

7.02 ANIFROLUMAB

**Solution concentrate for I.V. infusion 300 mg in 2 mL vial,
Saphnelo[®],
AstraZeneca Pty Ltd.**

1 Purpose of submission

- 1.1 The Standard Re-Entry resubmission requested a Section 100 Highly Specialised Drugs (S100 HSD) Authority Required (In Writing/HPOS) listing of anifrolumab for the treatment of patients with severe systemic lupus erythematosus (SLE) with high disease activity despite standard of care (SOC). This is the second submission for anifrolumab, the previous submission was in July 2022.
- 1.2 Anifrolumab is to be used in combination with SOC. As with the July 2022 submission, the listing was requested on a cost-utility basis versus SOC alone. Table 1 summarises the components of the overall clinical claim addressed by the resubmission.

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

Component	Description
Population	Adult patients with severe SLE with a high degree of disease activity (SLEDAI-2K ≥ 10) despite SOC (triple therapy).
Intervention	Anifrolumab 300 mg intravenous injection every four weeks added to SOC
Comparator	SOC alone (placebo).
Outcomes	SLE Responder Index (SRI(4)) (a composite outcome consisting of SLEDAI-2K, PGA, BILAG), BICLA response (a composite outcome consisting of BILAG, PGA, SLEDAI-2K), reduction in OCS use, annualised flare rate SDI, CLASI, active (swollen and tender) joint count, HRQoL, and adverse events.
Clinical claim	In patients with SLE and a high degree of disease activity (SLEDAI-2K ≥ 10) despite SOC (triple therapy comprising of an antimalarial, immunosuppressant (MTX, AZA, or mycophenolate) and 7.5 mg/day prednisone (or equivalent)), anifrolumab 300 mg IV added to SOC has superior effectiveness and inferior safety compared to SOC alone*.

Blue shading represents information previously considered by the PBAC.

Source: Table 1.1-4, p19 of the resubmission.

AZA=azathioprine; BICLA=BILAG-Based Composite Lupus Assessment; BILAG=British Isles Lupus Assessment Group; CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index; HRQoL=health related quality of life; MTX=methotrexate; OCS=oral corticosteroids; PGA=physician's global assessment; SDI=SLICC/ACR (Systemic Lupus International Collaborating Clinics/American College of Rheumatology) Damage Index; SLE=Systemic Lupus Erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SOC=standard of care; SRI(4)=4-point reduction on the SLE Responder Index.

* The safety claim was revised from non-inferior to inferior in the Pre-Sub-Committee Response (PSCR).

2 Background

Registration status

- 2.1 Anifrolumab was registered by the TGA on 29 March 2022 for the following indication:
"SAPHNELO (anifrolumab) is indicated as add on treatment of adult patients with moderate to severe, active systemic lupus erythematosus (SLE), despite standard

therapy. The safety and efficacy of SAPHNELO have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.”

- 2.2 In the July 2022 draft HTA review, the Canadian Agency for Drugs and Technologies in Health (CADTH)¹ did not recommend anifrolumab for reimbursement in the treatment of adults with SLE, on the basis that there was insufficient evidence to demonstrate that treatment with anifrolumab results in a meaningful clinical benefit when compared to placebo. The National Institute of Clinical Excellence (NICE)² did not make a recommendation on anifrolumab for treatment of SLE because the appraisal was terminated when NICE was advised that the sponsor would not be providing an evidence submission for the appraisal. The sponsor considered that there was unlikely to be enough evidence that the technology was a cost-effective use of National Health Service (NHS) resources for this population.

Previous PBAC consideration

- 2.3 Table 2 summarises the key concerns identified in the July 2022 submission and the response taken by the resubmission.

