusted OR; 95% CI = 1.69; 1.26, 2.27 in BLISS-SC), which is utilised in the economic model (SELENA-SLEDAI) and for assessment in the restriction (SLEDAI-2K).
- 6.19 The probability of response rates in the model was based on the proportion of patients who achieved a ≥ 4 -point reduction in the SELENA-SLEDAI at Week 24 in BLISS-SC in-line with the requested restriction. The difference in SELENA-SLEDAI response at Week 24 was not statistically significant (OR 1.34; 95% CI: 1.00, 1.81; $p=0.0522$).
- 6.20 Table 8 presents analyses for SDI progression, as included in the resubmission to substantiate its approach to the economic model. The resubmission used results for the proportion of patients with SDI worsening compared with baseline at Week 52 from BLISS-SC (highlighted in green), which was previously informed by Urowitz et al 2018 in the November 2019 submission.

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Table 8: SDI progression outcomes presented by the resubmission (and used in the economic model)

Change from baseline at Week 52	BEL (200mg SC/ 10mg/kg IV)		PBO		BEL v PBO
	Baseline mean (SD)	LS mean Δ (SD/SE)	Baseline mean (SD)	LS mean Δ (SD/SE)	LS mean Δ treatment diff. (95%CI)
LS mean change in SDI score at Week 52					
BLISS-SC ¹	0.6 (1.00)	0.0 (0.01) [†]	0.7 (1.19)	0.1 (0.02) [†]	-0.0 (-0.1, 0.0), p=0.1174
BLISS-52 ²	0.55 (0.06) [†]	0.08 (0.02) [†]	0.55 (0.05) [†]	0.10 (0.02) [†]	-0.02 (-0.06, 0.02), p=0.4222
BLISS-76 ²	0.94 (0.08) [†]	0.059 (0.031) [†]	0.99 (0.09) [†]	0.084 (0.032) [†]	-0.025 (-0.077, 0.027), p=0.3415
NE-ASIA ³	0.2 (0.55)	0.0 (0.15) [‡]	0.3 (0.61)	0.0 (0.19) [‡]	NR, p=0.8843 ⁴
EMBRACE ⁵	0.6 (0.98)	0.0 (0.01) [‡]	0.7 (1.06)	0.0 (0.02) [‡]	NR, p=0.7660 ⁴
Meta-analysis					-0.03 (-0.07, 0.01)
OR (95%CI)					
SDI worsening (Δ>0) compared with baseline at Week 52					Note: OR < 1 favours belimumab
BLISS-SC ⁶	13/556 (2.3%)		14/280 (5.0%)		0.47 (0.22, 1.02), p=0.0558
EMBRACE ⁷	8/299 (2.7%)		5/149 (3.4%)		0.90 (0.28, 2.86), p=0.8607
Meta-analysis					0.57 (0.30, 1.09), p=0.09
Patients remaining free from SDI progression at Week 52					Note: OR > 1 favours belimumab
BLISS-SC ⁶	446/556 (80.2%)		203/280 (72.5%)		1.54 (1.10, 2.16), p=0.0123
NE-ASIA ⁸	359/447 (80.3%)		160/226 (70.8%)		1.69 (1.17, 2.46), p=0.0056
Meta-analysis					1.61 (1.25, 2.06)

Bold indicates statistically significant results. Green highlights indicate results used in the modelled economic evaluation.

Abbreviations: Δ=change; BEL=belimumab; CI=confidence interval; IV=intravenous; LS=least squares; NR=not reported; OR=odds ratio; PBO=placebo; SC=subcutaneous; SD=standard deviation; SDI= SLICC/ACR Damage Index; SE=standard error

¹ Rank analysis of covariance (ANCOVA) model comparing belimumab and placebo with covariates for treatment group, baseline SLICC/ACR Damage Index score, baseline SELENA SLEDAI score (<=9 vs. >=10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (black vs. other).

² ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the baseline damage index score, baseline SELENA SLEDAI score (<=9 vs. >=10), baseline proteinuria level (<2 g/24 hour vs. >=2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs. other)

³ ANCOVA model comparing belimumab and placebo with independent variables treatment group, baseline SLICC/ACR Damage Index score, country, baseline SELENA SLEDAI score (<=9 vs. >=10) and complement levels (low C3 and/or C4 vs. no low C3 or C4).

⁴ Only subjects with a baseline and post baseline assessment are included in the analysis.

⁵ Exact Wilcoxon Rank Sum test.

⁶ logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, baseline SLICC/ACR Damage Index score, baseline SELENA SLEDAI score (<=9 vs. >=10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (black vs. other).

⁷ logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, baseline SLICC/ACR Damage Index Score, baseline SS-S2K score (<=9 vs. >=10), baseline complement levels [(At least one C3/C4 Low) vs. (No C3/C4 Low)] and region (US/Canada vs. Rest of World).

⁸ logistic regression model for the comparison between Belimumab and Placebo with independent variables treatment group, baseline SLICC/ACR Damage Index score, baseline SELENA SLEDAI score (<=9 vs. >=10) and complement levels (low C3 and/or C4 vs. no low C3 or C4).

[†] SE [‡] Unadjusted mean change

Source: Tables 55 – 57 of the resubmission; Tables 2.32, 2.34, 2.36 of BLISS-SC CSR, Table TE10.2, of BLISS-52 CSR; Table TE10.2 of BLISS-76 CSR; Tables 2.23, 2.24 of NE-Asia CSR; p97 and Tables 2.34, 2.36 of EMBRACE CSR

6.21 Although the odds ratio of 0.47 from BLISS-SC for SDI worsening was more conservative than the previously used hazard ratio of 0.391 from Urowitz et al 2018, it was more favourable than the results of the meta-analysis (BLISS-SC + EMBRACE) of OR = 0.57. Results from a Phase IV trial, BASE, indicated that at Week 52, SDI worsening compared with baseline was reported for 3.2% of patients in the placebo group and 2.8% in the belimumab 10 mg/kg group (OR = 0.87, 95% CI: 0.58, 1.31,

p=0.5033) (p114 BASE CSR). The results from BASE are similar to that from EMBRACE (OR = 0.90, 95% CI: 0.28, 2.86; p=0.8607).

- 6.22 Overall, belimumab did not confer any statistically significant benefits compared to placebo in terms of the LS mean change in SDI score or SDI worsening from baseline to Week 52, however, this may be due to the trials not being sufficiently powered for these endpoints. Nonetheless, the point estimates favoured belimumab. The ESC noted that the outcome used in the economic model, SDI worsening compared with baseline at Week 52, almost reached statistical significance (BLISS-SC OR; 95% CI = 0.47; 0.22, 1.02, p=0.0558). The Pre-Sub-Committee Response (PSCR) stated that this analysis applied a last observation carried forward (LOCF) assumption to patients with missing data, where patients lost to follow up (who had not experienced SDI progression) were assumed to remain free of SDI progression. Since more patients in the SOC arm were lost to follow up (23.6% SOC arm compared with 16.7% belimumab arm), the PSCR claimed that this analysis was biased against belimumab. The PSCR stated that if the same data are analysed using a non-responder imputation (all patients lost to follow-up were assumed to have SDI progression), the result is presented as a significantly higher proportion of patients treated with belimumab remaining free from SDI progression at Week 52 compared to placebo patients (BLISS-SC OR = 1.54, 95% CI: 1.10, 2.16, p=0.0123, Table 8). The ESC noted that patients lost to follow-up were handled differently for these outcomes, which introduced bias in different directions for the outcomes and influenced the significance of the results.
- 6.23 The ESC considered there remains uncertainty with regards to the effect of belimumab on SDI progression, given:
- the lack of statistically significant results for most measures of organ damage progression, but acknowledging the short duration of the studies and that the studies were not powered for this outcome;
 - The magnitude of the effect varied between studies;
 - The handling of patients lost to follow-up differed for each measure and reached statistical significance for the outcome of 'patients remaining free from SDI progression', in which patients lost to follow-up (who were more prevalent in the SOC arm) were assumed to be treatment failures.
- 6.24 The resubmission retained the real-world evidence studies Bruce et al 2015 and Urowitz et al 2018, despite no longer using the latter to inform the economic model inputs. The resubmission defended Urowitz et al 2018, to support the economic model's assumption of continuing SDI benefit over time whilst response to belimumab is maintained.
- 6.25 Urowitz et al 2018 compared organ damage progression in SLE patients who received belimumab in the BLISS-76 long term extension (LTE) study with propensity score matched patients on SOC from the Toronto Lupus Cohort. The study compared the

time to organ damage progression in patients with ≥ 1 year of follow-up, which indicated that patients treated with belimumab were 61% less likely to progress to a higher SDI score over any given year of follow-up compared with patients treated with SOC (hazard ratio =0.391; 95% CI: 0.253, 0.605). A patient treated with belimumab had a 3.5% annual probability of organ damage progression compared to an 8.7% probability with SOC alone. However, the ESC and the PBAC previously considered that Urowitz et al 2018 had a high risk of bias, was not reliable and had unclear applicability to the PBS population (paragraphs 6.29, 6.30, 6.46 and 7.9 of the Belimumab PSD, November 2019 PBAC meeting).

