

## 5.01 BELIMUMAB, Injection 200 mg in 1 mL pre-filled pen, Benlysta<sup>®</sup>, GlaxoSmithKline Australia Pty Ltd.

### 1 Purpose of Application

- 1.1 The submission requested a Section 100 Authority Required (Written/Telephone) 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). This is the first consideration of belimumab by the PBAC.
- 1.2 The basis for the requested listing was a cost-utility analysis versus SOC. The key components of the clinical issue addressed by the submission are presented in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission**

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, Adverse events
Clinical claim	Superior effectiveness Inferior safety <sup>a</sup>

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; SoC, standard of care; SRI, Systemic Lupus Erythematosus Responder Index

Source: Table 10, p2 of the submission.

<sup>a</sup> The submission claimed non-inferior safety of belimumab compared with SOC, except for the important identified risk for psychiatric events. The PSCR (p4) stated that the Sponsor acknowledged a claim of inferior (as opposed to non-inferior safety) may be more reasonable.

### 2 Requested listing

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

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity		Proprietary name and manufacturer
BELIMUMAB Single dose pre-filled pen (autoinjector) 200 mg	1	4	5	Published: \$ [REDACTED] Private: \$ [REDACTED]	Effective: \$ [REDACTED] Private: \$ [REDACTED]	BENLYSTA® SC GlaxoSmithKline
<b>Category/program</b>	Section 100 – Highly Specialised Drugs Program					
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives					
<b>Episodicity:</b>	Active					
<b>Condition:</b>	Systemic lupus erythematosus ( <del>SLE</del> )					

Public Summary Document – November 2019 PBAC Meeting

<b>Category/program</b>	Section 100 – Highly Specialised Drugs Program
<b>PBS indication:</b>	<del>Highly active auto-antibody positive</del> Active systemic lupus erythematosus (SLE) despite standard of care therapy
<b>Treatment phase:</b>	Initial
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Treatment criteria:</b>	<p>Must be treated by an immunologist or rheumatologist or other specialist physician experienced in the diagnosis and treatment of SLE.</p> <p>13595 [10111] Must be treated by a rheumatologist; or [13593] Must be treated by a clinical immunologist; or [13590] Must be treated by a nephrologist.</p>
<b>Clinical criteria:</b>	<p>Adult pPatient must have a confirmed and documented diagnosis of SLE (according to the ACR/EULAR SLE Classification Criteria 2019), AND Patient must have an anti-double stranded deoxyribonucleic acid (anti-dsDNA) serum antibody test result which is unequivocally positive [new concept] 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 low complement (C3, C4) levels despite standard therapy.</p> <p>AND [new concept] Patient must have a Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index 2000 (SELENA-SLEDAI-2K) score of at least 10 points, AND Patient must be currently receiving hydroxychloroquine and must have received this for at least three months, AND Patient must be currently receiving immunosuppressant medication and must have received this for at least three months (methotrexate 20mg per week, azathioprine 100 mg per day, or mycophenolate), AND Patient must be currently receiving prednisolone or equivalent <math>\geq 7.5</math> mg per day and must have received this for at least one month, AND Patient must not have severe renal or central nervous system systemic lupus erythematosus.</p> <p><del>Patient must be receiving standard of care therapy for SLE which includes a combination of an antimalarial agent, a corticosteroid and an IS agent unless there are contraindications / intolerances which preclude use of triple therapy. Patient must be unable to reduce the dose of corticosteroid to below 7.5 mg prednisone per day or equivalent</del></p> <p>Notes Use of an antimalarial agent and/or IS agent as a constituent of the standard of care triple therapy for SLE may be precluded if the agent is considered clinically inappropriate or cannot be tolerated at the minimum effective dose recommended in the current EULAR guidance for the management of SLE. A patient who has previously failed to respond to a course of PBS subsidised belimumab for the treatment of SLE will not be eligible to receive further PBS subsidised treatment with belimumab. [11365] Patient must not have previously received PBS-subsidised treatment with this drug for this condition.</p>
<b>Population criteria:</b>	<del>Patient must be at least 18 years of age</del>

Public Summary Document – November 2019 PBAC Meeting

Category/program	Section 100 – Highly Specialised Drugs Program
<b>Prescriber instructions</b>	<p><i>[new concept]</i> The authority application must be made in writing and must include:</p> <p>a) a completed authority prescription form; and</p> <p>(b) details of <del>prior</del> <i>current</i> therapy used (dosage, date of commencement and duration of therapy) <del>unless clinically inappropriate; and</del></p> <p>(c) a completed <del>SELENA-SLEDAI-2K</del> <i>SELENA-SLEDAI-2K</i> score sheet, including the date of assessment, and</p> <p>(d) a copy of the <del>pathology report</del> <i>pathology report showing low complement (C3, C4) and/or anti-dsDNA</i> <del>pathology report</del>, including the testing laboratory's reference range.</p> <hr/> <p><i>[13830]</i> The name of the specialist consulted must be provided at the time of application for initial supply.</p> <hr/> <p><i>[8607]</i> The date of the pathology report and name of the Approved Pathology Authority must be provided at the time of application.</p> <hr/> <p><i>[new concept]</i> History of systemic lupus erythematosus medication therapy should be based on documented use of treatment prescribed by a physician.</p> <hr/> <p><i>[new concept]</i> 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> <hr/> <p><i>[new concept]</i> 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> <hr/> <p><i>[new concept]</i> 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> <hr/> <p><i>[17036]</i> 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 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>
<b>Administrative advice</b>	<p><u>Note</u> <i>[7608]</i> Special Pricing Arrangements apply.</p> <hr/> <p><u>Note</u> <i>[7753]</i> 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 <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a> Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

Public Summary Document – November 2019 PBAC Meeting

<b>Category/program</b>	Section 100 – Highly Specialised Drugs Program
<b>Cautions</b>	It is recommended that the first subcutaneous injection of belimumab should be under the supervision of a healthcare professional in a setting that is sufficiently qualified equipped to manage hypersensitivity reactions., if necessary

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
BELIMUMAB Single dose pre-filled pen (autoinjector) 200 mg	1	4	5	Published: Public: \$1,400.00 Private: \$1,447.39 Effective: Public: \$ Private: \$	BENLYSTA® SC GlaxoSmithKline

<b>Category/program</b>	GENERAL - General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Systemic lupus erythematosus (SLE)
<b>PBS indication:</b>	Auto-antibody positive SLE e Systemic lupus erythematosus
<b>Treatment phase:</b>	Continuing
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required – by telephone
<b>Treatment criteria:</b>	Must be treated by an immunologist or rheumatologist or other specialist physician experienced in the diagnosis and treatment of SLE. 13595 [10111] Must be treated by a rheumatologist; or [13593] Must be treated by a clinical immunologist; or [13590] Must be treated by a nephrologist.
<b>Clinical criteria:</b>	<p><del>Patient must have previously been issued with an authority prescription to receive this drug [10972] Patient must have previously been issued with an authority prescription for this drug for this condition. [phase out 18091, 19469, 23815 draft]</del></p> <p>AND</p> <p><del>[new concept] Patient must have demonstrated or maintained an adequate response to PBS-subsidised treatment with this drug where an adequate response is defined as at least a 4-point reduction in Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index 2000 (SELENA-SLEDAI-2K) score, compared to the baseline assessment; OR Patient must have demonstrated or maintained at least a 4-point reduction in Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index 2000 (SELENA-SLEDAI-2K) score, compared to the baseline assessment prior to having a treatment break for clinical reasons.</del></p> <p>AND</p> <p><del>Patient must not receive more than 6 months of treatment under this restriction without undergoing a review and documented reassessment by the prescribing physician</del></p> <p><del>Note: A patient who has failed to respond or maintain a response to a course of PBS-subsidised will not be eligible to receive further PBS-subsidised treatment with belimumab for this condition</del></p>
<b>Prescriber instructions</b>	<p><del>The first assessment should, where possible, be completed by the same physician who initiated treatment with belimumab</del></p> <p><del>[17036] 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 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.</del></p>

Public Summary Document – November 2019 PBAC Meeting

<b>Category/program</b>	GENERAL - General Schedule (Code GE)
<b>Administrative advice</b>	<p><u>Note</u> [7608] Special Pricing Arrangements apply.</p> <p><u>Note</u> [14726; Complex Authority Required flag] 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).</p>

2.2 The key issues regarding the proposed restriction are summarised in Table 2 below, and discussed below the table.

**Table 2: Comparison of proposed PBS restriction and the trial populations**

Proposed PBS restriction	Trial inclusion criteria	PBAC Comment
<b>Initial restriction</b>		
Confirmed and documented diagnosis of SLE	BLISS-SC: Diagnosis of SLE according to 1997 American College of Rheumatology (ACR) criteria <sup>a</sup>	The PBAC considered diagnosis should be according to EULAR/ACR SLE criteria 2019.
Unequivocally positive anti-dsDNA	BLISS-SC: ANA (titre $\geq$ 1:80) and/or anti-dsDNA antibody ( $\geq$ 30 IU/mL) <sup>b</sup>	Proposed restriction more specific to SLE (requires positive anti-dsDNA). PSCR stated this was to target patients most likely to respond. The PBAC considered that low complement (C3, C4) should be an alternative to anti-dsDNA.
SELENA-SLEDAI score $\geq$ 10	BLISS-SC : $\geq$ 8 NE-ASIA and EMBRACE: $\geq$ 8 BLISS-52 and BLISS-76: $\geq$ 6	The PBS population may have more severe disease than trial population. Score $\geq$ 10 supported by a pre-specified subgroup analysis from BLISS-SC. <sup>c</sup> SLEDAI-2K is more commonly used in clinical practice. The PBAC considered SLEDAI-2K $\geq$ 10 should be included in the PBS restriction.
Unable to reduce the dose of corticosteroid to below 7.5 mg prednisone per day or equivalent	Not required in trial eligibility criteria. BLISS-SC: 14% of patients were not taking oral corticosteroids and a further 26% were taking $\leq$ 7.5 mg/day at baseline.	PSCR stated this was to target use to patients with highest clinical need. Pre-specified subgroup analyses from BLISS-SC supported a greater treatment effect in patients on corticosteroids at baseline (regardless of dose). <sup>c</sup> The PBAC considered that patients must have taken prednisolone or equivalent $\geq$ 7.5 mg per day for at least one month to receive belimumab.
Concomitant triple therapy (antimalarial, corticosteroid and immunosuppressant) unless contraindicated or intolerant	Triple (or attempted) therapy not required in trial eligibility criteria. BLISS-SC: only 24% of patients were on triple therapy at baseline.	The ESC noted this was based on a post hoc analysis. <sup>c</sup> The PBAC considered patients should be on triple therapy simultaneously at the time of application.
No exclusion criteria incorporated into proposed PBS restriction	Excluded patients with: Severe lupus nephritis Severe CNS lupus, Prior B-cell targeted therapy	The PSCR stated this is covered in the PI. The PBAC considered patients with severe active lupus nephritis and CNS lupus should be excluded from the PBS restriction, consistent with the trial.
<b>Continuing restriction</b>		
$\geq$ 4 point reduction in SELENA-SLEDAI score	BLISS-SC: SRI - composite of SELENA-SLEDAI $\geq$ 4, PGA, BILAG A.	The PBS restriction is broader than the trial definition of response, however outcomes were driven by SELENA-SLEDAI in clinical trials.