Table 2: Summary of key matters of concern and how the resubmission addressed them

Component	Matter of concern raised at the July 2022 PBAC meeting	How the resubmission addresses the concern
Requested restriction	<p>Some differences were noted in the restriction for anifrolumab and the wording proposed by the PBAC for belimumab (para 3.5, anifrolumab PSD, July 2022):</p> <ul style="list-style-type: none"> The restriction does not limit access to patients based on laboratory evidence of serological activity. The criterion that patients must not have “severe renal active lupus nephritis or severe active central nervous system” was consistent with previous PBAC advice for belimumab (para 3.6, belimumab PSD, July 2020); however, the evaluation considered that the word ‘renal’ could be removed to align more closely with the TGA approved indication. The restriction did not include a criterion to prevent patients from re-trialling anifrolumab. The ESC considered that there may be a need to allow patients who no longer need treatment to discontinue, without excluding them from future treatment for flares (particularly if it had been efficacious previously). <p>The PBAC also suggested 6 repeats was required for the requested maximum quantities of initial/continuing</p>	<p>The clinical criterion for initial treatment was changed to remove the word ‘renal’ in severe lupus nephritis.</p> <p>The requested maximum quantities were changed to 6 repeats for initial/continuing treatment (i.e. 1 initial plus 6 repeats) to allow for assessment of response at 24 weeks and six months of continuing treatment.</p> <p>A separate grandfathering restriction was proposed for eligible patients enrolled in the patient access program. If listed, the resubmission estimated approximately [REDACTED]¹ patients will be eligible for anifrolumab on the PBS. This was reduced to [REDACTED]¹ in the PSCR.</p> <p>The resubmission requests a special pricing arrangement, with an effective price that</p>

¹ CADTH reimbursement recommendation (draft) – anifrolumab, July 2022, available from: <https://www.cadth.ca/anifrolumab>, accessed 14/11/2022.

² NICE anifrolumab, available from: <https://www.nice.org.uk/guidance/ta793/resources/anifrolumab-for-treating-active-autoantibodypositive-systemic-lupus-erythematosus-terminated-appraisal-pdf-82611615622597>, accessed 14/11/2022.