- 6.26 Bruce et al 2015 investigated factors associated with the development and progression of organ damage in the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort (patients treated with SOC). Patients were enrolled within 15 months of developing four or more 1997 ACR classification criteria for SLE. The authors modelled the progression of organ damage (SDI score) over time using a seven-state model, based on the patients' SDI scores at each visit. Initially, there were 11 states, however as there were relatively few patients in the states above five, these were subsequently collapsed to SDI ≥ 5 . As per the previous submission, the transition probabilities for the SOC cohort were sourced from Bruce et al 2015. The ESC and the PBAC previously considered that the reliability and applicability of the Bruce et al 2015 model predictions were unclear, as outlined in paragraph 6.48 below.
- 6.27 The resubmission maintained that reducing SLE disease activity reduces organ damage accrual over the longer term. It reiterated that the treatment durations in the randomised trials have been too short and/or underpowered to ascertain the benefit of belimumab in the prevention of organ damage progression. It also argued that as a 'by-product' of its impact on SLE disease activity, belimumab lessens the requirement for high doses of corticosteroid to treat SLE flares in the short term, thereby reducing corticosteroid related organ damage in the longer term. Results of a key secondary endpoint in BLISS-SC, conducted in the subgroup who were receiving >7.5 mg/day of prednisone at baseline, showed a numerically higher proportion of belimumab patients reduced their steroid dose by $\geq 25\%$ to ≤ 7.5 mg/day during Weeks 40 to 52 compared to placebo patients; however the difference was not statistically significant (OR= 1.65; 95% CI: 0.95, 2.84; $p=0.0732$).
- 6.28 The resubmission proposed biological reasoning and referenced non-randomised studies to further support its claim that SLE disease activity is an appropriate surrogate measure for the target clinical outcome (TCO) of organ damage progression, as measured by the SDI score. It argued that the usefulness of SDI as a TCO in the economic evaluation is maximised as per the PBAC Surrogate to Final Outcome Working Group (STFOWG) Report, which states (p20), "If the TCO is irreversible and patient-centred, rather than reversible and disease centred, and there is a long duration of follow-up of the measurement of the TCO, the usefulness of the results of

these measures for assessing their clinical relevance and for their use in modelled economic evaluations is maximised.”

- 6.29 The resubmission conceded that while providing support to the underlying rationale for including SDI in the economic model, the available studies do not provide the specific parameters required to relate response to SDI in the structure of the economic model. However, it argued that on balance the evidence provided supported the proposition that disease activity corresponds with future organ damage and that treatment with belimumab to reduce disease activity will prevent future organ damage. It maintained that it is appropriate for the economic model to include a benefit of belimumab with respect to SDI and the prevention of organ damage, given that belimumab has a proven effect on SLE disease activity. However, as shown in Table 8, only one of three SDI outcomes at Week 52 showed a statistically significant advantage for belimumab over SOC.
- 6.30 Table 9 presents the results of other outcomes included in the economic model (annual rate of any flares and severe flares). Treatment with belimumab was associated with a statistically significantly reduced risk of flares, with the relative risk being lower for severe flares compared to any flare.

Table 9: Other outcomes used in the economic model (highlighted green)

Annual rate of flares ^a	BEL (200mg SC)				Placebo				BEL vs Placebo
	Pt-years at risk	Total flares	Unadjusted rate ^b	Adjusted rate	Pt-years at risk	Total flares	Unadjusted rate ^b	Adjusted rate	Adjusted Rate Ratio (95%CI)
Any flare (mild / moderate / severe)									
BLISS-SC	506.5	847	1.7	2.0	244.9	493	2.0	2.5	0.81 (0.69,0.97) ^c
Severe flare									
BLISS-SC	506.5	82	0.2	0.2	244.9	70	0.3	0.4	0.54 (0.33,0.88) ^c

Abbreviations: BEL=belimumab; SC=subcutaneous. Blue highlights indicate results previously seen by the PBAC.

^a Five subjects did not have a post baseline flare assessment. Severe flares that were triggered only by an increase in SELENA SLEDAI score to >12 were reported as mild/moderate flares if the change from the previous visit was at least three points and were excluded otherwise.

^b Unadjusted rate per subject-year = total number of flares/total patient years in trial.

^c From negative binomial regression with the number of flares as the dependent variable and adjusting for baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels, (low C3 and/or C4 vs. no low C3 or C4) and race (black vs. other). Adjustment is also made for subject's follow-up time by including log follow-up time (years) as an offset variable.

Source: Table 30, p112 of BLISS-SC CSR

Comparative harms

- 6.31 Table 10 presents a summary of adverse events (AEs) from the pivotal BLISS-SC trial; which was unchanged from the previous submission.

Table 10: Summary of key adverse events in the pivotal trial

Trial ID	BEL 200mg SC n/N (%)	PBO n/N (%)	OR (95% CI)	RD (95% CI)
Belimumab SC formulation (BLISS-SC)				
Any AE	449/556 (80.8%)	236/280 (84.3%)	0.78 (0.53, 1.15)	-0.04 (-0.09, 0.02)
Related AE	173/556 (31.1%)	73/280 (26.1%)	1.28 (0.93, 1.77)	0.05 (-0.01, 0.11)
Serious AE	60/556 (10.8%)	44/280 (15.7%)	0.65 (0.43, 0.99)	-0.05 (-0.10, 0.00)
Severe AE	55/556 (9.9%)	40/280 (14.3%)	0.66 (0.43, 1.02)	-0.04 (-0.09, 0.00)
Discontinuation due to AE	40/556 (7.2%)	25/280 (8.9%)	0.79(0.47, 1.33)	-0.02 (-0.06, 0.02)
Deaths	3 ^a /556 (0.5%)	2/280 (0.7%)	0.75 (0.13, 4.54)	0 (-0.01, 0.01)
Local injection site reactions	34/556 (6.1%)	7/280 (2.5%)	2.54 (1.11, 5.81)	0.04 (0.01, 0.06)
Injection site pain	10/556 (1.8%)	1/280 (0.4%)	5.11 (0.65, 40.12)	0.01 (0.00, 0.03)

Bold typography indicate statistically significant differences. Blue highlights indicate results previously seen by the PBAC.

Abbreviations: CI = confidence interval; n = number of participants with event; N = total participants in group

^a Two deaths considered possibly related to study agent. One was hospitalized 15 days after last dose of belimumab and died of tuberculosis of the central nervous system. The other was hospitalized 9 days after the last dose of belimumab and experienced urosepsis 15 days after the last dose, and subsequently died 9 days after urosepsis onset. The third death (from bacterial sepsis) was considered probably not related to study agent.

- 6.32 The incidence of any AE, related AE, severe AE, and discontinuations due to AE were similar between belimumab and SOC. The proportion of patients with serious AEs was significantly lower for belimumab versus placebo in BLISS-SC. In BLISS-SC, local injection site reactions occurred in 6.1% and 2.5% of subjects in the belimumab and placebo groups, respectively. All local injection site reactions were mild or moderate in severity. The most frequently reported AEs for belimumab were headache, viral upper respiratory tract infection, urinary tract infection, nasopharyngitis and nausea.
- 6.33 The TGA PI⁵ (p13) stated, “there were more deaths reported with (belimumab) than with placebo during the controlled period of the intravenous clinical trials... No single cause of death predominated. Aetiologies included infection, cardiovascular disease and suicide... In the controlled trial of (belimumab) administered subcutaneously (N = 836), a total of 5 deaths occurred during the placebo-controlled, double-blind treatment period (0.7% [2/280] of patients receiving placebo and 0.5% [3/556] of patients receiving [belimumab]). Infection was the most common cause of death. The physicians should discuss this imbalance with their patients prior to initiating therapy.”
- 6.34 Across the five trials, more patients died in the belimumab 200 mg SC or 10 mg/kg IV arms (10/1920 = 0.52%) than in the placebo arms (6/1242 = 0.48%). Deaths in the belimumab arms are higher if the 1 mg/kg arms (from BLISS-52 and BLISS-76) are also included (14/2479 = 0.56%). The results⁶ for BASE indicated that on-treatment all-cause mortality, infection and malignancy rates were similar between belimumab and

⁵ The TGA PI was based on a Phase II belimumab study and the BLISS trials

⁶ Sheikh S, Scheinberg M, Cheng-Chung Wei J, et al Headline results for a Phase 4, 52 Week, Randomised, Double-blind, Placebo-controlled study to assess adverse events of special interest (AESI) in adults with active, auto-antibody-positive systemic lupus erythematosus (SLE) receiving belimumab. *Annals of the Rheumatic Diseases* 2019;78:266.

placebo, with imbalances observed in serious depression, serious suicidal ideation/behaviour and self-injury events, and serious infusion/hypersensitivity reactions.