Public Summary Document – November 2019 PBAC Meeting

Proposed PBS restriction	Trial inclusion criteria	PBAC Comment
compared with baseline. Assessed at 6 months	Assessed at 12 months	PBAC considered $\geq 4$ point reduction in SLEDAI-2K should be used in the continuation criteria.

Source: Appendix 1, p92 of Bliss-SC protocol; Table A1, pp1-5 of Appendix B to submission; p38 of BLISS-SC protocol; p38 of BLISS-SC CSR; p30 of BLISS 52 CSR; p31 of BLISS 76 CSR

ACR= American College of Rheumatology; ANA=anti-nuclear antibody; anti-dsDNA=anti-double stranded deoxyribonucleic acid; CNS=central nervous system; EULAR = European League Against Rheumatism; PI=Product Information; PSCR=Pre-Sub-Committee Response; SLE=systemic lupus erythematosus; SELENA=Safety of Estrogen in Lupus Erythematosus National Assessment; SLEDAI=Systemic Lupus Erythematosus Disease Activity Index; SOC=standard of care.

<sup>a</sup> Requires a patient to have 4 or more of specific criteria from the following 11 categories: malar “butterfly” rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurological disorder, haematological disorder, immunologic disorder (which may include anti-DNA, among others), ANA.

<sup>b</sup> From 2 independent time points

<sup>c</sup> There were significant limitations with these subgroup analyses, as outlined in Paragraph 6.20

2.3 The proposed PBS restriction was narrower than the eligibility criteria for the key trials as it required patients to: be positive for anti-ds DNA (the trials also allowed ANA titre  $\geq 1:80$ ); have a SELENA-SLEDAI score  $\geq 10$  (the trials all used lower scores); be on prednisone  $\geq 7.5$  mg/day (prednisone was not required at baseline in any of the trials); and be on concomitant triple therapy (not required in any of the trials). The PBAC noted that these criteria would target patients who have a high clinical need and who are most likely to respond based on results of subgroup analyses of the trials (refer to Paragraphs 6.19 to 6.20) and an Italian study of belimumab use in the ‘real world’ setting which found that predictors of response were SLEDAI-2K  $\geq 10$ , polyarthritis and prednisone  $\geq 7.5$  mg/day<sup>1</sup>. Further, the PBAC noted that the ‘2019 update of the EULAR recommendations for the management of SLE’ stated that the ‘patients who are more likely to respond to belimumab include those with high disease activity (e.g. SLEDAI > 10), prednisone dose > 7.5 mg/day and serological activity (low C3/C4, high anti-dsDNA titres), with cutaneous, musculoskeletal and serological manifestations responding the most’.<sup>2</sup>

#### Diagnostic criteria

2.4 The proposed restriction states “Patient must have a confirmed and documented diagnosis of SLE”, however no clear diagnostic criteria were specified. All trials included in the submission’s meta-analysis required patients to have a diagnosis of SLE according to the 1997 American College of Rheumatology (ACR) criteria. The Economics Sub-Committee (ESC) and PBAC considered that specific SLE diagnostic criteria would be required to reduce the risk of leakage into poorly defined connective tissue disorders. The PBAC considered that the restriction should require patients to

<sup>1</sup> Laccarino L, et al. Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. J Autoimmun 2018; 86: 1–8. <https://www.sciencedirect.com/science/article/pii/S0896841117304389?via%3Dihub>

<sup>2</sup> Fanouriakis A, et al 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus Annals of the Rheumatic Diseases 2019;78:736-745. Available at: <https://ard.bmj.com/content/78/6/736>

have a confirmed and documented diagnosis of SLE according to the 2019 European League Against Rheumatism (EULAR) / American College of Rheumatology (ACR) classification criteria for SLE<sup>3</sup>. The PBAC noted that this includes a requirement for a positive ANA. As such, the PBAC considered that a separate criterion specifying positive ANA would not be required.

#### Anti-dsDNA serum antibody test

- 2.5 The proposed restriction limits access to patients with an anti-dsDNA serum antibody test result that is unequivocally positive. The evaluation noted the phrase 'unequivocally positive' may be open to interpretation by prescribers and difficult to audit. The Pre-Sub-Committee Response (PSCR) stated that a particular reference range was not specified as different assays are used to determine anti-dsDNA levels, with not all laboratories reporting IU/mL. The PBAC considered that it was not necessary to define a particular reference range for anti-dsDNA levels.
- 2.6 In the clinical trials, patients were required to have unequivocally positive autoantibody test results defined as an ANA titre  $\geq$  1:80 and/or a positive anti-dsDNA ( $\geq$  30 IU/mL) serum antibody test from two independent time points. Nearly all SLE patients test positive to ANA, however it has low specificity and is not used as a monitoring test for disease activity. Anti-dsDNA is highly specific to SLE, however it has low sensitivity.
- 2.7 Complement levels are also used to gauge disease activity. In the clinical trials, a numerically larger treatment effect was observed in patients with positive anti-dsDNA and low complement levels. The PSCR stated: "An additional criterion for access to belimumab could be low complement levels (C3 or C4) as the belimumab studies showed subjects with this criterion had greater likelihood of achieving a response. This was independent of anti-dsDNA levels and hence if this were added, the requirement should be anti-dsDNA positive OR low complement."
- 2.8 The ESC noted that the requested restriction (based on anti-dsDNA positivity) was narrower than the eligibility criteria of the key trials (which were based on anti-dsDNA positivity and/or ANA titre), and the PSCR stated patients who were anti-dsDNA positive at baseline were "a high treatment responding subgroup". In the submission's meta-analysis, there was generally a greater treatment effect in patients who were anti-dsDNA positive, however there were limitations with these subgroup analyses as outlined in Paragraphs 6.19-6.20.
- 2.9 The PBAC considered that the clinical criteria should require patients to have 'laboratory evidence of disease activity with elevated anti-dsDNA titre OR low complement (C3, C4) levels'.

---

<sup>3</sup> Aringer M, Costenbader K, Daikh D, et al. 2019 European League against Rheumatism/American College of rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78:1151–9.

Disease activity index (initiation and continuation)

- 2.10 The requested restriction requires patients to have a SELENA-SLEDAI score  $\geq 10$  to be eligible for initial treatment and achieve/maintain a  $\geq 4$  point reduction in SELENA-SLEDAI to qualify for continuing treatment. This differed to the eligibility and response criteria in the clinical trials, which required patients to have SELENA-SLEDAI  $\geq 8$  (pivotal trial) or  $\geq 6$  (supportive trials) at baseline, and defined responders according to the SLE responder index (SRI) at Week 52.
- 2.11 The ESC noted that, in the pivotal BLISS-SC trial, there was a greater treatment effect in patients with a SELENA-SLEDAI score  $\geq 10$  at baseline.
- 2.12 The evaluation considered that the SELENA-SLEDAI may not be the most appropriate tool to assess PBS eligibility, given its lack of use in routine clinical practice, and inherent limitations as a disease activity index. The PSCR stated SELENA-SLEDAI “was chosen because it is a well validated, easy to administer (easier than the BILAG) disease activity index; it is practical for both clinical and research purposes and can be completed by a physician or a trained nurse. The SELENA-SLEDAI version is that which was used in the belimumab trials.” The PSCR also included input from a specialist clinician stating that SLEDAI “is easy and practical to use in a clinical care setting. Either the SELENA-SLEDAI or SLEDAI-2K could be used, but since the SLEDAI-2K is more commonly used in clinical practice, it may be preferred”. (This is further discussed in Paragraph 4.7 and Table 3.)
- 2.13 Overall, the PBAC considered that the PBS restriction should require patients to have a SLEDAI-2K score  $\geq 10$  at baseline in order to target use to patients more likely to respond. The PBAC noted that the SLEDAI-2K is more commonly used in clinical practice and thus considered it would be preferred over the SELENA-SLEDAI tool.
- 2.14 The evaluation considered that it may not be appropriate to rely solely on a  $\geq 4$  point reduction in SELENA-SLEDAI to qualify for continuing treatment. The primary outcome for the BLISS-SC trial was SRI response, which is a composite outcome of  $\geq 4$  point reduction in SELENA-SLEDAI score, and no worsening in PGA, and no new BILAG A organ domain score or 2 new BILAG B organ domain scores. The PSCR argued : “A  $\geq 4$ -point reduction in SELENA-SLEDAI can also be considered a good proxy for SRI4 composite response. All SRI responders in the trials would necessarily have to have achieved a  $\geq 4$ -point reduction in SELENA-SLEDAI.” The ESC noted that across all trials in the submission’s meta-analysis only 48/1,561 (3%) patients had a SELENA-SLEDAI response but were not SRI responders and noted that the SRI outcomes were driven by SELENA-SLEDAI.
- 2.15 The PBAC noted that the SRI outcomes were driven by SELENA-SLEDAI, and other tools (such as the BILAG) would not be practical to use routinely in clinical practice. As such, the PBAC considered that the continuation criteria should be based on a  $\geq 4$ -point reduction in SLEDAI-2K.

Baseline medications

- 2.16 The proposed restriction limits access to patients who are unable to reduce their corticosteroid dose below 7.5 mg/day of prednisone/equivalent. The PSCR stated this was to target patients with the greatest clinical need and that the risks of corticosteroid-induced organ damage were “substantially increased with continuous corticosteroid doses > 7.5 mg/day”. Corticosteroid use at baseline was not a requirement in the BLISS-SC trial; 14% of patients in the trial were not taking oral corticosteroids and a further 26% were taking ≤ 7.5 mg/day at baseline. The subgroup analyses generally supported a greater treatment effect in patients on corticosteroids at baseline (regardless of dose).
- 2.17 The ESC noted that the proposed restriction does not specify the duration of corticosteroid use, though corticosteroid use and doses may fluctuate. The PBAC considered that the restriction should require patients to be receiving ≥ 7.5 mg per day prednisone/equivalent at the time of commencement of belimumab and for at least one month prior, in order to target patients with the greatest clinical need and who may be more likely to respond.
- 2.18 The proposed restriction required patients to be receiving standard of care, including a combination of an antimalarial agent, a corticosteroid and an immunosuppressive agent, unless contraindicated or intolerant. The ESC noted this was not an eligibility criterion in any of the trials, and only 24% of patients in the BLISS-SC trial were taking triple therapy at baseline.
- 2.19 The PBAC considered that the restriction should require patients to be receiving hydroxychloroquine for at least 3 months and immunosuppressant medication for at least 3 months (methotrexate 20mg weekly, azathioprine 100mg daily or mycophenolate) in order to target patients with the greatest clinical need and who may be more likely to respond.
- 2.20 The PBAC considered that patients should be receiving these medicines at the time of commencement of belimumab and for the minimum period of time prior to commencement of belimumab (one month for corticosteroids and three months for hydroxychloroquine and immunosuppressants).

Other issues

- 2.21 The proposed restriction does not limit eligibility based on clinical manifestations of SLE or concomitant therapies. The clinical trials excluded patients with severe active lupus nephritis and severe active central nervous system lupus, and patients receiving other biologics and IV cyclophosphamide. These points are reflected in the draft TGA Product Information (PI), which states that, “The safety and efficacy of (belimumab) have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus”. As such, the PBAC considered that the restriction

should specifically exclude patients with severe active lupus nephritis and severe active central nervous system lupus.

- 2.22 The PBAC considered that, given the complexity of SLE management, prescribing should be limited to rheumatologists, clinical immunologists and nephrologists.