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Component	Matter of concern raised at the July 2022 PBAC meeting	How the resubmission addresses the concern
	<p>treatment that would be sufficient to allow for assessment of response at 24 weeks and 24 weeks of continuing therapy on the PBS (para 3.3, anifrolumab PSD, July 2022).</p> <p>The sponsor was requested to propose a grandfather restriction, given that the submission stated a patient access program (PAP) was planned to commence post TGA approval (para 3.4, anifrolumab PSD, July 2022).</p>	<p>represents ██████% reduction on the published price in the July 2022 submission.</p>
Clinical evidence & clinical claim	<p>The PBAC considered that the magnitude of benefit was uncertain due to the (para 7.5, anifrolumab PSD, July 2022):</p> <ul style="list-style-type: none"> • Differing results between TULIP-1 and TULIP-2 with respect to SRI(4), despite similar trial designs and patient characteristics. • Changes in trial design which likely biased results in favour of anifrolumab: (1) a change in the primary endpoint for TULIP-2 from SRI(4) response to BICLA response; and (2) a change in the threshold for use of restricted medications during both TULIP-1 (in the final 2 weeks of the 52-week trial) and TULIP-2. The PBAC noted these amendments were introduced following unblinding of TULIP-1 <p>The PBAC considered the claim of superiority to SOC alone in terms of effectiveness was supported based on the small improvement in disease activity observed. The PBAC acknowledged that the low level of certainty in the evidence and the small difference between anifrolumab and placebo likely reflects, in part, the complex and variable nature of the condition and the challenges associated with assessing outcomes in SLE. The PBAC noted that there is no core outcomes set for SLE (i.e. there is a lack of consensus on core outcomes for use in clinical trials in SLE, unlike in rheumatoid arthritis where the American College of Rheumatology (ACR) response criteria are used, or psoriasis where the Psoriasis Area and Severity Index (PASI) score is used). The PBAC considered that a claim of inferior but manageable safety was reasonable (paras 7.6 and 7.7, anifrolumab PSD, July 2022).</p>	<p>The resubmission presented new data from TULIP LTE (NCT02794285), which was a long-term safety extension study to Week 216 (i.e., 4 years) for patients who completed the TULIP 1 or TULIP 2 trials. In addition, nine published meta-analyses of TULIP-1, TULIP-2 and MUSE were also presented.</p> <p>The resubmission maintained that discordant SRI(4) response between the TULIP trials, was primarily driven by sensitivity of SRI(4) to single organ (arthritis) improvement as the discordant placebo group was enriched for patients with lower baseline joint counts. The resubmission presented a post-hoc analysis conducted by Bruce et al. 2022a, which identified that the subgroup of discordant BICLA non-responders/SRI(4) responders was larger in the TULIP-1 placebo group (Bruce, Furie et al. 2022a).</p> <p>The resubmission stated that based on the clinician hearing, the revised medication rules in the TULIP trials reflect current clinical practice in Australia.</p> <p>The clinical claim was unchanged from the previous submission.</p>
Economic evaluation	<p>The PBAC considered the ICER was highly uncertain and favoured anifrolumab. The PBAC considered the resubmission should present a revised economic evaluation addressing the concerns raised, including a reduction in the anifrolumab price to achieve acceptable incremental cost-effectiveness (paras 7.10, 7.11 and 7.14, anifrolumab PSD, July 2022). The concerns with the economic model included:</p> <ul style="list-style-type: none"> • the trial follow-up (52 weeks) was comparatively short in relation to the time horizon applied (30 years). • there was a lack of direct evidence on organ damage and mortality and limited clinical evidence of the 	<p>The resubmission presented a revised base-case, which included:</p> <ul style="list-style-type: none"> • extrapolation beyond the first year was based on evidence from TULIP-LTE (to 216 weeks). • Excluded the effect on the rate of flares in anifrolumab non-responders and the impact of SLEDAI-2K on the rate of hospitalisation. • Duration of flares was informed by data of Australian SLE patients in the Asia-Pacific Lupus Cohort (APLC) study. • Reduced effective DPMQ (public) to \$ ██████ (from \$ ██████ in the July 2022 submission)

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Component	Matter of concern raised at the July 2022 PBAC meeting	How the resubmission addresses the concern
	<p>relationship between SLEDAI-2K and the long-term outcomes to which it contributed.</p> <ul style="list-style-type: none"> the multicollinearity of regressors, the appropriateness of model fit and the extrapolation of the regression coefficients across the time horizon. ESC also considered there was a high chance of double counting the SLEDAI-2K effect. the PBAC considered the changes in SLEDAI-2K were implausible as patient discontinued anifrolumab at Year 1, however the greatest difference between the arms in SLEDAI-2K occurred after Year 10. It was unreasonable that differences would commence so long after the patient had discontinued anifrolumab. there was a 10% difference in survival between the arms at Year 30 despite fewer than 10% of patients still being on treatment at Year 15. compared with data from ALRB, the model appeared to overestimate the average mean SLEDAI-2K for patients receiving only SOC. small changes in flare duration had very large impacts on the ICER, which the PBAC considered may not be plausible. Further, the PBAC considered that flare duration was likely overestimated in the model. 	<p>and \$█ in the July 2022 pre-PBAC response).</p> <ul style="list-style-type: none"> The pre-PBAC response offered a lower effective DPMQ of \$█ (public).
Financial estimates & risk share	<p>The PBAC noted the pre-PBAC responses' estimate of the total number of scripts in Year 6 was still substantially higher than estimated for belimumab (para 6.61, anifrolumab PSD, July 2022). The PBAC considered that the pre-PBAC responses' adjustment to the proportion of eligible patients was appropriate as it was more closely aligned with the proportion in the TULIP trials and ALRB data. However, the PBAC considered that the uptake rates applied in the pre-PBAC response may have been overestimated in the later years. Further, the PBAC noted that the financial estimates assumed 100% compliance, which it considered was unreasonable in the context of an IV infusion (para 7.12, anifrolumab PSD, July 2022).</p> <p>The PBAC considered that a RSA with a rebate for use over the expenditure caps would be required given the uncertain size of the patient population (para 7.13, anifrolumab PSD, July 2022).</p>	<p>The financial estimates were revised incorporating reduction in the proposed effective price, total patient years, proportion of eligible patients, increased uptake rates and grandfathered patients in Year 1. Further revisions to the financial estimates were provided in the PSCR.</p> <p>The resubmission stated that to address any areas of uncertainty to the PBS and the government, the sponsor was willing to consider a RSA.</p>