- 6.35 The resubmission presented the same data as the previous submission, on potential safety concerns beyond those identified in the clinical trials from the Periodic Benefit Risk Evaluation Report (PBRER) for belimumab (9 March 2018 to 8 March 2019) and Risk Management Plan (RMP). Important identified risks associated with belimumab included psychiatric events including depression and suicidality; hypersensitivity and infusion- or injection-related systemic reactions; and infections.

Benefits/harms

- 6.36 Table 11 presents a summary of the comparative benefits and harms for belimumab versus placebo in the pivotal trial, BLISS-SC.

Table 11: Summary of comparative benefits and harms across the 52-week BLISS-SC trial

Benefits					
Responder rates at Week 52 for the primary composite outcome of SRI and its component indexes					
Index	Belimumab	Placebo	Events/100 patients		RD (95% CI)
			Belimumab	Placebo	
SRI	340/554	135/279	61.4	48.4	0.13 (0.06, 0.20), p=0.0004
SELENA-SLEDAI	345/554	137/279	62.3	49.1	0.13 (0.06, 0.20), p=0.0003
PGA	450/554	203/279	81.2	72.8	0.08 (0.02, 0.15), p=0.0070
BILAG	448/554	207/279	80.9	74.2	0.07 (0.01, 0.13), p=0.0318
Harms					
	Belimumab	Placebo	Events/100 patients		RD (95% CI)
			Belimumab	Placebo	
Local injection site reactions	34/556	7/280	6.1	2.5	0.04 (0.01, 0.06)
Injection site pain	10/556	1/280	1.8	0.4	0.01 (0.00, 0.03)

Abbreviations: BILAG=British Isles Lupus Assessment Group; CI=confidence interval; PGA=Physician's Global Assessment; SELENA=Safety of Estrogen in Lupus Erythematosus National Assessment; SLE=Systemic lupus erythematosus; SLEDAI= SLE Disease Activity Index; SRI=SLE responder index.

Source: compiled during the evaluation. Blue highlights indicate results previously seen by the PBAC.

- 6.37 On the basis of direct evidence presented in the resubmission, for every 100 patients treated with belimumab in comparison to placebo (for standard of care):
- Approximately 13 additional patients would achieve response to treatment based on the SLE responder index (SRI) at Week 52;
 - Approximately 13 additional patients would achieve response to treatment based on the SELENA-SLEDAI component of the SRI;
 - Approximately 8 additional patients would achieve response to treatment based on the PGA component of the SRI;

- Approximately 7 additional patients would achieve response to treatment based on the BILAG component of the SRI; and
- Approximately 6 additional patients would experience local injection site reactions, of which 2 patients would experience injection site pain, over 52 weeks. (This was based on the belimumab arm only because in the PBS setting, patients on standard of care would not receive a placebo injection.)

Clinical claim

- 6.38 The resubmission described belimumab as superior in terms of effectiveness and inferior in terms of safety compared with placebo when used in combination with SOC. Previously, the PBAC considered that the claim of superior comparative effectiveness was reasonable based on the proportion of patients who were SRI responders, but that an improvement in SDI progression had not been adequately demonstrated. Although the resubmission provided additional analyses on SDI outcomes, only one of the three SDI outcomes at Week 52 showed a statistically significant advantage for belimumab over SOC.
- 6.39 The PBAC previously considered that the claim of inferior comparative safety versus SOC alone was reasonable. The PBAC was particularly concerned about the potential risk of psychiatric events (paragraphs 6.40 – 6.41, Belimumab PSD November 2019 PBAC meeting).
- 6.40 The ESC re-iterated the PBAC’s previous advice that the claim of superior comparative effectiveness was reasonable, and that the effect size in terms of SRI and SELENA-SLEDAI was modest. The ESC considered that the effect on SDI progression remains uncertain (given the lack of statistically significant results for most measures of organ damage progression, but acknowledging the short duration of the trials and that the trials were not powered for this outcome), but that it is clinically plausible to expect a benefit with belimumab for this outcome.
- 6.41 The ESC considered the benefit applied in the economic model should appropriately account for the uncertainty in the clinical evidence.
- 6.42 The ESC noted the clinical need for new treatments for SLE and that currently available therapies for SLE are associated with adverse events that can have a significant impact on patient quality of life. The ESC also noted that there is a strong consumer preference for the recently-available SC formulation as opposed to the intravenous formulation (which has been TGA-registered since 2012).
- 6.43 The PBAC considered that the claim of superior comparative effectiveness was reasonable with a modest effect size in terms of SRI and SELENA-SLEDAI. The PBAC considered that, while a benefit in terms of SDI progression appears to be clinically plausible, the magnitude of the effect remains uncertain.

- 6.44 The PBAC considered that the claim of inferior comparative safety was reasonable. The PBAC noted that adverse events associated with belimumab included psychiatric events including depression and suicidality, hypersensitivity and infusion- or injection-related systemic reactions, and infections.

Economic analysis

- 6.45 The resubmission presented a stepped economic evaluation, starting with trial-based cost per responder analysis informed by BLISS-SC and then implementing a modelled cost-utility analysis (Table 12).

Table 12: Key components of the modelled economic evaluation (Step 6)

Component	Description
Type of analysis	Cost-utility analysis.
Outcomes	SDI progression, % treatment responders (≥ 4 -point reduction in SLEDAI-2K), SLE flares, life years, QALYs.
Time horizon	60 years in the model (lifetime) base case (versus 52 weeks in the trials)
Discounting.	Annual discount rate of 5% to costs and outcomes.
Methods used to generate results	Markov cohort model. The cohort was categorised by SDI status at baseline based on SDI categories at baseline (0, 1 and >1) in BLISS-SC
Health states	Dead plus 30 alive health states defined by treatment (BEL vs SOC), time (<6 months “induction” vs >6 months) and SDI score (0, 1, 2, 3, 4, ≥ 5): a) “BEL induction” (SDI 0 to ≥ 5) b) “SOC induction” (SDI 0 to ≥ 5) c) “BEL responder” (SDI 0 to ≥ 5) d) “SOC responder” (SDI 0 to ≥ 5) e) “SOC non-responder” (SDI 0 to ≥ 5) SLE flares were modelled indirectly via disutility and costs estimates, rather than as a health state.
Cycle length	6 months. Half-cycle corrections to costs and benefits.
Transition probabilities	Transition probabilities for - SDI progression for SOC responders and non-responders informed by Bruce et al 2015 (SLICC inception cohort). - Transition probabilities for SDI progression for BEL responders estimated by applying OR for SDI worsening at Week 52 of BEL versus placebo in BLISS-SC (OR=0.47; 95%CI: 0.22, 1.02). - Transition probabilities for deaths by SDI health state based on sum of estimates presented in Bruce et al 2015 and age-related (other cause) mortality rates informed by Australian life tables. - Belimumab continuation (i.e. response at Week 24) informed by BLISS-SC and discontinuation informed by a pooled analysis of BLISS-52 and BLISS-76. - Rate of flares for SOC and belimumab informed by BLISS-SC.
Utility values	Utility values for belimumab responders and non-responders sourced from Wang et al 2014. Disutility values for flares sourced from a TTO study by Pollard et al 2015.
Costs	The model included - Drug costs for belimumab; - Background costs by SDI health state (including SOC drugs), estimated from the Monash Lupus Cost Regression Study, and - Costs associated with treatment of SLE flares, estimated from the Monash Lupus Cohort Regression Study.
Software package	TreeAge Pro 2019

Abbreviations: ACR = American College of Rheumatology; BEL = belimumab; SDI = SLICC/ACR damage index; SELENA= Safety of Estrogen in Lupus Erythematosus National Assessment; SLEDAI= SLE Disease Activity Index; SLICC = Systemic Lupus International Collaborating Clinics; SRI= SLE Response Index.