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

### **3 Background**

#### ***Registration status***

- 3.1 The belimumab subcutaneous (SC) formulation was submitted under the TGA/PBAC Parallel Process. Belimumab is also available as an intravenous (IV) formulation, which was TGA registered on 19 October 2012, however is not PBS-listed. The PBAC has not considered a previous submission for the IV formulation of belimumab in SLE.
- 3.2 At the time of evaluation for PBAC consideration, the approved TGA PI for the IV formulations, the draft TGA PI for the SC formulation and the TGA Round 1 CER were available.
- 3.3 At the time of the PBAC meeting, belimumab had received a positive TGA Delegate's appraisal. The TGA Delegate confirmed that the indication for belimumab SC would be the same as the approved TGA indication for belimumab IV, which is: "... 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  $\geq 30$  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."

### **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.<sup>4,5</sup>

---

<sup>4</sup> Connelly K, Morand EF, Hoi AY. Asian ethnicity in systemic lupus erythematosus: an Australian perspective. *Intern Med J* 2013;43:618–24.

<sup>5</sup> Vincent FB, Bourke P, Morand EF, Mackay F, Bossingham D. Focus on systemic lupus erythematosus in Indigenous Australians: towards

- 4.2 The clinical heterogeneity of SLE and the lack of highly specific and sensitive pathognomonic features or tests pose a diagnostic challenge. All trials included in the submission enrolled patients with a diagnosis of SLE according to the 1997 American College of Rheumatology (ACR) criteria in which a patient must have  $\geq 4$  of the manifestations present, either serially or simultaneously, during any interval of observations. However, other more recent diagnostic criteria exist including the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria and the 2019 EULAR / ACR classification criteria for SLE.
- 4.3 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 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.
- 4.4 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.
- 4.5 For assessing response, the main instrument presented by the submission 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).
- 4.6 While numerous validated disease activity indexes (DAIs) exist, all were created for research and clinical trial purposes. Due to the administrative burden of use and the limitations in detecting a clinically meaningful change in patient outcomes, DAIs are not used in routine clinical practice. Furthermore, there is high inter-rater variability in the assessment of disease activity, even among trained and experienced clinicians<sup>6</sup>.

---

a better understanding of autoimmune diseases. *Intern Med* 2013;43:227–34.

<sup>6</sup> 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.

- 4.7 The SRI was developed by the belimumab investigators following retrospective exploratory analyses of a Phase II belimumab randomised controlled trial (RCT)<sup>7</sup>, and was the first composite index to be used in SLE RCTs. A composite index was thought to make the instrument more responsive than the individual component DAIs. However, there has been no evidence of the superiority of composite indexes over single validated indexes. Since the development of the SRI, there has been improved, validated revisions in single DAIs which capture disease activity better than the components of the SRI. For example, the SLEDAI-2K is an updated and better validated tool than the SELENA-SLEDAI, and the revised BILAG-2004 has replaced the original ‘classic’ BILAG (see Table 3). The PSCR argued that there is little difference between the SLEDAI-2K and the SELENA-SLEDAI (refer to Table 3).

---

<sup>7</sup> 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 submission**

Single disease activity indexes		
Original	Modified	Scoring system
<b>Measures disease activity in individual organ systems</b>		
BILAG or "classic BILAG"	BILAG-2004	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	<b>Global measures of disease activity</b> 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 $\geq 20$ 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. The PSCR stated that "The SLEDAI-2K and the SELENA-SLEDAI differ very little and are almost identical apart from the 'arthritis' item which is two joints or more in SLEDAI-2K and more than 2 joints in SELENA-SLEDAI. The 'proteinuria' item also differs slightly between the two indices; '>0.5 g/24 hours' in SLEDAI-2K and 'new onset or recent increase of more than 0.5 g/24 hours' in SELENA-SLEDAI. The total possible score is identical for both, and both have been validated to capture disease activity in the past 30 (not only past 10) days." Note, the description for SELENA-SLEDAI in scientific literature and the submission (Figure 10) is that disease activity is captured at the time of visit or in the preceding 10 days. The SELENA-2K instrument was originally developed to measure disease activity within the last 10 days, and was subsequently extended to 30 days.
	SLEDAI-2K	
PGA		A visual analogue scale using three benchmarks for assessing disease activity over the last two weeks (see Figure 11, p59 of the submission). 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.
<b>Other relevant indexes</b>		
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.

- 4.8 The Hopkins Lupus Cohort study<sup>8</sup> defined three "patterns" of SLE disease activity: 1) relapsing remitting, 2) chronic activity and 3) long quiescence, as assessed by the PGA and the modified SLEDAI. The measure of disease activity may vary by pattern of disease, and also the instrument used to measure disease activity.

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

<sup>8</sup> Petri, M., Buyon, J. & Kim, 1999. Classification and definition of major flares in SLE clinical trials. *Lupus*, 8(8), pp.685–691.

## 5 Comparator

- 5.1 The submission nominated placebo 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 evaluation considered that placebo may not be the only relevant comparator given some patients may be treated with belimumab IV or rituximab.
- 5.2 Off label rituximab IV infusion is also recommended in the guidelines for patients with severe renal or extra-renal organ-threatening disease refractory to other immunosuppressant agents and/or belimumab, or in patients with contraindications to these drugs. The evaluation considered that there may be an overlapping patient population who could be prescribed either rituximab or belimumab. Expert opinion presented in the submission indicated that, “younger patients with persistent high disease activity would be considered for rituximab along with those with refractory skin conditions, renal manifestations, refractory joint conditions and persistently high inflammatory markers”. Therefore, the evaluation considered that for a subset of patients, rituximab may also be a relevant comparator.
- 5.3 The ESC and PBAC considered that neither belimumab IV nor rituximab are widely used in clinical practice and considered that placebo (as a proxy for SOC) was the appropriate comparator.
- 5.4 While rituximab is used in some centres, the PBAC noted that such use is generally limited to specific subsets of patients such as those with severe CNS and renal SLE, in whom belimumab is not proposed for listing. The PBAC also noted that a trial of rituximab in SLE failed to reach its primary endpoint<sup>9</sup>. Overall, the PBAC considered that rituximab was not an appropriate comparator in the requested population.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the clinical need for effective treatments given the lack of new therapies, and the impact that flares, fear of flares and organ damage can have on patient quality of life. The clinician discussed the importance of targeting use of belimumab to the right patients and considered that use should be restricted to patients with elevated anti-dsDNA, prednis(ol)one dose  $\geq 7.5$  mg/day and SELENA-SLEDAI score  $\geq 10$  despite treatment with triple therapy. The clinician outlined the importance of treating patients with high

---

<sup>9</sup> Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum.* 2010;62(1):222–233.

disease activity who meet the proposed PBS criteria in order to slow or delay organ damage.

- 6.2 The clinician stated that the SELENA-2K tool is used more widely in clinical practice than the SELENA-SLEDAI, but that there is little difference between the two tools. The clinician confirmed that, BILAG, which was also used to assess response in the clinical trials, was impractical to use in clinical practice.

### ***Consumer comments***

- 6.3 The PBAC noted and welcomed the input from individuals (9), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments outlined the limited options for patients with moderate to high disease activity that is non-renal or non-cerebral, and that belimumab would provide an important option for serologically active patients who are significantly steroid dependant or who have failed, or are intolerant of, currently available options like methotrexate, azathioprine or mycophenolate.
- 6.4 The comments outlined the impacts that SLE can have on patient quality of life (e.g. reduced ability to work) and that it can result in long-term profound disability. The comments also outlined the significant adverse events with currently available therapies.

### ***Clinical trials***

- 6.5 The submission was based on five RCTs comparing belimumab + SOC to SOC alone, including:
- 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).
- 6.6 Details of the trials presented in the submission are provided in Table 4.

Public Summary Document – November 2019 PBAC Meeting

**Table 4: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Pivotal trial: SC formulation</b>		
BLISS-SC	<p>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).</p> <p>Stohl W, Schwarting A, Okada M et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus.</p>	<p>March 2016</p> <p>Arthritis &amp; Rheumatology 2017; 69 (5): 1016-1027.</p>
<b>Supportive trials: IV formulation</b>		
BLISS-52	<p>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).</p> <p>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.</p>	<p>January 2010.</p> <p>Lancet 2011; 377: 721-731.</p>
BLISS-76	<p>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).</p> <p>Furie R, Petri M, Zamani O et al. A phase 3, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits BLyS&lt; in patients with systemic lupus erythematosus.</p>	<p>March 2010</p> <p>Arthritis &amp; Rheumatology 2011; 63 (12): 3918-3930.</p>
NE-Asia	<p>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.</p> <p>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.</p>	<p>August 2017</p> <p>Annal Rheumatol Disease 2018; 77: 355-363.</p>
EMBRACE	<p>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).</p>	<p>February 2019</p>

Source: Tables 21, pp32-33 of the submission.

6.7 The key features of the included evidence 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
<b>Belimumab SC formulation (pivotal trial)</b>						
BLISS-SC	839	R, DB, MC, 52 wks	Low	Autoantibody positive; SELENA-SLEDAI score $\geq$ 8 at screening	Primary: SRI response (and components) at Wk 52  Secondary: time to 1 <sup>st</sup> severe flare; prednisone dose reduction $\geq$ 25% from baseline to $\leq$ 7.5 mg/day during Wk 40 to 52; percent patients with $\geq$ 4-point reduction from baseline in SELENA-SLEDAI score at Wk 52; mean change/percent change in PGA at Wk 24	Proportion achieving a $\geq$ 4 point reduction in SELENA-SLEDAI at Wk 24; rate of SLE flares
<b>Belimumab IV formulation (supportive evidence)</b>						
BLISS-52	867	R, DB, MC, 52 wks	Low	Autoantibody positive; SELENA-SLEDAI score $\geq$ 6 at screening		NA
BLISS-76	826	R, DB, MC, 76 wks	Low	Autoantibody positive; SELENA-SLEDAI score $\geq$ 6 at screening		NA
NE-Asia	707	R, DB, MC, 52 wks	Low	Autoantibody positive; SELENA-SLEDAI score $\geq$ 8 at screening; Asian race		NA
EMBRACE	503	R, DB, MC, 52 wks	Low	Autoantibody positive; SELENA-SLEDAI score $\geq$ 8 at screening; Black race		NA
<b>Other studies used in the economic model</b>						
Bruce et al. 2015	1,722	Cohort <sup>a</sup>	NA	Patients within 15 months of recognition of $\geq$ 4 criteria for the 1997 ACR classification for SLE	Time to first increase in SDI score; mortality	SDI progression transition probabilities for SOC; SLE-related deaths by SDI health state irrespective of treatment
Urowitz et al. 2018	179 <sup>b</sup>	Post hoc PSM	High	Autoantibody positive; SELENA-SLEDAI / SLEDAI-2K score $\geq$ 6 at baseline	Change in SDI score at Yr 5; time to organ damage progression	SDI status at baseline (HR for SDI progression)

Abbreviations: ACR=American College of Rheumatology; DB=double blind; HR=hazard ratio; MC=multicentre; NA=not applicable; PC=placebo controlled; R=randomised; PCS=physical component summary; PSM=propensity score matched; SDI=Systemic Lupus International Collaborating Clinics/American College of rheumatology damage Index; SELENA= Safety of Estrogens in Lupus Erythematosus National Assessment; SLE=Systemic lupus erythematosus; SLEDAI=SLE Disease Activity Index; SOC=standard of care; SRI=SLE Response Index; wk=week; yr=year.