Source: Table 80, p209 of the resubmission.

6.46 The modelled health states were defined by SDI scores (SDI 0, 1, 2, 3, 4, and ≥ 5), time (<6 months “induction” phase vs ≥ 6 months), current treatment and response status (belimumab or SOC induction or belimumab responder, SOC responder and SOC non-responder). The differentiation between SOC responders and non-responders in the model structure was a key change from the previous submission. The model did not track patients by SLEDAI-2K score, but assumed patients with ≥ 4 point reduction from baseline (“BEL responder”) remained on belimumab after the first cycle:

- All patients entered the model in one of the “BEL induction” or “SOC induction”

health states respectively, depending on SDI score at baseline. Patients that survive the current cycle either maintain the same SDI score or experience a one unit increase in SDI score in the subsequent cycle up to the SDI ≥ 5 state.

- In the belimumab arm, all patients commence treatment and those that survive the cycle either meet the response criteria and remain on treatment or don't meet the response criteria and discontinue, irrespective of SDI progression. Responders transition from one of the "BEL induction" health states to one of the "BEL responder" health states, whereas non-responders transition to one of the "SOC non-responder" health states, in the subsequent cycle according to the SDI score / progression. Treatment discontinuation thereafter was based on an annual discontinuation rate converted to a six-month probability.
- In the SOC arm, patients who meet the response criteria transition from one of the "SOC induction" to one of the "SOC responder" health states according to SDI score / progression. Patients who do not meet the response criteria transition to one of the "SOC non-responder" health states according to SDI score / progression.
- The model assumed patients could only experience a one unit increase in SDI score (or maintain the same SDI score) per cycle.

6.47 Data from BLISS-SC informed the probability of treatment response after the first cycle of the model (61.0% vs 53.2% of belimumab vs SOC patients had ≥ 4 point reduction in SELENA-SLEDAI at Week 24 respectively), the rate of flares and the probability of SDI progression for the belimumab cohort. The rate of belimumab treatment discontinuation after the first year was based on a pooled analysis of BLISS-52 and BLISS-76.

6.48 Bruce et al 2015 informed the probability of SDI progression for both SOC responders and non-responders (and SLE-related mortality for SOC and belimumab) over the 60-year time horizon. This approach was unchanged from the November 2019 model, and meant that SOC responders did not have the reduced probability of SDI progression that was assumed for belimumab responders. The evaluation considered that this favours belimumab by inflating the difference between belimumab responders and SOC responders (who should have the same SDI progression rates in the model). The PSCR argued that a reduced probability of SDI progression is not required because the underlying data for SOC patients from Bruce et al 2015 includes responders and non-responders. The PSCR stated that, if the model were to apply a specific reduction to SOC responders the transition rates in the non-responder arm would have to be increased to achieve the same overall proportions, which the PSCR considered would add uncertainty to the model. Overall, the ESC considered that the resubmission's approach (in terms of model structure) may be reasonable if the PBAC accepts that data from Bruce et al 2015 appropriately reflects overall outcomes of SLE patients receiving SOC regardless of response rate.

- 6.49 The ESC and the PBAC previously considered that the reliability and applicability of the Bruce et al 2015 model predictions were unclear. As an inception cohort, the majority of patients had no organ damage at baseline and the time to first SDI worsening was relatively long (median approx. 9 years if SDI=0 at baseline) and there were also relatively few deaths recorded (41 deaths at the time of the analysis). Hence, the model predictions at the higher SDI health states rely on the analysis assumption that covariates have the same impact for all transitions where $SDI \geq 1$. The description of the method was vague and the impact of other simplifying assumptions was unknown (paragraph 6.26, Belimumab PSD November 2019 PBAC meeting). Further, the ESC previously noted that a constant progression was applied over time as patients age, which was unlikely to reflect the progression of the condition and the aging process more generally (paragraph 6.45, Belimumab PSD November 2019 PBAC meeting). The PBAC maintained its previous view that the long-term reliability, applicability and external validity of the Bruce et al 2015 model predictions to the modelled Australian population were unclear.
- 6.50 The model assigned utilities to “BEL induction”, “SOC induction”, “BEL responder”, “SOC responder” and “SOC non-responder” health states irrespective of SDI score, based on EQ-5D data (by SLEDAI score) in Wang et al 2014. By differentiating between SOC responders and non-responders in the revised model structure, belimumab non-responders now transition to the SOC non-responder arm and experience the same reduced utility as SOC non-responders. This is appropriate.
- 6.51 Quality of life during induction and for non-responders was informed by EQ-5D results for SLEDAI >4 ; quality of life for responders was informed by EQ-5D results for SLEDAI ≤ 4 . This approach was unchanged from the previous submission and favoured belimumab and was inappropriate as:
- The resubmission incorrectly assumed that quality of life estimates by SLEDAI score in the literature correspond to treatment response in the model (defined by a ≥ 4 point reduction in SELENA-SLEDAI from baseline);
 - The approach meant that that quality of life was not a function of SDI in the model. That is, quality of life for patients with an SDI score of zero was the same as those with SDI scores of ≥ 5 , which was inconsistent with the literature.
- 6.52 Given that the SDI score was the main clinical outcome in the model, and the model tracks all patients across both arms by the SDI health state, it would be more reasonable to assign quality of life on the basis of SDI. The ESC previously considered that EQ-5D estimates by SDI health state in Aggarwal et al 2009 were more applicable to the requested PBS population than those in Wang et al 2014 (paragraph 6.55-6.56, Belimumab PSD November 2019 PBAC meeting). Applying these utility values in the resubmission’s model increased the ICER from \$55,000 to $< \$75,000/QALY$ to \$135,000 to $< \$155,000/QALY$.

- 6.53 The resubmission argued that Wang et al 2014 was the most appropriate source to inform utility values in the economic model, on the basis that:
- The data collection from Wang et al 2014 is more contemporaneous than Aggarwal et al 2009, applies more up to date SLE diagnostic criteria and includes a larger number of patients.
 - Patient characteristics (age, ethnicity, SDI) in Wang et al 2014 were more closely aligned to the target PBS population/BLISS-SC.
 - Whilst Aggarwal et al 2009 has a more applicable baseline SLEDAI score of 6.2, this is of limited relevance given that the utility values were reported for SLEDAI thresholds of ≤ 5 and > 5 . However, the evaluation and the ESC considered that the (higher) baseline SLEDAI in Aggarwal et al 2009 (mean 6.2) compared with Wang et al 2014 (mean 2.9) is more closely aligned to the proposed PBS eligibility criterion of SLEDAI-2K score ≥ 10 . Further, the utility values by SDI are also reported in both Wang et al 2014 (thresholds ≤ 1 and >1) and Aggarwal et al 2009 (thresholds ≤ 2 and >2).
 - Wang et al 2014 includes more patients with a lower SLEDAI score, and is therefore more able to reflect the QoL of patients with well controlled SLE than are the Aggarwal utility values, and as such, better reflect patients responding to therapy.
- 6.54 The latter argument is based on the assumption that PBS patients who respond to therapy will have a reduction in disease severity such that their SLEDAI scores will be closer to the Wang et al 2014 scores (mean 2.9, median 2.0) rather than the Aggarwal et al 2009 scores (mean 6.2, median 5.0). Given that patients need to have a minimum SLEDAI-2K score of 10 to initiate PBS therapy, and demonstrate ≥ 4 -point reduction in SLEDAI-2K score to continue therapy, a PBS “responder” with the least severe disease activity at baseline could have a SLEDAI-2K score of 6 to continue treatment ($10 - 4 = 6$), which is closer to the mean SLEDAI score in Aggarwal (6.2, median 5.0). Based on the resubmission’s reasoning, a patient would need to demonstrate a reduction in SLEDAI-2K score by 7 – 8 points to be better represented by Wang et al 2014. The ESC considered that this is unlikely, given that in BLISS-SC, the least squares mean change in SELENA-SLEDAI from baseline at Week 52 was $- 4.39$ ($- 4.07$ at Week 24).
- 6.55 The PSCR stated that neither the Aggarwal 2009 nor Wang 2014 utilities were highly representative of the Australian population, when compared with a group of patients likely to be eligible for belimumab on the PBS – the Monash HDAS cohort. The PSCR argued that on balance, Wang 2014 was more applicable when analysing a range of variables, including age (mean age of 34 and 43 years in Wang 2014 and Aggarwal 2009, respectively, compared with 35 years in the Monash HDAS cohort). The ESC considered that since the economic model is longitudinal, and more time is spent in the older than younger health states, this argument was not supported. The other variables discussed in the PSCR (SLE duration, SLEDAI score, and SDI score) indicated

that neither Wang 2014 nor Aggarwal 2009 showed particular applicability to the Monash HDAS cohort.

- 6.56 Overall, the ESC considered that Aggarwal 2009 is the more appropriate source for base case utilities as:
- the ESC agreed with the PSCR that neither study is highly representative of the Australian PBS population, but overall, considered that Aggarwal 2009 is the more appropriate source for base case utilities as they are based on SDI health states which is consistent with the structure of the model; and
 - more conservative utilities (Aggarwal 2009) should be used, particularly in the context of the other uncertainties in the economic model.
- 6.57 The pre-PBAC response argued that the revised structure of the model includes health states that are defined by both SDI and SLEDAI response and thus the revised model structure is able to accommodate either measure of utility. The pre-PBAC response also stated that the structure of the proposed PBS restriction and continuation rule is aligned with SLEDAI-based utility values, and the model structure is more suited to the use of SLEDAI response utility values from Wang 2014 because patients are initiated to treatment based on baseline SLEDAI and only patients with a SLEDAI response can continue treatment. However, the PBAC noted that the way the utilities were applied in the base case of the model (based on Wang 2014) meant that patients would have the same quality of life regardless of their SDI health state.
- 6.58 The PBAC considered that the large difference in QALYs generated using the Wang 2014 utilities was not adequately justified. The PBAC considered that it would be implausible for patients to have the same quality of life regardless of their SDI level. While acknowledging that using the Aggarwal 2009 utilities would result in patients having the same quality of life regardless of SLEDAI response, the PBAC considered that it was more reasonable to base the utilities on SDI progression (using Aggarwal 2009), given the longer term aim of treatment is to avoid organ damage. Overall, the PBAC considered that the utilities based on SDI health state from Aggarwal 2009 were more appropriate than the utilities based on SLEDAI response from Wang 2014.
- 6.59 Table 13 provides a summary of the key drivers in the modelled economic evaluation. The base case analysis was highly sensitive to the utility values used, the probability of belimumab treatment discontinuation and the probability of “losing response” on SOC.

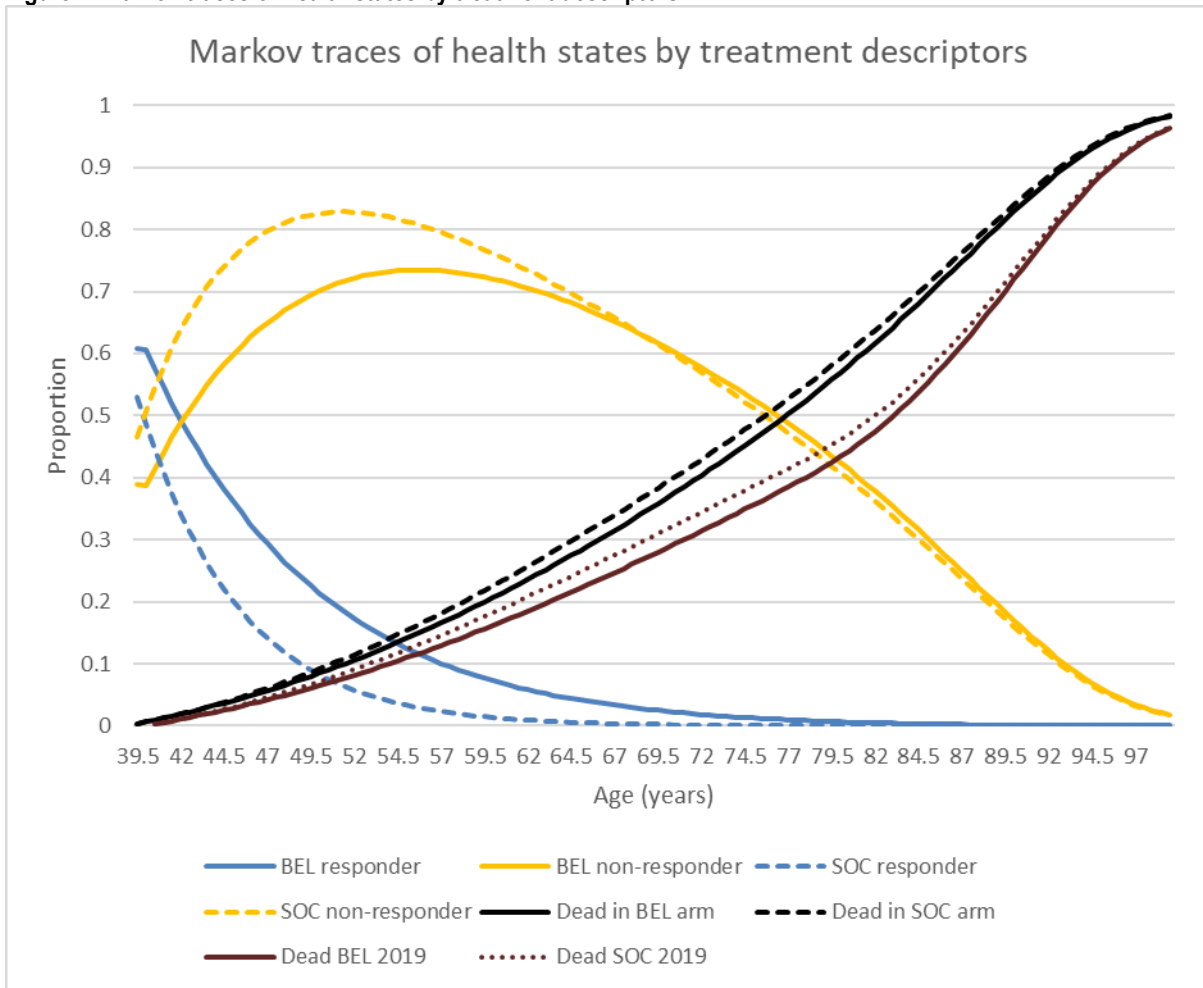
Table 13: Key drivers of the model

Description	Method/Value	Impact
Choice of utility values	For the base case, the model used estimates from Wang et al 2014 based on SLEDAI >4 or ≤4. The ESC re-iterated its previous consideration that the estimates from Aggarwal based on SDI ≤ 2 and >2 would be more appropriate.	High, favours belimumab.
Probability of SDI progression	SDI progression for SOC responders and non-responders was based on Bruce et al 2015. SDI progression for BEL responders was estimated by applying OR for SDI worsening at Week 52 of BEL versus placebo in BLISS-SC (OR=0.47; 95%CI: 0.22, 1.02).	Moderate, favours belimumab.
Probability of BEL discontinuation	For the base case, the model assumed a 9.2% annual discontinuation after the first year of follow-up. This is lower than the discontinuation in BLISS-SC at the end of 52 weeks.	High, favours belimumab.
Probability of losing SOC response	For the base case, the model estimated 8.08% based on the reduction in % responders between Weeks 24 (53.2%) & Week 52 (48.9%) as a % of responders at Week 24 in BLISS-SC (1 – 48.9/53.2), based on the proportion of patients with SELENA-SLEDAI ≥4 point reduction from baseline. However, based on the SRI response in BLISS-SC, there is no evidence indicating that the % of SOC responders continue to decrease between Weeks 24 and 52.	High, favours belimumab.

Source: compiled during the evaluation

6.60 Figure 1 presents a Markov trace of the health states by treatment descriptors for the revised model. A comparison against the dead states in the November 2019 model is also included. The figure illustrates that there are more belimumab responders than SOC responders, and more SOC patients die compared to belimumab patients over the time horizon of the model. However, while there are more SOC non-responders than belimumab non-responders in the earlier half of the model, the lines cross over half way (at age 69 years) and there are more belimumab non-responders than SOC non-responders thereafter. Fewer than 10% of patients remain on belimumab treatment beyond 18 years in the model, with 1% of patients still on belimumab treatment at 38 years into the modelled time horizon.

Figure 1: Markov traces of health states by treatment descriptors



Note: Dead BEL and Dead SOC from the 2019 model have been shifted right to align with model cohort age in March 2020 model.
 Source: Compiled during the evaluation using Belimumab_SLE-Model_Jul19.