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

<sup>a</sup> Natural history of SLE in terms of organ damage in SOC group.

<sup>b</sup> 179 patients from each cohort were matched, of 259 patients in the belimumab arm and 706 in the comparator arm.

6.8 BLISS-SC was the pivotal RCT that supported the use of the 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.

6.9 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 ( $\geq$ 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  $\geq 8$  at screening, compared to  $\geq 6$  in BLISS-52 and BLISS-76.

- 6.10 As noted in ‘Requested listing’, only 24% of patients in BLISS-SC trial were taking triple therapy at baseline. In BLISS-SC, at baseline, 59% of patients were taking steroids and antimalarials (with or without immunosuppressants), and only 46% of patients were on immunosuppressants. Across all trials, approximately half of all patients were taking immunosuppressants at baseline, except in NE-Asia (65% of patients on immunosuppressants).

## Comparative effectiveness

### SRI response

- 6.11 The primary efficacy outcome in the belimumab trials was the proportion of patients classified as responders, based on the SRI at Week 52. The SRI utilises the SELENA-SLEDAI score to determine global improvement, BILAG domain scores to ensure no significant worsening in previously unaffected organ systems, and PGA to ensure that improvements in disease activity are not achieved at the expense of the patient’s overall condition, which may have been missed by either the SELENA-SLEDAI or BILAG<sup>10</sup>, as shown in Table 6.

**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 (the components were used in supportive/secondary analyses)	$\geq 4$ -point reduction from baseline in SELENA-SLEDAI <sup>a</sup>	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 $\geq 1$ A or $\geq 2$ 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; SLE, 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.

<sup>a</sup> EMBRACE used SLEDAI-2K (S2K) rules instead of SELENA-SLEDAI (SS) rules when scoring for proteinuria for the primary SRI outcome. Source: p48 of the submission; Furie et al 2009

- 6.12 Table 7 presents the results of the primary outcome, response as measured by the composite index, SRI, and the results of the component indexes of the SRI (secondary outcomes), at Week 52 across all trials. Results for the adjusted odds ratio (ORs) and

<sup>10</sup> Furie RA, Petri MA, Wallace DJ, Ginzler EM, Merrill JT, Stohl W, et al. Novel evidence-based systemic lupus erythematosus responder index. *Arthritis Rheum.* 2009 Sep 15;61(9):1143-51.

unadjusted risk difference (RDs) are presented below.<sup>11</sup>

**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)
<b>SRI response rate at Week 52</b>				
BLISS-SC <sup>a</sup>	340/554 (61.4)	135/279 (48.4)	1.68 (1.25, 2.25) <sup>b</sup> , p=0.0006	<b>0.13 (0.06, 0.20), p=0.0004</b>
BLISS-52	167/290 (57.6)	125/287 (43.6)	1.83 (1.30, 2.59) <sup>e</sup> , p=0.0006	<b>0.14 (0.06, 0.22), p=0.0007</b>
BLISS-76	118/273 (43.2)	93/275 (33.8)	1.52 (1.07, 2.15) <sup>e</sup> , p=0.0207	<b>0.09 (0.01, 0.18), p=0.0231</b>
NE-Asia	240/446 (53.8)	87/217 (40.1)	1.99 (1.40, 2.82) <sup>f</sup> , p=0.0001	<b>0.14 (0.06, 0.22), p=0.0008</b>
EMBRACE (SS) <sup>g</sup>	146/298 (49.0)	62/149 (41.6)	1.42 (0.94, 2.15) <sup>h</sup> , p=0.0937	0.07 (-0.02, 0.17), p=0.1374
EMBRACE (S2K) <sup>g</sup>	145/298 (48.7)	62/149 (41.6)	1.40 (0.93, 2.11) <sup>h</sup> , p=0.1068	0.07 (-0.03, 0.17), p=0.16
Meta-analysis (including EMBRACE – SS results)			<b>1.69 (1.45, 1.97), p&lt;0.00001</b>	<b>0.12 (0.08, 0.15), p&lt;0.00001</b>
<b>≥4 point reduction from baseline in SELENA-SLEDAI score at Week 52</b>				
BLISS-SC <sup>a</sup>	345/554 (62.3)	137/279 (49.1)	1.69 (1.26, 2.27) <sup>b</sup> , p=0.0005	<b>0.13 (0.06, 0.20), p=0.0003</b>
BLISS-52	169/290 (58.3)	132/287 (46.0)	1.71 (1.21, 2.41) <sup>e</sup> , p=0.0024	<b>0.12 (0.04, 0.20), p=0.0029</b>
BLISS-76	128/273 (46.9)	98/275 (35.6)	1.63 (1.15, 2.32) <sup>e</sup> , p=0.0062	<b>0.11 (0.03, 0.19), p=0.0071</b>
NE-Asia	249/446 (55.8)	91/217* (41.9)	2.01 (1.42, 2.86) <sup>f</sup> , p<0.0001	<b>0.14 (0.06, 0.22), p=0.0007</b>
EMBRACE (S2K) <sup>g</sup>	█/298 (█)	█/149 (█)	█ (█, █) <sup>h</sup> , p=█	█ (█, █), p=█
Meta-analysis			<b>1.70 (1.46, 1.99), p&lt;0.00001</b>	<b>0.12 (0.08, 0.16), p&lt;0.00001</b>
<b>No worsening (increase of &lt;0.30 points from baseline) in PGA by Week 52</b>				
BLISS-SC <sup>a</sup>	450/554 (81.2)	203/279 (72.8)	1.61 (1.15, 2.27) <sup>b,c</sup> , p=0.0061	<b>0.08 (0.02, 0.15), p=0.0070</b>
BLISS-52	231/290 (79.7)	199/287 (69.3)	1.74 (1.18, 2.55) <sup>e,c</sup> , p=0.0048	<b>0.10 (0.03, 0.17), p=0.0042</b>
BLISS-76	189/273 (69.2)	173/275 (62.9)	1.32 (0.92, 1.90) <sup>e,c</sup> , 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) <sup>f,c</sup> , p=0.0149	<b>0.09 (0.01, 0.16), p=0.0195</b>
EMBRACE <sup>g</sup>	█/298 (█)	█/149 (█)	█ (█, █) <sup>h,c</sup> , p=█	█ (█, █), p=█
Meta-analysis			<b>1.50 (1.27, 1.77), p&lt;0.00001</b>	<b>0.08 (0.05, 0.11), p&lt;0.00001</b>
<b>No new 1A/2B BILAG domain scores at Week 52</b>				
BLISS-SC <sup>a</sup>	448/554 (80.9)	207/279 (74.2)	1.46 (1.04, 2.07) <sup>b,d</sup> , p=0.0305	<b>0.07 (0.01, 0.13), p=0.0318</b>
BLISS-52	236/290 (81.4)	210/287 (73.2)	1.62 (1.09, 2.42) <sup>e,d</sup> , p=0.0181	<b>0.08 (0.01, 0.15), p=0.0181</b>
BLISS-76	189/273 (69.2)	179/275 (65.1)	1.20 (0.84, 1.73) <sup>e,d</sup> , 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) <sup>f,d</sup> , p=0.0007	<b>0.12 (0.05, 0.19), p=0.0010</b>
EMBRACE <sup>g</sup>	█/298 (█)	█/149 (█)	█ (█, █) <sup>h,d</sup> , p=█	█ (█, █), p=█
Meta-analysis			<b>1.47 (1.24, 1.74), p&lt;0.0001</b>	<b>0.07 (0.04, 0.10), p&lt;0.0001</b>

**Bold** typography indicates statistically significant results.

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 217 in its RevMan analyses. This and the corresponding ORs and RDs was corrected during evaluation.

<sup>a</sup> Three ITT patients did not have a baseline PGA assessment and, therefore, do not contribute to SRI/component analyses.

<sup>b</sup> 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).

<sup>c</sup> Baseline PGA was also included in the model.

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

<sup>e</sup> 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).

<sup>11</sup> The primary SRI outcome in EMBRACE used SLEDAI-2K (S2K) rules instead of SELENA-SLEDAI (SS) rules when scoring for proteinuria. However, EMBRACE included SRI response using the SS scoring rules for proteinuria as a secondary outcome. The submission presented results of EMBRACE based on SS for the SRI and S2K for ≥4 point reduction from baseline in SELENA-SLEDAI score at Week 52. The SRI result for EMBRACE (S2K) is also presented below (one less patient was counted as a responder in the belimumab arm, compared to when using SS scoring).

<sup>f</sup> Logistic regression model with independent variables treatment group, country, baseline SELENA SLEDAI score ( $\leq 9$  vs  $\geq 10$ ) and complement levels (low C3 and/or C4 vs. no low C3 or C4).

<sup>g</sup> 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.

<sup>h</sup> Logistic regression model with covariates treatment group, baseline SS-S2K score ( $\leq 9$  vs  $\geq 10$ ), 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, p80-84 and Tables 48-51, p112-115 of the submission; 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.

- 6.13 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). Of note however, the response rate in the placebo arms of the trials were high and the treatment effect of belimumab over placebo was marginal, as reflected by the low risk differences.
- 6.14 The high placebo response rates may have been due to regression to the mean because some patients may have commenced therapy during a disease flare (patients had to meet minimum SELENA-SLEDAI scores at screening). Over time, the level of disease activity would reduce in some patients, for example as the flare becomes controlled. The high placebo response rates may also be due to enhanced monitoring and greater compliance to background medications in the clinical trial setting.
- 6.15 There were more responders in both the belimumab and placebo trial arms when measured by the PGA and BILAG compared to the SELENA-SLEDAI. Across all trials and for the pooled analyses, the relative treatment effect of belimumab was lower when measured by both the PGA and BILAG compared to the SELENA-SLEDAI. Only three trials (BLISS-SC, BLISS-52 and NE-Asia) achieved statistically significant results for the SRI and all of its component indexes.
- 6.16 The ESC noted that longer-term comparative data from BLISS-76 found that by Week 76, SRI response ceased to reach statistical significance (adjusted OR of 1.31, 95% CI 0.92 to 1.87)<sup>12</sup> despite being superior at Week 52 (adjusted OR of 1.52, 95% CI = 1.07, 2.15). The ESC acknowledged that SRI response at Week 76 was a secondary efficacy endpoint and the trial was not powered to detect a difference in this outcome, but considered these data raised concerns about the long-term efficacy of belimumab.
- 6.17 The ESC 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. The ESC also noted that SLE is more common and more severe in Indigenous Australians and the applicability of the BLISS-SC results to these patients is uncertain.

---

<sup>12</sup> Kandala N, et al. Belimumab: a technological advance for systemic lupus erythematosus patients? Report of a systematic review and meta-analysis. *BMJ Open* 2013;3: <https://bmjopen.bmj.com/content/3/7/e002852>

- 6.18 The PBAC noted that, in the BLISS-SC trial, more patients were able to reduce their corticosteroid dosage by  $\geq 25\%$  (to  $\leq 7.5$  mg/day) in the belimumab group than in the placebo group (18.2% versus 11.9%, respectively) although the difference was not statistically significant (OR = 1.65 (95% CI: 0.95, 2.84). Fewer patients in the belimumab group (8.1% versus 13.2%, respectively) had an increase in corticosteroid dosage through to week 52 (OR = 0.55 (95% CI: 0.34, 0.87). The PBAC considered that the clinical significance of these results was unclear.