6.61 A Markov trace by SDI health state constructed by the evaluation showing the difference between the model and Bruce et al 2015 indicated that the modelled cohort was less likely to transition to the higher SDI health states and more likely to die, which was consistent with the assumptions used to estimate the transition probabilities. However, the model predicted higher SDI progression rates at 52 weeks for SOC patients (11.2%) compared to SOC patients in BLISS-SC (5%, Table 8), which exaggerated the difference between the belimumab and SOC arms of the model. The PSCR stated that the value predicted in the economic model for SOC patients (11.2%) is generally consistent with the values observed in BLISS-SC, which are between 5% and 27.5% (which are the proportions of patients in the placebo arm who have SDI worsening Week 52 (5%), and the proportion who are not free from SDI progression at Week 52 (100% minus 72.5%, Table 8), depending on whether a responder or non-responder imputation for missing data is used.

- 6.62 The resubmission presented Markov traces by responder status, in response to the PBAC’s comments that belimumab only demonstrated a modest clinical benefit compared with placebo. The resubmission stated that the incremental effect of belimumab at Week 52 of the economic model (12%) is slightly less than that of the BLISS-SC trial (13%). It argued that, “the incremental effect of belimumab increases over time due to the higher probability of losing response in the SOC arm of the model. However, this incremental effect never rises above 16.1%. Given that the incremental effect of belimumab increases by 6% from week 24 to week 52, it is not unreasonable to expect this effect might increase by a further 4% over the following 4 years”.
- 6.63 This assumption is not adequately supported by the clinical evidence. In BLISS-SC, there was a steady increase in SRI responders up to approximately Week 20, after which the proportion of responders plateaued. There is no evidence indicating that the proportion of belimumab responders continues to increase or that SOC responders continue to decrease. The difference between belimumab and SOC responders peaked at Week 40 of the trial (14.43%) before reducing to 12.98% by Week 52. Therefore, the ESC considered that the difference of 16% between belimumab and SOC responders as estimated in the model is not supported by the clinical evidence, and favours belimumab.
- 6.64 Table 14 provides the results of the stepped economic evaluation.

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Table 14: Results of the stepped economic evaluation

Step and component	BEL + SOC	SOC	Increment
Step 1: Trial-based, incremental cost per additional SRI responder at 52 weeks, assuming			
- Drug costs only, - All patients remain on belimumab for 52 weeks			
Costs (52 weeks)	\$ [REDACTED]	\$0	\$ [REDACTED]
SRI responders at 52 weeks	0.614	0.484	0.13
Incremental cost/extra SRI responder at 52 weeks			\$ [REDACTED]*
Step 2: Trial-based, incremental cost per additional SELENA-SLEDAI responder at 24 weeks, assuming			
- Drug costs only, - All patients remain on belimumab for 24 weeks			
Costs (24 weeks)	\$ [REDACTED]	\$0	\$ [REDACTED]
SELENA-SLEDAI responders at 24 weeks	0.610	0.532	0.078
Incremental cost/extra SELENA-SLEDAI responder at 24 weeks			\$ [REDACTED]*
Step 3: Trial-based / simple model, incremental cost per additional SELENA-SLEDAI responder at 52 weeks, assuming			
- Drugs costs only, - Belimumab non-responders at 24 weeks stop treatment, and Belimumab responders at 24 weeks continue treatment			
Costs (52 weeks)	\$ [REDACTED]	\$0	\$ [REDACTED]
SELENA-SLEDAI responders at 52 weeks	0.610	0.532	0.078
Incremental cost/extra SELENA-SLEDAI responder at 52 weeks			\$ [REDACTED]*
Step 4: Modelled economic evaluation, incremental cost per QALY at 52 weeks, assuming:			
- Probability of SDI progression (Bruce et al 2015, BLISS-SC), - Age-related mortality (life tables), - QALYs (Wang et al 2014) - Disutility from SLE flares (BLISS-SC, Pollard et al 2015, Squance et al 2014).			
Costs (52 weeks)	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs (52 weeks)	0.699	0.683	0.016
Incremental cost/extra QALY gained at 52 weeks			\$ [REDACTED]
Step 5: Modelled economic evaluation, incremental cost per QALY at 60 years, assuming:			
- Step 4 assumptions, - Incorporation of SDI mortality (Bruce et al. 2015) - 60 year time horizon			
Costs (discounted)	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs (discounted)	10.485	9.949	0.537
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 6: Modelled economic evaluation, incremental cost per QALY at 60 years, assuming:			
- Step 5 assumptions, - Costs included for SDI health states (background costs) - Costs included for treating SLE flares			
Costs (discounted)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life Years gained (discounted)	15.60	15.39	0.20
QALYs (discounted)	10,485	9,949	0.537
Incremental cost / Life Years gained			\$ [REDACTED]
Incremental cost/extra QALY gained (base case in resubmission)			\$ [REDACTED]
Previous submission			
Incremental cost/extra QALY gained			\$ [REDACTED]

* There were small discrepancies in results compared to the resubmission, differences are likely due to rounding.

Source: compiled during the evaluation in reference to Table 98, p249 of the resubmission.

The redacted table shows that the base case ICER was in the range of \$55,000 to < \$75,000 per QALY in both the previous submission and the resubmission.

6.65 Table 15 presents results of sensitivity analyses.

Table 15: Results of key sensitivity analyses on base case in resubmission

Analyses	Incremental cost	Incremental QALY	ICER
Base Case of resubmission	\$ [REDACTED]	0.5366	\$ [REDACTED]
Univariate Sensitivity Analyses			
Belimumab organ damage OR (base case 0.47) OR=1 as no reported result reached statistical significance EMBRACE point estimate: 0.90 Meta-analysis BLISS-SC + EMBRACE: 0.57	\$ [REDACTED] \$ [REDACTED] \$ [REDACTED]	0.4019 (LYG=0) 0.4260 0.5101	\$ [REDACTED] \$ [REDACTED] \$ [REDACTED]
Quality of life using EQ5D values for organ damage states of 0.74 for SDI ≤ 2 and 0.68 for SDI > 2 (Aggarwal) (#1) (base case 0.846 for SLEDAI ≤ 4 for treatment responders and 0.619 for SLEDAI > 4 for non-responders; Wang et al)	\$ [REDACTED]	0.2528	\$ [REDACTED]
Time horizon (base case 60 years) ^a 10 years 20 years (#2) 40 years	\$ [REDACTED] \$ [REDACTED] \$ [REDACTED]	0.2669 0.4166 0.5202	\$ [REDACTED] \$ [REDACTED] \$ [REDACTED]
Annual probability of discontinuation – BEL (base case 9.2%) 3% 15%	\$ [REDACTED] \$ [REDACTED]	1.1981 0.2541	\$ [REDACTED] \$ [REDACTED]
Probability of losing SOC response (base case 8.08%) -50% (0.0404) +50% (0.1212)	\$ [REDACTED] \$ [REDACTED]	0.2269 0.6837	\$ [REDACTED] \$ [REDACTED]
Multivariate Sensitivity Analysis			
#1 + #2 ^b	\$ [REDACTED]	0.1514	\$ [REDACTED]

Source: Table 103, pp.253-254 of the resubmission and calculated during the evaluation.

^a Time horizon sensitivity analyses performed for ESC ADV.

^b Multivariate sensitivity analysis with Aggarwal 2009 utilities and 20 year time horizon, performed for PBAC meeting.

The redacted table shows ICERs in the range of \$55,000 to < \$75,000 per QALY, to \$155,000 to < \$255,000 per QALY.

6.66 The base case analysis was highly sensitive to:

- The probability of belimumab treatment discontinuation. The model assumed an annual probability of discontinuation of 9.2%, which the PSCR stated is a conditional probability only applied after one year of follow-up. This was based on the annual probability (9.2%) of study withdrawals (all reasons) from a pooled analysis of BLISS-52 and BLISS-76 (long term extension studies) for years 1 to 6. The main reasons for withdrawal in the long term extension studies were adverse events, patient request and “other” (the most common reason for the latter two was a desire to become pregnant). The ESC noted that the discontinuation rate applied in the model does not account for the 22% of patients who did not continue with treatment at the end of the double-blind trials (i.e. who did not enter the long term extension studies). Thus, the probability of belimumab discontinuation may be underestimated in the first year of the model if patients discontinue for reasons other than non-response.
- The probability of losing SOC response. As there is no data on the persistence of

a placebo response, the resubmission estimated the probability of losing SOC response (in each 6-month cycle) based on the reduction in the proportion of responders at Week 24 versus Week 52 in the placebo arm of BLISS-SC (8.08%). As placebo response in trials were high (set to 52.8% in the model at 6 months), the assumed rate of loss of SOC response over time therefore directly impacts the incremental benefit for belimumab. The PSCR argued that decreasing the probability of losing an SOC response would imply a placebo response that is more durable than a belimumab response. However, the ESC considered that there was no evidence that the proportion of SOC responders continues to decrease (as outlined in paragraphs 6.61 and 6.62).

- 6.67 The ESC considered that a key issue was that the economic model assumed that belimumab reduced the rate of SDI progression and consequently reduced mortality. In the pivotal BLISS-SC trial, belimumab did not demonstrate any improvement in survival at Week 52, although the ESC acknowledged that the trial was not powered to detect differences in survival. For SDI progression, the model applied an odds ratio of 0.47 for belimumab versus SOC (based on the outcome of SDI worsening at Week 52 observed in BLISS-SC), despite this difference not being statistically significant (95% CI: 0.22, 1.02), although the PSCR argued that significance depended on how missing data were imputed. The ESC noted that differences in significance of results resulting from how missing data were imputed reduced confidence in results. Assuming no difference in SDI progression or mortality (applying an odds ratio of 1) increases the ICER/QALY from \$55,000 to < \$75,000 to \$95,000 to < \$115,000.
- 6.68 The ESC noted that the ICER relied heavily on the extrapolated period beyond the 52 week randomised trial period (with the ICER/QALY decreasing from \$355,000 to < \$455,000 per QALY at 52 weeks in Step 4 of the stepped economic evaluation, to \$55,000 to < \$75,000 per QALY once the time horizon was increased to 60 years, and SDI mortality and SDI health state costs were included). To help mitigate the uncertainty associated with the economic model (structure and input parameters) and the uncertain long-term effects of belimumab, the ESC considered that a shorter time horizon should be applied.

Drug cost/patient/year: \$ [REDACTED]

- 6.69 In the modelled economic evaluation and financial estimates, the average cost of treatment per patient per script (28 days) was \$ [REDACTED] (assuming a 78:22% split for public and private hospitals respectively, Table 16), corresponding to an annual cost of \$ [REDACTED] assuming 13 scripts per year (assumes full compliance and no discontinuation).
- 6.70 The model applied a six monthly drug cost of \$ [REDACTED] per cycle regardless of induction or continuing treatment. This assumption slightly overestimated the costs

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for belimumab in the first year, given induction treatment is only for 24 weeks and not six-months (26 weeks).

Table 16: Belimumab drug cost per patient for proposed and comparator drugs

	BLISS-SC	Economic model	Financial estimates
Mean dose	NR	200mg SC once weekly	200mg SC once weekly
Cost/patient/script (28 days)	\$ [redacted] (public hospital) \$ [redacted] (private hospital)	\$ [redacted] (78.27%:21.73% public:private)	\$ [redacted] (78.27%:21.73% public:private)
Cost/patient in Yr 1	\$ [redacted] [^]	\$ [redacted] [#]	\$ [redacted] [*]

[^] BLISS SC reported 16.7% discontinuation for belimumab at Week 52, and 96% compliance, cost for year 1 is calculated as \$ [redacted] x (1-16.7%) x (0.96).

[#] Results estimated in the model by reducing time horizon to 1 year and removing all costs apart from cost of belimumab. Includes response rate of 61.1% for belimumab at 6mth and an annual discontinuation rate of 9.2%.

^{*} Patients who do not respond were assumed to discontinue at 6mth (response rate at 6month for belimumab was assumed to be 61%). Number of scripts required per year assumed to equal 10.3 scripts. The financial model assumed 100% compliance.

Source: compiled during the evaluation

Estimated PBS usage & financial implications

6.71 This resubmission was not considered by DUSC. With the exception of a few changes, the financial analyses are largely the same as the November 2019 submission.

6.72 The resubmission reasonably used an epidemiological, prevalence only approach to estimate the financial impact of listing. Table 17 shows the estimated use of belimumab and cost to the PBS/RPBS. A patient cohort was tracked over time based on the following methods and assumptions:

- The model estimated the number of patients meeting the eligibility criteria each year based on an average SLE prevalence rate of 65.26 per 100,000 population, with 15.36% of the SLE population meeting the PBS criteria. The PBAC previously considered that 15.36% was likely overestimated (paragraphs 6.63 and 7.12, Belimumab PSD, November 2019 PBAC meeting). Retaining the same estimate of proportion of patients meeting PBS eligibility criteria is inconsistent with the revised PBS restriction, which is tighter than what was proposed in November 2019. Hence a smaller proportion of patients would meet PBS eligibility criteria. The resubmission provided arguments regarding expert opinion on the uptake of PBS listed belimumab as supportive of the 15.36%. The PSCR stated that the commentary reached this conclusion from the opinion of 3 out of 4 experts who based their estimates on current access to biologics, rather than reimbursed access. The PSCR stated that the one expert who acknowledged reimbursed access predicted 20% of patients (implying that the value of 15.36% is not overestimated). However, the ESC considered the estimate was poorly justified and that 15.36% remains a likely overestimate.
- The resubmission estimated the overall uptake of belimumab (uptake rates 20% - 50%) on the premise that approximately 60% of patients will respond, and 90% of

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those responders will continue on treatment long-term. However, the PBAC considered that the uptake rates proposed in the previous submission (15% - 40%) were highly uncertain, given that the use of IV belimumab was low, the treatment effect is modest and use may be associated with potentially severe adverse events, which may temper uptake.

- As per the previous analyses, the resubmission assumed an annual discontinuation rate of 9.2% and a belimumab treatment response rate at 26 weeks of 61.0% (corresponding to a continuation rate of 58.17% in Year 1 and 90.80% in subsequent years). This was consistent with the annual discontinuation rate assumed in the economic model.

Table 17: Estimated use of belimumab and cost to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian population	26,301,274	26,727,025	27,147,199	27,562,195	27,970,435	28,372,315
Eligible SLE patients						
Uptake rate	20%	30%	40%	50%	50%	50%
Total treated patients						
Continuing patients						
Initiating patients						
Total belimumab scripts						
Initial						
Continuing						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Previous submission						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$

Abbreviations: SLE=Systemic lupus erythematosus.

Source: Tables 111, 112 and 114, p274-276 of the resubmission.

The redacted table shows that at Year 6, the estimated total number of belimumab scripts was 10,000 to < 20,000 and the net cost to the PBS would be \$10 million to < \$ 20 million.

- 6.73 The resubmission estimated a net cost to the PBS/RPBS of \$50 million to < \$60 million over the first six years of listing, compared to \$40 million to < \$50 million in the previous submission. This increase was driven by the higher projected Australian population (given that estimates are based on 2021 – 2026, instead of 2020 – 2025) and the higher estimated uptake rates. The estimates did not include any changes to the use of other medications on the PBS/RPBS or other healthcare resources, which was reasonable.
- 6.74 The PBAC agreed with the ESC that the financial estimates were likely over estimated as the proportion of patients meeting the PBS eligibility criteria and the uptake rates were likely overestimated. The ESC also noted that the prevalence estimates identified in the resubmission varied widely (from 50 to 79 patients per 100,000).
- 6.75 Given the high unmet clinical need in patients with highly active SLE, the risk of use outside the restriction is high because only a small subpopulation of SLE patients are

anticipated to meet the proposed PBS restriction. Increased use of belimumab in severe lupus nephritis may occur outside the PBS restriction, given the positive headline results for BLISS-LN.

Quality Use of Medicines

- 6.76 No quality use of medicines information was presented in the resubmission. Previously, DUSC considered that patient and carer familiarisation on appropriate administration and storage of the injections would be required. DUSC also considered that as SLE most commonly affects women of childbearing age, treatment breaks due to pregnancy might affect duration of treatment (DUSC Advice for the November 2019 PBAC meeting).