#### Subgroup analyses

- 6.19 The proposed PBS restriction was narrower than the eligibility criteria for the key trials in that it required patients to: be positive for anti-ds DNA (the trials also allowed ANA titre  $\geq 1:80$ ); have a SELENA-SLEDAI score  $\geq 10$  (the trials all used lower scores); be on prednisone  $\geq 7.5$  mg/day (prednisone was not required at baseline in any of the trials) and be on concomitant triple therapy (not required in any of the trials). The PSCR stated that, for the meta-analysis results, the sub-population identified in the proposed PBS restriction had a greater response rate than the trial ITT populations: patients with anti-dsDNA positive or SELENA-SLEDAI  $\geq 10$  had odds ratios for SRI response of 1.84 (95% CI = 1.47, 2.29) and 2.10 (95% CI = 1.72, 2.57) respectively). Further, the odds ratio for patients on corticosteroids at baseline (regardless of dose) was 1.77 (95% CI = 1.49, 2.10). This compares with an adjusted odds ratio for the trial ITT populations of 1.69 (95% CI = 1.45, 1.97).
- 6.20 The ESC considered that these subgroup analyses should be interpreted with caution as the subgroup results are compared with the ITT results rather than the complement, and the subgroup analyses were not subject to any multiple comparison procedures. Further, in the BLISS-SC trial (where these subgroup analyses were pre-specified), the p-values for interaction did not indicate a statistically significant interaction between these variables and treatment response.<sup>13</sup> While acknowledging the limitations, the PBAC considered that the subgroup analyses provided information as to the likely predictors of response and generally aligned with the results of other studies (Laccarino et al 2018).

#### Outcomes used in the economic model

- 6.21 The SRI results were not used in the submission's economic model. Rather, the probability of response used in the economic model was based on the proportion of patients who achieved a  $\geq 4$ -point reduction in the SELENA-SLEDAI at Week 24 in BLISS-SC in-line with the requested continuation restriction. The difference in SELENA-SLEDAI response at Week 24 was not statistically significant at the nominal 0.05 level (OR [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]).

---

<sup>13</sup> No significant treatment-by-subgroup interactions were observed for any of these subgroups. The interaction p-values were: 0.960, 0.212 and 0.246 for anti-ds DNA positivity; SELENA-SLEDAI score  $\geq 10$ ; and use of prednisone at baseline (pp 1183, 1187, 1188 of the CSR).

6.22 Table 8 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 reduction in risk being greater for severe flares compared to any flare.

**Table 8: Other outcomes used in the economic model (highlighted)**

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

Blue shading indicates the adjusted rates for any flare or severe flare used to derive the QALY losses per cycle applicable to belimumab and SOC health states.

Abbreviations: BEL=belimumab; SC=subcutaneous.

<sup>a</sup> Five patients 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.

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

<sup>c</sup> 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

### SDI progression/organ damage

6.23 Belimumab did not demonstrate a statistically significant benefit compared to placebo for the least squares (LS) mean change in SDI score from baseline to Week 52 (treatment difference [95% CI] = -0.0 [-0.1, 0.0] in BLISS-SC trial) or SDI worsening from baseline to Week 52 (OR [95% CI] = 0.47 [0.22, 1.02], p=0.0558 in BLISS-SC trial). The PSCR stated that BLISS-SC was not powered to detect differences in these outcomes. The pre-PBAC response further stated that a 52-week follow-up is likely too short to expect a significant difference in these outcomes. The PBAC acknowledged these arguments, but considered that the submission had not adequately demonstrated an improvement in SDI progression.

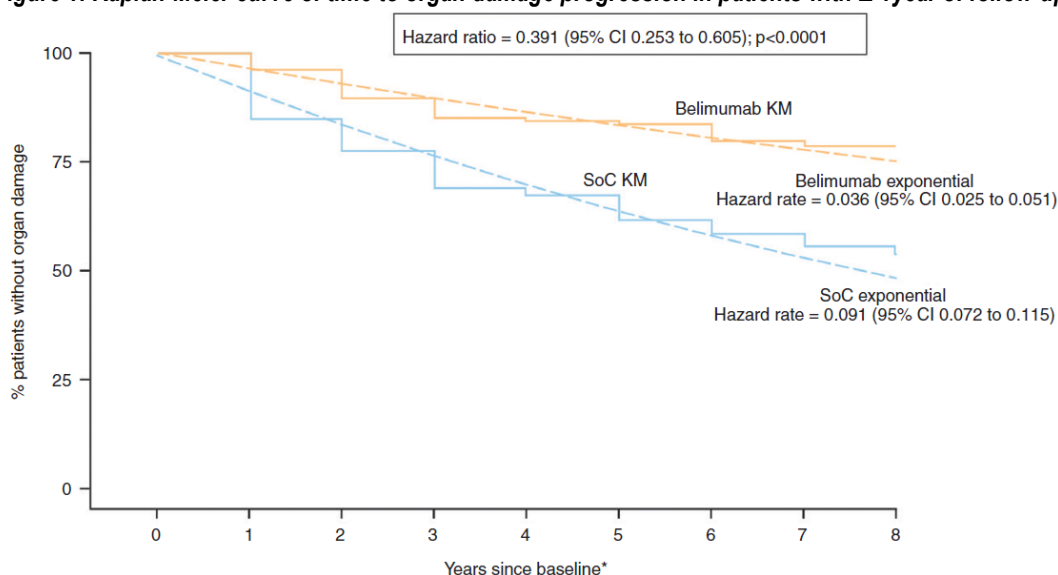
6.24 'Real-world' evidence was used to inform SDI progression in the model, comprising: (i) the natural history of SLE in terms of developing organ damage progression over time for patients treated with SOC (Bruce et al 2015); and (ii) the reduction in organ damage progression for patients treated with belimumab in the BLISS-76 long-term extension (LTE) study compared to patients treated with SOC in a propensity score matched historical cohort (Urowitz et al 2019).

6.25 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 were recruited from 2000 to 2011. 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  $\geq 5$ . The submission used the transition probabilities across the health states conditional on current SDI score for the modelled cohort from Bruce et al.

- 6.26 The ESC and PBAC 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  $\geq 1$  and to death. The description of the method was vague and the impact of other simplifying assumptions was unknown.
- 6.27 Urowitz et al 2018 compared organ damage progression in patients with SLE who received belimumab in the BLISS-76 LTE study (conducted from 2006 to 2014) with propensity score matched patients treated with SOC from the Toronto Lupus Cohort (1990 to 2004). Propensity score matching is a commonly used statistical technique that allows matching of patients within two treatment groups based on their propensity score – the probability of treatment assignment conditional on observed baseline characteristics. The method attempts to mimic some of the characteristics of a randomised controlled trial to analyse observational data. Propensity scores were calculated using a logistic regression including 14 predictors of organ damage (correlated to 17 variables available in both groups). Patients from the BLISS-76 LTE study were matched 1:1 to patients from the Toronto Lupus Cohort based on a similar propensity score within a calliper value defined as 20% of the standard deviation for the distribution of the propensity score in the full sample.
- 6.28 The study compared the time to organ damage progression in patients with  $\geq 1$  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. Figure 1 shows the Kaplan-Meier curve from Urowitz et al 2018, which displays the time to organ damage progression in patients with  $\geq 1$  year of follow-up.

Figure 1: Kaplan-Meier curve of time to organ damage progression in patients with ≥ 1 year of follow-up



Total number of patients at risk at each time point

Belimumab	179	166	137	121	112	88	65	31	0
SoC	179	135	111	83	71	57	44	30	28

Source: Figure 3, p7 of Urowitz et al 2019.

6.29 The evaluation and the ESC considered that the propensity score matching (PSM) analysis had a high risk of bias because:

- only observed variables can be balanced leading to residual confounding;
- matching reduced the sample size with 179 of 259 (69%) patients in the BLISS-76 LTE matched to controls. A sensitivity analysis was provided for the outcome of change in SDI from baseline to 5 years using inverse propensity score weights (IPSW), which is a method that uses the entire sample, and found similar results for that outcome. However, the IPSW analysis was not provided for the time to organ damage progression outcome, and therefore it was unknown whether the estimated treatment effect for matched patients was similar to the effect in unmatched patients;
- a historical control was used. The analysis could not match on year of entry, thus differences in outcomes may be due to improvements in SOC over time. The Toronto Lupus Cohort included patients back to 1990, whereas BLISS-76 enrolled patients from December 2006. The submission attempted to adjust for changes in medicine use and argued there were no revolutionary changes in SLE treatment over that period, however the evaluation considered there may have been evolutionary changes that were unaccounted for. While the submission conducted sensitivity analyses for the covariate “decade of study entry”, the evaluation

considered it was unlikely that this would adequately control for time effects. The PSCR stated that an analysis of mortality rates showed no difference in rate since 1996<sup>14</sup>. While the PBAC acknowledged that SLE mortality rates have likely remained stable since 1996, the PBAC considered there was still a high risk of residual confounding (e.g. because only observed variables can be balanced); and

- baseline in BLISS-76 LTE was the date of first exposure to belimumab whereas baseline in the Toronto Lupus Cohort was the date they first obtained SLEDAI-2K score  $\geq 6$ .

6.30 Further, the applicability of the matched cohort to the PBS population was unclear. Overall, the ESC and PBAC considered that the PSM analysis was not reliable due to the high risk of bias and the economic model's assumption of an improvement in SDI progression with belimumab (and linear persisting benefits), based on the PSM analysis was not reasonable.

### Comparative harms

6.31 Table 9 presents a summary of adverse events (AEs) from the pivotal BLISS-SC trial.

**Table 9: 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)
<b>Belimumab SC formulation (BLISS-SC)</b>				
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%)	<b>0.65 (0.43, 0.99)</b>	-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 <sup>a</sup> /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%)	<b>2.54 (1.11, 5.81)</b>	<b>0.04 (0.01, 0.06)</b>
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.

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

<sup>a</sup> 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 patients 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.

<sup>14</sup> Jorge, AM, Lu N, Zhang Y, et al. Unchanging premature mortality trends in systemic lupus erythematosus: a general population-based study (1999-2014). *Rheumatology* 2018; 57: 337-344.

- 6.33 The draft TGA PI (p6) states “there were more deaths reported with belimumab than with placebo during the controlled period of the clinical trials. No single cause of death predominated. Aetiologies included infection, cardiovascular disease and suicide. The physicians should discuss this imbalance with their patients prior to initiating therapy.” Across the five trials, 0.52% (10/1920) patients died in the belimumab 200 mg SC or 10 mg/kg IV arms and 0.48% (6/1242) in the placebo arms. Deaths in the belimumab arms are higher if the 1 mg/kg arms (from BLISS-52 and BLISS-76) are also included (0.56%, 14/2479).
- 6.34 The headline results<sup>15</sup> for BASE, a recent one-year, randomised, double-blind post marketing safety study, stated that on-treatment all-cause mortality, infection and malignancy rates were similar between belimumab and placebo. However, imbalances were observed in serious depression, serious suicidal ideation/behaviour and self-injury events, and serious infusion/hypersensitivity reactions.
- 6.35 Important identified risks associated with belimumab as outlined in the most recent Periodic Benefit Risk Evaluation Report (PBRER) for belimumab (9 March 2018 to 8 March 2019) included psychiatric events including depression and suicidality; hypersensitivity and infusion- or injection-related systemic reactions; and infections. The pre-PBAC response stated the ‘upgrading of “psychiatric events” to an “important identified risk” was cautionary and has not been confirmed as representing a true signal’.