Financial Management – Risk Sharing Arrangements

- 6.77 In November 2019, the PBAC considered that a RSA with a [REDACTED] rebate over the cap would be required given the uncertain patient population, treatment duration and uncertain potential for leakage (paragraph 7.14, Belimumab PSD November 2019 PBAC meeting). The resubmission (p259) confirmed that the sponsor is amenable to discussing appropriate risk sharing arrangements to address any areas of uncertainty to the PBS and the Australian Government. However, it argued that the proposed PBS criteria for belimumab limits use to patients with significant clinical need and who will most likely benefit from treatment. The resubmission argued that this means all belimumab use will be in patients deemed appropriate if approved by the PBAC and as such, there is no risk outside the restriction. It stated that the sponsor should not be penalised with rebates for appropriate use of belimumab due to uncertainty in the patient population and treatment duration. Given that several contributing factors could lead to an overestimation of the financial implications of belimumab, and the potential for use outside the proposed PBS restriction, the ESC maintained the view that a RSA would be required. The sponsor stated in the pre-PBAC response that it will be prepared to enter an appropriate RSA based on the parameters put forward in the resubmission. The PBAC maintained the view that a RSA with a [REDACTED] rebate above the cap would be required given the uncertain patient population, treatment duration and potential for leakage.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend belimumab for the treatment of patients with active auto-antibody positive SLE with a high degree of disease activity despite ongoing standard therapy. The PBAC maintained its view from November 2019 that the evidence demonstrated a modest clinical benefit in a subset of patients. The PBAC

considered that the incremental cost effectiveness ratio (ICER) was likely to have been underestimated by the submission, and that a price reduction would be required for belimumab to be considered suitably cost-effective. The PBAC also considered that the financial estimates were overestimated.

- 7.2 The PBAC acknowledged the clinical need for effective treatments for SLE, particularly for the group of patients who are not responding to current therapies. The PBAC noted the consumer comments describing the desire for a specific treatment option in this setting.
- 7.3 The PBAC noted that, unchanged from the November 2019 submission, standard of care (SOC) was the nominated comparator and considered that this was appropriate.
- 7.4 The PBAC noted that the clinical evidence was largely unchanged from the November 2019 submission, although additional analyses of Systemic Lupus Damage Index (SDI) outcomes were presented. The PBAC maintained its view that belimumab demonstrated a modest clinical benefit compared with placebo. The BLISS-SC trial found that belimumab plus SOC resulted in a 13% increase in the proportion of Systemic Lupus Erythematosus Responder Index (SRI) responders at Week 52 compared with placebo plus SOC (RD = 0.13; 95% CI: 0.06, 0.20).
- 7.5 The PBAC agreed with ESC that it is clinically plausible to expect a benefit in SDI progression with belimumab, but that the magnitude of the effect on SDI progression remains uncertain given:
- the lack of statistically significant results for most measures of organ damage progression, but acknowledging the short duration of the studies and that the studies were not powered for this outcome;
 - the magnitude of the effect varied between studies; and
 - the handling of patients lost to follow-up differed between the measures and reached statistical significance for the outcome of 'patients remaining free from SDI progression', in which patients lost to follow-up (who were more prevalent in the SOC arm) were assumed to be treatment failures.
- 7.6 The PBAC considered that the resubmission had likely underestimated the ICER as some of the assumptions applied in the economic model may not be reasonable and likely favoured belimumab. The PBAC considered that a key issue was that the economic model did not apply the utility values as recommended by the ESC previously (which were the EQ-5D estimates by SDI health state in Aggarwal 2009); rather it retained the utility values from Wang 2014 (EQ-5D estimates by SLEDAI). The PBAC considered that the large difference in QALYs generated using the Wang 2014 utilities was not adequately justified. The PBAC considered that it would be implausible for patients to have the same quality of life regardless of their SDI level. While acknowledging that using the Aggarwal 2009 utilities would result in patients having the same quality of life regardless of SLEDAI response, the PBAC considered

that it was more reasonable to base the utilities on SDI progression (using Aggarwal 2009), given the longer term aim of treatment is to avoid organ damage. Overall, the PBAC considered that the utilities based on SDI health state from Aggarwal 2009 were more appropriate than the utilities based on SLEDAI response from Wang 2014.

- 7.7 The PBAC agreed with the ESC that there were several other key issues with the model that may not be reasonable and likely favoured belimumab:
- the model used data from Bruce et al 2015 to inform the probability of SDI progression for SOC responders and non-responders. The PBAC maintained its view from November 2019 that the long-term reliability, applicability and external validity of the Bruce et al 2015 model predictions to the modelled Australian population were unclear (as outlined in Paragraph 6.48).
 - the economic model assumed that belimumab reduced the rate of SDI progression and consequently reduced mortality. The economic model applied an odds ratio of 0.47 for belimumab versus SOC (based on the outcome of SDI worsening at Week 52 observed in BLISS-SC). The PBAC noted that the EMBRACE trial reported a much higher odds ratio (0.90, 95% CI: 0.28, 2.86) for the same outcome. The PBAC considered that the magnitude of the SDI progression (and the consequent reduction in mortality) applied in the model may have been overestimated given the magnitude of the effect varied between studies, with the resubmission applying the most favourable result. The PBAC also agreed with the ESC that differences in significance of SDI progression results arising from how missing data were imputed reduced confidence in results.
- 7.8 The PBAC considered that a time horizon of 60 years was too long given the aforementioned issues, and considered that a shorter time horizon may help mitigate the uncertain long-term incremental effects of belimumab, and the uncertain SDI progression applied to the SOC arm (based on Bruce et al 2015).
- 7.9 Overall, the PBAC considered the base case ICER presented in the resubmission was underestimated. The PBAC noted that the ICER increased if utilities were based on organ damage rather than response, the time horizon was reduced, the impact of treatment on organ damage (and consequent reduction in mortality) was reduced or removed, a higher proportion of patients discontinued belimumab treatment or the SOC response was maintained for a longer period. The PBAC considered that a price reduction would be required for belimumab to be considered suitably cost-effective.
- 7.10 The PBAC considered that the financial estimates were likely overestimated as:
- the proportion of patients estimated to meet the PBS eligibility criteria (15.36%) was likely overestimated. The PBAC recalled that it was based on the Monash Lupus Clinic study, which the PBAC previously considered may not be representative of the PBS population. Further, the PBAC noted that the proportion was unchanged since the previous submission despite the proposed

PBS restriction now defining a narrower population as it requires patients to be on simultaneous triple therapy (rather than any prior exposure, as assumed in the previous submission); and

- the uptake rates were likely overestimated. The resubmission applied uptake rates of 20% to 50%, which were higher than the rates applied in the previous submission (15% to 40%). The PBAC recalled that it had considered the previous uptake rates were highly uncertain, given that the use of IV belimumab was low, the treatment effect is modest and use may be associated with potentially severe adverse events, which may temper uptake. The PBAC considered that the uptake rates applied previously, though highly uncertain, were more reasonable than the higher rates proposed in the resubmission.

7.11 The PBAC considered there is a high risk of use outside the restriction given that only a small subset of SLE patients will meet the proposed PBS restriction. The PBAC maintained the view that a risk share agreement with a [REDACTED] rebate over the cap would be required given the uncertain size of the patient population, uncertain treatment duration and potential for use outside the restriction.

7.12 The PBAC considered that any resubmission would need to be a major submission, and would need to revise the economic model and financial estimates to address the issues raised above.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

GSK remains disappointed by the PBAC's decision not to recommend Benlysta® (belimumab) administered subcutaneously for the treatment of patients with systemic lupus erythematosus (SLE), which is the only new therapy to be approved by the Therapeutic Goods Administration for this indication in 50 years.

GSK welcomes the PBAC's acknowledgement of the clinical need for effective treatments for SLE, particularly for the group of patients who are not responding to current therapies, given the debilitating impact this condition can have on people's lives and specifically their individual quality of life.

GSK considers that both the impact of the disease and the overarching value of therapy proposed in the submission is aligned to the lived experience of patients with SLE and their treating clinicians and varies significantly from that ascribed by the PBAC. Specifically, we disagree with the negligible improvement in a patients' quality of life insisted on by the PBAC for patients who respond to therapy. Further, we do not consider that due weight has been attributed to the totality of the evidence supporting Benlysta, particularly with regards to disease flares, steroid dose and organ damage.

GSK accepts there is some uncertainty in the evidence in this area, however, the efficacy of Benlysta is supported by four randomised controlled trials with over seven years of long-term clinical data. The PBAC has the flexibility to accept data uncertainty where there is a large clinical need with no alternative treatment options available and at a relatively small cost to the government. GSK made it clear to the PBAC, through our submission and all associated meetings, that we were offering the lowest possible price for Benlysta in order to achieve this listing and still maintain continuous supply of the medicine.

This is the second submission to the PBAC that has been rejected despite attempts put forward to mitigate the uncertainties identified. GSK can see no way forward and reluctantly will not be resubmitting to the PBAC for this subset of patients living with severe SLE.

This evaluation raises concerns regarding the viability of any future treatments for SLE being listed on the PBS, given the wealth of evidence available to support Benlysta and the difficulty in achieving outcomes for this heterogeneous group of patients with high clinical need. We sincerely thank those patients, advocacy organisations and clinicians who provided advice on this submission.