### ***Benefits/harms***

- 6.36 Table 10 presents a summary of the comparative benefits and harms for belimumab versus placebo in the pivotal trial, BLISS-SC.

---

<sup>15</sup> Sheikh S, Scheinberg M, Cheng-Chung Wei J, et al LB0012 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, autoantibody-positive systemic lupus erythematosus (SLE) receiving belimumab. *Annals of the Rheumatic Diseases* 2019;78:266. The Clinical Study Report is anticipated to be available at the end of 2019.

Table 10: Summary of comparative benefits and harms across the 52-week BLISS-SC trial

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

6.37 On the basis of direct evidence presented in the submission, for every 100 patients treated with belimumab in comparison to placebo (for SOC) over 52 weeks:

- Approximately 13 additional patients would achieve response to treatment based on the SLE responder index (SRI);
  - 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; and
  - Approximately 7 additional patients would achieve response to treatment based on the BILAG component of the SRI.
- Approximately 6 additional patients would experience local injection site reactions, of whom 2 patients would experience injection site pain. This is because in the PBS setting, patients on SOC would not receive a placebo injection.

### **Clinical claim**

6.38 The submission described belimumab as superior in terms of effectiveness and non-inferior in terms of safety compared with placebo when used in combination with SOC. The submission acknowledged the important identified risk associated with belimumab treatment for psychiatric events, however argued that based on external expert opinion, there remains uncertainty regarding whether the imbalance in the preliminary review of the BASE suicidality data represented a true safety signal.

6.39 The PSCR acknowledged that a claim of inferior (as opposed to non-inferior) safety may be more reasonable.

- 6.40 The PBAC considered that the claim of superior comparative effectiveness was reasonable based on the proportion of patients who were SRI responders. However, belimumab demonstrated only modest efficacy results compared to placebo. Further, the PBAC considered that the benefit of belimumab with respect to SDI and preventing organ damage was not adequately supported because there was no randomised controlled trial evidence that belimumab reduces organ damage, and the PBAC considered that the PSM analysis had a high risk of bias.
- 6.41 The PBAC considered that the claim of inferior comparative safety versus SOC alone was reasonable, and were particularly concerned about the potential risk of psychiatric events.

***Economic analysis***

- 6.42 The submission 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 based on the real-world studies (Bruce et al 2015 and Urowitz et al 2018). The key components are shown in Table 11.

Public Summary Document – November 2019 PBAC Meeting

**Table 11: Key components of the modelled economic evaluation (Step 6)**

Component	Description
Type of analysis	Cost-utility analysis.
Outcomes	SELENA-SLEDAI responders ( $\geq 4$ -point reduction), 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 proportion reported in Urowitz et al. 2018.
Health states	Dead plus 24 alive health states defined by treatment (belimumab vs SOC), time (<6 months “induction” vs >6 months) and SDI score (0, 1, 2, 3, 4, $\geq 5$ ): a) “BEL induction” (SDI 0 to $\geq 5$ ) b) “SOC induction” (SDI 0 to $\geq 5$ ) c) “BEL responder” (SDI 0 to $\geq 5$ ) d) “SOC” (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 informed by Bruce et al 2015 (SLICC inception cohort). - SDI progression for belimumab estimated by applying HR for SDI progression estimated in Urowitz et al 2018 to transition probabilities for SOC (above). - SLE-related deaths by SDI health state irrespective of treatment based on Bruce et al 2015. - Age-related mortality rates informed by Australian life tables. - Belimumab continuation (i.e. response at Week 24) and discontinuation informed by BLISS-SC. - Rate of flares for SOC and belimumab informed by BLISS-SC. The applicability of the SLICC inception cohort in Bruce et al 2015 and patients in Urowitz et al 2018 to the Australian population was unclear but likely reflected a lower risk population. All-cause mortality in the model was informed by the maximum of the SDI-related mortality in Bruce et al 2015 and age/gender related mortality from the Australian life tables. The model also generated a survival advantage for belimumab, as belimumab patients have a lower rate of SDI progression in the model, and the mortality rate increases with higher SDI states. This was not adequately supported by the data presented, as belimumab did not demonstrate a significantly reduced rate of SDI progression or any survival gains in the randomised clinical trials.
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. The model did not allow flares in the first cycle (i.e. for the “induction” health states); this was adjusted for in a multivariate sensitivity analysis.
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. The estimated costs were generally reasonable.
Software	TreeAge Pro 2019

Abbreviations: ACR = American College of Rheumatology; BEL = belimumab; PSM=propensity score matched; 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 75, p189 of the submission.

6.43 The modelled health states were defined by SDI scores (SDI 0, 1, 2, 3, 4, and  $\geq 5$ ), current treatment (belimumab+SOC or SOC) and time (<6months “induction” phase vs  $\geq 6$  months). The model did not track patients by SELENA-SLEDAI score, but assumed patients with  $\geq 4$  point reduction from baseline remained on belimumab after the first cycle. Table 12 outlines some of the key inputs and assumptions in the model, which are explained further below.

**Table 12: Outline of the key inputs and assumptions in the economic model**

Health state	Probability of response at 24 weeks	Utilities (base case)	SDI progression (used to estimate costs and mortality)
<b>First 6 months only</b>			
“BEL induction” (SDI 0 to $\geq 5$ )	Based on BLISS-SC: % with $\geq 4$ reduction in SELENA-SLEDAI score at Week 24 (61% of patients respond and continue BEL at Week 24; non-responders move to “SOC”)	0.619 (SLEDAI $>4$ ; based on Wang et al 2014, EQ-5D). i.e. all patients were assumed to have SLEDAI $>4$	NA
“SOC induction” (SDI 0 to $\geq 5$ )	No separate health states for SOC responders and non-responders (despite 53.2% of placebo patients responding at Week 24)	0.619 (as above)	NA
<b><math>\geq 6</math> months</b>			
“BEL responder” (SDI 0 to $\geq 5$ )	NA	0.846 (SLEDAI $\leq 4$ , based on Wang et al 2014, EQ-5D)	Applied the HR reported in the PSM analysis (Urowitz 2018) for SDI progression (HR = 0.39) to the “SOC” probabilities. Applied constantly over time. PSCR stated the HR includes all BEL patients non just responders (and stated that it was therefore conservative)
“SOC” (SDI 0 to 5 $\geq 5$ ) Includes BEL non-responders	NA	0.74 (weighted average by % PBO responders BLISS-SC (53.2% x 0.846 + 46.8% x 0.619). BEL non-responders are attributed a utility that includes a weighted % of ‘responders’.	Based on Bruce 2015 Applied regardless of whether patient was a “responder” or not. Constant probabilities applied over time.

Abbreviations: BEL=belimumab; HR=hazard ratio; NA=not applicable; PBO=placebo; PSCR=Pre-Sub-Committee response; SDI=SLICC/ACR damage index; SLE=systemic lupus erythematosus; SLEDAI=SLE Disease Activity Index; SOC=standard of care.

Source: Compiled during preparation of ESC Advice.

6.44 In summary:

- All patients entered the model in one of the “BEL induction” or “SOC induction” health states, depending on SDI score at baseline. Patients that survived each cycle either maintained the same SDI score or experienced a one unit increase in SDI score in the subsequent cycle.
- In the belimumab arm, all patients commenced on treatment and those that met the response criteria at Week 24 remained on treatment, irrespective of SDI

progression. Treatment discontinuation thereafter was based on an annual discontinuation rate for patients with SDI  $\leq 4$  or mandatory discontinuation for patients with SDI  $\geq 5$ . Responders remained in one of the “BEL responder” health states whereas non-responders transitioned to one of the “SOC” health states, according to SDI score / progression.

- In the SOC arm, all patients commenced on SOC who survived the first cycle transitioned from one of the “SOC induction” health states to one of the “SOC” health states according to SDI score / progression. Patients that survived subsequent cycles remained in one of the “SOC” health states.
- 6.45 To estimate the probability of SDI progression for SOC (and SLE-related mortality for SOC and belimumab) over the 60 year time horizon, the submission relied on estimates from the analysis of the SLICC inception cohort in Bruce et al 2015. The majority of the inception cohort had no organ damage at baseline, thus the time to first SDI worsening was relatively long and there were also relatively few deaths recorded. Thus, the submission estimated transition probabilities for the higher SDI health states and for SLE-related mortality based on an assumption that covariates have the same impact for all transitions where SDI  $\geq 1$  and to death. Therefore, the transition probabilities for the SOC arm may not be reliable, particularly towards the higher SDI health states. Further, the ESC 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.
- 6.46 To estimate the probability of SDI progression for belimumab, the submission used the hazard ratio for time to SDI progression reported by Urowitz et al 2018, which compared patients in the BLISS-76 LTE to propensity score matched controls in the Toronto Lupus Cohort (refer to Figure 1). This hazard ratio (0.39) was applied to the “SOC” probabilities from Bruce et al (outlined above), which had the impact of slowing SDI progression in the “BEL responder” states. As outlined in the ‘Comparative effectiveness’ section, the ESC considered that the propensity score matched analysis had a high risk of bias and was not reliable. Further, the ESC considered that the economic model’s assumption of linear persisting benefits, based on the propensity score matched analysis, was not reasonable. This was the main treatment effect in the model.
- 6.47 Data from BLISS-SC informed the probability of continuing belimumab treatment after the first cycle of the model (61.0% had  $\geq 4$  point reduction in SELENA-SLEDAI at Week 24 on belimumab), the rate of treatment discontinuation after the first cycle (which could not be verified), and the rate of flares for belimumab and SOC.
- 6.48 In the base case, utilities were applied irrespective of SDI score, based on EQ-5D data, by SLEDAI score, in Wang et al 2014. “Induction” was informed by estimates for SLEDAI  $> 4$ , “BEL responder” was informed by estimates for SLEDAI  $\leq 4$ , and “SOC” was informed by an average of the two, weighted by the proportion of “responders” and

“non-responders” for placebo in BLISS-SC. The evaluation and the ESC considered that submission’s approach considerably favoured belimumab and was inappropriate for a number of reasons.

- The submission inappropriately attributed the quality of life estimates by SLEDAI score (from the literature) to treatment response in the model (i.e. patients who responded in the model were attributed the utility value for a  $\geq 4$  point reduction in SLEDAI from baseline).
  - The model did not track SELINA-SLEDAI ‘responders’ in the SOC arm, rather the model implicitly aggregated SOC responders (53.2%) and non-responders (46.8%) in the same health state, and as such did not differentiate between responders and non-responders in the SOC arm. This meant:
    - utilities in the SOC arm were informed by a weighted average of responders and non-responders. Belimumab non-responders transitioned to the SOC arm and were assigned the same utility as everyone in the SOC arm (responders and non-responders combined). This meant that belimumab non-responders were attributed a utility value that incorporated a proportion of patients responding.
    - SOC responders did not have the reduced SDI progression that was assumed for belimumab responders (rather all SDI progression in the “SOC” state was informed by the SLICC inception cohort from Bruce et al 2015). This favoured belimumab because there were high SOC response rates in the clinical trials. There is no evidence to suggest that SOC responders should have different transition probabilities (or utility gains) to belimumab responders.
  - The approach meant that quality of life was not a function of SDI in the model. That is, quality of life for patients with a SDI score of zero was the same as those with SDI scores of  $\geq 5$ , which was not clinically plausible.
- 6.49 The PSCR argued that the HR derived from Urowitz et al 2018 is based on evidence for a group of patients treated with belimumab (responders and non-responders) versus SOC but it is applied to only responders in the model and so is biased against belimumab. The PSCR further argued that “as such, there is no need to apply a differential rate of progression for SOC responders and non-responders because the baseline rate of progression reflects all SOC patients”. However, the ESC considered that, as the treatment effect for belimumab was based on a long-term extension study (BLISS-76 LTE), patients were more likely to be treatment responders. Overall, the ESC considered that these issues highlighted the structural problems with the model, and given the large impact that utilities have on the model results (discussed below), the overall direction of bias was likely against SOC.
- 6.50 Table 13 provides a summary of the key drivers in the modelled economic evaluation.

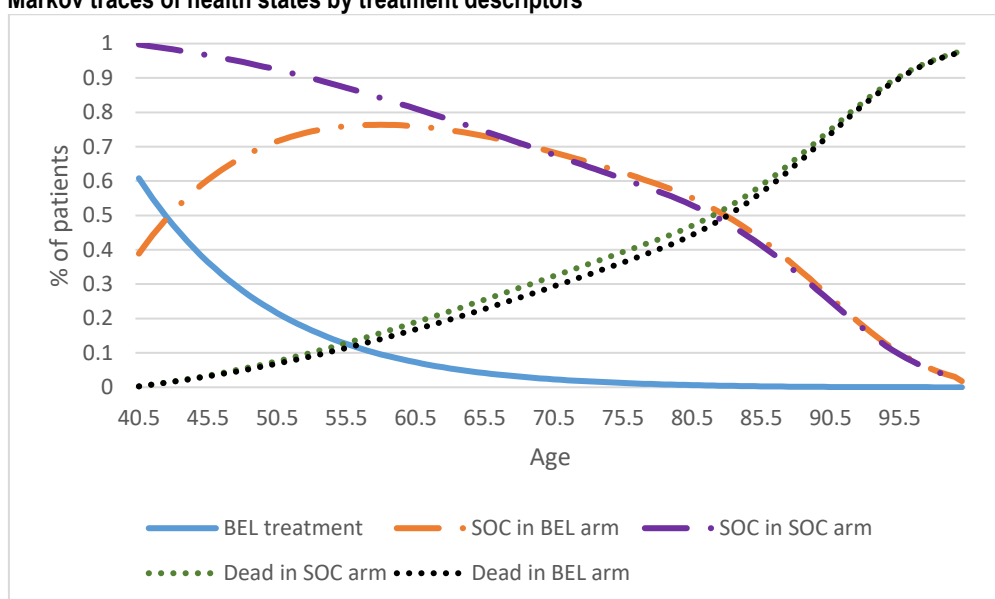
**Table 13: Key drivers of the model**

Description	Method/Value	Impact
Approach to modelling utilities by SLEDAI score	For the base case, the submission assigned utilities to “BEL induction”, “SOC induction”, “BEL responder” and “SOC” health states irrespective of SDI score. The submission’s approach for the base case was inappropriate (see comment above).	High, favours belimumab.
Source of utility estimates	For the base case, the submission used estimates from Wang et al 2014. However, the ESC considered that estimates from Aggarwal et al 2009 were preferred given the population was more application to the requested PBS population.	High, favours belimumab.

Source: compiled during the evaluation

6.51 Figure 2 presents a Markov trace of the health states by treatment descriptors (“BEL treatment” which included “BEL induction” and “BEL responder” health states, “SOC”, and “dead”). The figure illustrates that few patients (less than 10%) remained on belimumab treatment beyond 20 years, those that discontinued belimumab transitioned to the “SOC” health states, and there was a small difference in mortality in favour of belimumab.

**Figure 2: Markov traces of health states by treatment descriptors**



Source: Compiled during the evaluation using Belimumab\_SLE-Model\_Jul19.

6.52 A Markov trace by SDI health state presented in the submission indicated that the model was tracking patients through the SDI health states as intended (based on Bruce et al 2015), with patients in the belimumab arm spending less time in the higher SDI health states compared to SOC. However, the model predicted higher SDI progression rates at 52 weeks for SOC patients (11.4%) compared with patients in BLISS-SC (5%) and the Toronto Lupus Cohort (8.7%) in Urowitz et al 2018; indicating inconsistencies across the different sources of data. The pre-PBAC response stated the lower SOC progression rates in BLISS-SC were because the trial used a last observation carried

Public Summary Document – November 2019 PBAC Meeting

forward analysis and approximately 20% of patients in the placebo arm were lost to follow-up and assumed to be free of progression. Overall, the PBAC considered that the reliability and applicability of the Bruce et al 2015 model predictions were unclear.

6.53 Table 14 provides the results of the stepped economic evaluation.

**Table 14: Results of the stepped economic evaluation**

Step and component	BEL + SOC	SOC	Increment
<b>Step 1:</b> Trial-based, incremental cost per additional SRI responder at 52 weeks, assuming - Drug costs only, All patients remain on BEL for 52 weeks			
Costs (52 weeks)	\$ [REDACTED]	\$0	\$ [REDACTED]
SRI responders at 52 weeks	0.614	0.484	0.13
<b>Incremental cost/extra SRI responder at 52 weeks</b>			<b>\$70,769</b>
<b>Step 2:</b> Trial-based, incremental cost per additional SELENA-SLEDAI responder at 24 weeks, assuming - Drug costs only, All patients remain on BEL for 24 weeks			
Costs (24 weeks)	\$ [REDACTED]	\$0	\$ [REDACTED]
SELENA-SLEDAI responders at 24 weeks	0.610	0.532	0.078
<b>Incremental cost/extra SELENA-SLEDAI responder at 24 weeks</b>			<b>\$ [REDACTED]</b>
<b>Step 3:</b> Trial-based / simple model, incremental cost per additional SELENA-SLEDAI responder at 52 weeks, assuming - Drugs costs only, BEL non-responders at 24 weeks stop treatment, and BEL responders at 24 weeks discontinue treatment			
Costs (52 weeks)	\$ [REDACTED]	\$0	\$ [REDACTED]
SELENA-SLEDAI responders at 52 weeks	0.610	0.532	0.078
<b>Incremental cost/extra SELENA-SLEDAI responder at 52 weeks</b>			<b>\$ [REDACTED]</b>
<b>Step 4:</b> Modelled economic evaluation, incremental cost per QALY at 52 weeks, assuming: - Probability of SDI progression (Bruce et al 2015, Urowitz et al 2018), 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)	0.732	0.685	0.047
<b>Incremental cost/extra QALY gained at 52 weeks</b>			<b>\$ [REDACTED]</b>
<b>Step 5:</b> 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)	12.128	11.521	0.607
<b>Incremental cost/extra QALY gained</b>			<b>\$ [REDACTED]</b>
<b>Step 6:</b> 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)	16.03	15.79	0.24
QALYs (discounted)	12.128	11.521	0.607
<b>Incremental cost / Life Years gained</b>			<b>\$ [REDACTED]</b>
<b>Incremental cost/extra QALY gained (base case in submission)</b>			<b>\$ [REDACTED]</b>

Source: Table 94, p221 of submission.

6.54 Table 15 presents results of sensitivity analyses, predominantly around the utility assumptions. The base case analysis was highly sensitive to the modelling approach for assigning utilities to health states and the source of utility values. Taken together, the model estimated considerable quality of life gains in the belimumab arm such that the results were relatively insensitive to other model assumptions, including the treatment effect. When quality of life was based on SDI health state, the model became much more sensitive to the other parameters.

**Table 15: Results of key sensitivity analyses**

Analyses	Incremental cost	Incremental QALY	ICER
Base case of submission: QOL by SLEDAI score for BEL and SOC health states; Wang et al 2014 EQ-5D estimates (0.846 SLEDAI≤4 for responders, 0.619 SLEDAI>4 for non-responders).	\$ [REDACTED]	0.607	\$ [REDACTED]
SA1: QOL by SLEDAI score for BEL and SOC health states; Aggarwal et al. 2009 EQ-5D estimates (0.75 SLEDAI≤5 for responders, 0.69 SLEDAI>5 for non-responders).	\$ [REDACTED]	0.289	\$ [REDACTED]
SA2: QOL by SLEDAI score for BEL and SOC health states; Aggarwal et al 2009 SF-6D estimates (0.66 SLEDAI≤5 for responders; 0.61 SLEDAI>5 for non-responders).	\$ [REDACTED]	0.251	\$ [REDACTED]
SA3: QOL by SDI health state; Aggarwal et al. 2009 EQ-5D estimates (0.74 for SDI≤2; 0.68 for SDI>2).	\$ [REDACTED]	0.239	\$ [REDACTED]
SA4: QOL by SDI health state; Aggarwal et al. 2009 SF-6D estimates (0.65 for SDI≤2, 0.6 for SDI>2).	\$ [REDACTED]	0.208	\$ [REDACTED]
SA5: QOL by SDI health state; Wang et al. 2014 EQ-5D estimates (0.843 for SDI≤1, 0.663 for SDI>1).	\$ [REDACTED]	0.360	\$ [REDACTED]
<b>Multivariate sensitivity analysis addressing other more minor model issues<sup>a</sup></b>			
SA3: QOL by SDI health state; Aggarwal et al. 2009 EQ-5D estimates (0.74 for SDI≤2; 0.68 for SDI>2), plus addressing 3 minor issues in the model <sup>a</sup>	\$ [REDACTED]	0.230	\$ [REDACTED]

Source: Table 98, pp.227-228 of submission and estimated using Belimumab\_SLE-Model\_Jul19.

Abbreviations: SELENA= Safety of Estrogen in Lupus Erythematosus National Assessment; SLEDAI= SLE Disease Activity Index; SRI= SLE Response Index

<sup>a</sup> Minor model issues were: additive mortality (SLE mortality added to age-related mortality from lifetables, instead of using a maximum function), disutility in the first cycle (inclusion of a disutility from flares in induction); and use of a global discounting formula.-

6.55 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. This alternative approach increased the ICER by 69% to 192% (\$75,000/QALY - \$105,000/QALY to \$105,000/QALY - \$200,000/QALY), depending on the utility values used.

6.56 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. This was because patients included in Aggarwal et al 2009 had more severe and progressed disease compared with Wang et al 2014, given patients were older (42.5 vs 33.8 years), had longer SLE duration (9.3 vs 4.8 years), higher SLEDAI score (6.2 vs 2.9) and SDI score (2.0 vs 0). The pre-PBAC response stated that patients in Wang et al 2014 were better matched to the Monash HDAS cohort (defined by the Monash Medical Centre Lupus Clinic as patients who ever had a SLEDAI-2K

score  $\geq 10$  during follow-up) in terms of age, SDI and ethnicity. However, the PBAC considered that patients in Wang et al 2014 may have had less severe disease than the Monash HDAS cohort based on duration of illness (4.8 years in Wang et al versus 7.7 years in the Monash HDAS cohort) and median SDI (0 versus 1), and because only 29% of patients in the HDAS group had SLEDAI-2K score  $\geq 10$  at baseline.

- 6.57 The ESC noted that assigning the EQ-5D estimates by SDI health state in Aggarwal et al 2009 resulted in an ICER of \$105,000/QALY - \$200,000/QALY. The ICER increased to \$105,000/QALY - \$200,000/QALY in a multivariate sensitivity analysis that also addressed other minor model issues (additive mortality, disutility in the first cycle and global discounting). The ESC considered that this represented a more plausible ICER than that presented in the submission, but considered this ICER likely remained optimistic as it included a benefit for belimumab for SDI progression, which was not supported by the clinical data.
- 6.58 The ESC considered that many of the limitations of the model could not be tested in sensitivity analyses.

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

- 6.59 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.

**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)

Source: compiled during the evaluation

**Estimated PBS usage & financial implications**

- 6.60 This submission was considered by DUSC.
- 6.61 The submission used an epidemiological approach to estimate the financial impact of listing. The submission stated a prevalence approach was taken, but also accounted for “entry to” (incidence driven by population growth), and “exit from” (deaths) to the patient pool. The commentary noted that the estimated total population each year includes background death, therefore the assumed death rate (SLE-related + background) may be slightly overestimated. DUSC emphasised that when using a prevalence approach, the application of incidence and death rates is unnecessary, as incidence and death are accounted for in prevalence rates. As a high rate of survival would be expected over the six-year forward estimates period, a prevalence-only approach would have been appropriate and less complex.

- 6.62 The submission used an SLE prevalence rate of 65.26 per 100,000 population, which was derived from an average of three estimates from six sources. There is a lack of definitive evidence concerning the prevalence of SLE in the Australian population. DUSC and the PBAC considered there is uncertainty with the applied rate of prevalence as there is significant variation in prevalence of SLE in Australia according to racial demographics, geographical location, age and gender.
- 6.63 The submission estimated that 15.36% of patients with SLE would meet the proposed PBS criteria, based on the Monash Lupus Clinic study. The PBAC considered this may be overestimated as: two of the four experts opinions presented in the submission suggested that 5% of all SLE patients may be considered for a biologic (i.e. rituximab or belimumab); and the PBAC considered that simultaneous triple therapy should be required to qualify for belimumab (rather than any prior exposure, as assumed in the submission). Additionally, DUSC and the PBAC considered that the Monash Lupus Clinic study may not be representative of the PBS population (in particular, there may be under-representation of Indigenous Australians in the Monash Lupus Clinic study).
- 6.64 The submission assumed uptake rates of 15% to 40% per year. The PBAC considered the uptake rates are highly uncertain. While there is a clinical need, the PBAC noted that current non-PBS use of IV belimumab is low (data supplied by the sponsor indicated that 'recent annual sales volumes' of the vials for IV infusion were: ■ vials of 120 mg; and ■ vials of 400 mg), even in the context of use requiring private funding or public hospital access (the latter would require drug and therapeutic committee approval). Further, the PBAC considered that the treatment effect is modest and use may be associated with potentially severe adverse events, which may temper uptake.
- 6.65 Treatment persistence was informed by responder rates and treatment discontinuations as determined in the economic evaluation. This was based on the SRI response rate in BLISS-SC of 61%. DUSC considered that the response rates in practice might differ from the trial. DUSC considered that the response rate might be higher in subpopulations not adequately represented in the trial i.e. Asian and Indigenous Australians; on the other hand, response rates in practice are often lower than trial populations due to the differences in monitoring.
- 6.66 The assumed continuation rate was 58.17% in Year 1 and 90.80% in subsequent years. The commentary noted long-term extension studies indicated that <50% of patients continue with belimumab after approximately one year, and of those remaining on treatment, <50% continue with treatment over several years. DUSC considered the discontinuation rate applied (9.2%) seemed low in the context of the extension study. DUSC noted the estimates did not take into account treatment breaks not due to treatment failure e.g. pregnancy. Overall, DUSC considered that the proportion of patients continuing treatment in years 2-6 was likely overestimated. However, the PBAC noted that retention rates of many bDMARDs are higher in clinical practice than in trials, and thus considered that the continuation rates were uncertain.

6.67 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.

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

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
SLE population						
Eligibility criteria (without BEL)						
Prevalent patients						
<b>Incident patients</b>						
Deaths in year						
Eligible population (With BEL)						
Uptake	%	%	%	%	%	%
<b>Initiating belimumab</b>						
Not initiating belimumab						
Deaths						
Remaining eligible						
<b>Treated patients</b>						
Initiated year 1						
Initiated year 2						
Initiated year 3						
Initiated year 4						
Initiated year 5						
Initiated year 6						
<b>Total belimumab scripts</b>						
Initial						
Continuing						
<b>Net cost to PBS/RPBS</b>						
PBS	\$	\$	\$	\$	\$	\$
RPBS	\$	\$	\$	\$	\$	\$

Abbreviations: SLE=Systemic lupus erythematosus.  
Source: Tables 101-110, pp.234-246 of the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS/RPBS would be \$10 - \$20 million per year.

6.68 The submission estimated a net cost to the PBS/RPBS of \$30 - \$60 million over the first six years of listing. The estimates did not include any changes to the use of other medications on the PBS/RPBS or other healthcare resources.

**Quality Use of Medicines**

6.69 DUSC considered patient and carer familiarisation on appropriate administration and storage of the injections would be required.

### **Financial Management – Risk Sharing Arrangements**

- 6.70 The submission did not propose a risk sharing arrangement (RSA), however it stated that the Sponsor is amenable to discussing appropriate arrangements to address any areas of uncertainty.
- 6.71 The PBAC considered there may be potential for use outside the restriction (e.g. in patients with less severe SLE or poorly defined connective tissue diseases). However, the PBAC considered that use outside the restriction may be tempered by the potential for severe adverse events and the modest treatment effect. Overall, the PBAC considered that the risk of leakage was unclear.

*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 considered that the evidence demonstrated a modest clinical benefit. The PBAC considered that the economic model presented in the submission did not provide a reliable basis for estimating the cost-effectiveness of belimumab.
- 7.2 The PBAC considered that there is a clinical need for effective treatments for SLE, particularly for the group of patients requested by the submission. The PBAC noted that there have been no new developments in the treatment of SLE for decades and that an analysis showed there have been no improvements in mortality rates since 1996 (Jorge et al 2018).
- 7.3 The PBAC noted that the proposed restriction was narrower than the clinical trial eligibility criteria in order to target use to those patients who have the greatest clinical need and who are most likely to respond based on results of subgroup analyses of the trials. The PBAC noted that such targeting was generally consistent with: recommendations made in international clinical guidelines (including the '2019 update of the EULAR recommendations for the management of SLE'); predictors of response identified in an Italian study of use of belimumab in the 'real world' setting; and the advice of the clinician who presented at the hearing and many of the consumer comments.
- 7.4 In order to target use to those patients who have the greatest clinical need and who are most likely to respond, the PBAC considered the restriction should require patients to:
- have laboratory evidence of disease activity with elevated anti-dsDNA titre or low complement (C3, C4) levels;
  - have a SLEDAI-2K score  $\geq 10$  at baseline. The PBAC considered that the PBS

restriction should be based on the SLEDAI-2K tool as it is more commonly used in clinical practice than SELENA-SLEDAI;

- have  $\geq 4$ -point reduction in SLEDAI-2K score to continue belimumab;
- require patients to be on the following medicines at the time of initiation of belimumab:
  - 7.5 mg per day or more of prednisone (or equivalent) at the time of commencement of belimumab and for at least one month prior;
  - hydroxychloroquine for at least three months; and
  - immunosuppressant medication for at least three months (methotrexate 20mg weekly, azathioprine 100mg daily or mycophenolate).

7.5 The PBAC also considered the restriction should:

- require patients to have a confirmed and documented diagnosis according to the 2019 EULAR / ACR classification criteria for SLE to reduce the risk of leakage;
- limit prescribing of belimumab to rheumatologists, clinical immunologists and nephrologists, given the complexity of SLE management; and
- exclude patients with severe active lupus nephritis and severe active CNS lupus, consistent with the clinical trial evidence.

7.6 The PBAC considered that SOC was the appropriate comparator.

7.7 The PBAC considered 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 SRI responders at Week 52 compared with placebo plus SOC (RD = 0.13; 95% CI: 0.06, 0.20). 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.

7.8 The PBAC also 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.

7.9 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. The PBAC considered that the propensity score matched analysis by Urowitz et al 2018 (used to support an improvement in organ damage progression in the economic model) was not reliable due to a high risk of unmeasured confounders.

- 7.10 The PBAC noted that a recent post-marketing safety study (BASE) observed imbalances between belimumab and placebo in serious depression, serious suicidal ideation/behaviour and self-injury events. Psychiatric events were listed as an 'important identified risk' in the regulatory risk management plan. The PBAC considered that, given the potential severity of these adverse events, belimumab had inferior safety versus SOC alone.
- 7.11 The PBAC agreed with the issues regarding the economic evaluation raised by the evaluation and ESC, as outlined in the 'Economic analysis' section above. Overall, the PBAC considered that the economic model did not provide a reliable basis for estimating the cost-effectiveness of belimumab (for the reasons outlined in the 'Economic analysis' section above.) In particular, the PBAC considered that the structure and inputs of the model were not reasonable because:
- the economic model's assumption of an improvement in SDI progression with belimumab (and linear persisting benefits) based on the propensity score matched analysis was not reasonable;
  - the submission's approach to modelling utility based on SLEDAI response (rather than SDI progression, upon which the model structure was based) was inappropriate because the model did not differentiate between responders and non-responders in the SOC arms. In effect, belimumab non-responders (who transitioned to the SOC arms) were attributed a utility value that incorporated a proportion of patients responding. Further, SOC responders did not have the reduced SDI progression that was assumed for belimumab responders. The PBAC acknowledged the arguments in the PSCR and pre-PBAC response as to why differential rates of progression were not applied for SOC responders and non-responders; however, overall the PBAC considered that these issues highlight the structural problems with the model.
- 7.12 The PBAC considered the financial estimates were uncertain and likely overestimated because:
- the prevalence rate is uncertain as there is significant variation according to racial demographics, geographical location, age and gender;
  - the proportion of patients with SLE who meet the PBS criteria was likely overestimated as expert opinion (presented in the submission) suggested the proportion would be lower, and the submission's approach did not account for simultaneous triple therapy being required to qualify for belimumab. Additionally, the PBAC considered that the underpinning data may not be representative of the PBS population.
  - the PBAC considered the uptake rates are highly uncertain. While there is a clinical need for effective therapies for SLE, the PBAC noted that current non-PBS use of IV belimumab is low. Further, the PBAC considered that the treatment effect is modest and use may be associated with adverse events, which may

temper uptake.

- The proportion of patients continuing treatment in subsequent years was uncertain given higher rates of discontinuation in the extension studies and because continuation rates in clinical practice may differ from those observed in clinical study settings.
- 7.13 Further, the PBAC considered that a prevalence-only approach would be appropriate (as outlined in Paragraph 6.61).
- 7.14 Given the uncertain patient population, treatment duration and uncertain potential for leakage, the PBAC considered that an RSA a 100% rebate over the cap would be required.
- 7.15 The PBAC considered that any resubmission would need to be a major submission and would need to address the following issues:
- update the restriction as outlined in ‘Requested listing’ above;
  - update the economic model to address the issues raised in the ‘economic analysis’ section and Paragraph 7.11 above
  - revise the financial estimates to address the issues raised in the ‘Estimated PBS usage and financial implications’ section and Paragraphs 7.12 and 7.13; and
  - propose an RSA with a 100% rebate over the cap to mitigate the uncertain patient population, treatment duration and the potential for use outside the restriction.
- 7.16 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**

The sponsor had no comment.