Source: Table intro 1, pp.xxxiv-xxxvi of the resubmission.

ALRB=Australian Lupus Registry and Biobank; ARTG=Australian Register of Therapeutic Goods; AZA=azathioprine; BICLA=BILAG-Based Composite Lupus Assessment; BILAG=British Isles Lupus Assessment Group; HCQ=hydroxychloroquine; ICER=incremental cost-effectiveness ratio; IV=intravenous; MTX=methotrexate; NSAIDs=nonsteroidal anti-inflammatory drugs; QALY=quality adjusted life year; RSA=risk sharing agreement; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SOC=standard of care; SRI(4)=4-point reduction in SLE Responder Index; PSD = Public Summary Document; PSCR = Pre-Sub-Committee Response.

The redacted values correspond to the following range:

1 < 500

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

3 Requested listing

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

MEDICINAL PRODUCT medicinal product pack <i>Initial / grandfathered</i>	Dispensed Price for Max. Qty		Max. qty packs	Max. qty units	№.of Rpts	Available brands
	Published	Effective				
ANIFROLUMAB Single dose vial, concentration for infusion 300 mg	\$ [redacted] (public) \$ [redacted] (private)	Submission \$ [redacted] (public) \$ [redacted] (private) Pre-PBAC response \$ [redacted] (public) \$ [redacted] (private)	1	1	6	SAPHNELO®
<i>Continuing / grandfathered</i>						
ANIFROLUMAB Single dose vial, concentration for infusion 300 mg	\$ [redacted] (public) \$ [redacted] (private)	Submission \$ [redacted] (public) \$ [redacted] (private) Pre-PBAC response \$ [redacted] (public) \$ [redacted] (private)	1	1	6	

Source: Tables 1.4-1 and 1.4-2 of the resubmission.

Initial treatment

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – In Writing/HPOS upload or Online PBS Authorities immediate assessment
Episodicity: Active
Condition: Systemic lupus erythematosus
PBS Indication: Active systemic lupus erythematosus
Treatment Phase: Initial
Treatment criteria: Must be treated by a rheumatologist; or Must be treated by a clinical immunologist; or <i>Alternatively</i> Must be treated by a specialist physician experienced in the management of this condition
Clinical criteria: Patient must have a confirmed and documented diagnosis of systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) SLE Classification Criteria 2019
AND
Clinical criteria: Patient must have persistent disease activity as supported by a SLE Disease Activity Index 2000 (SLEDAI-2K) score of at least 10 points
AND
Clinical criteria: Patient must be currently receiving hydroxychloroquine and must have received this for at least 12 weeks
AND

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<p>Clinical criteria: Patient must be currently receiving immunosuppressant medication and must have received this for at least 12 weeks (minimum dose of methotrexate 20 mg per week, azathioprine 100 mg per day, or mycophenolate 1,000 mg per day)</p>
<p>AND</p>
<p>Clinical criteria: Patient must be currently receiving prednisolone or equivalent ≥ 7.5 mg per day and must have received this for at least 4 weeks</p>
<p>AND</p>
<p>Clinical criteria: Patient must not have severe active lupus nephritis or severe active central nervous system systemic lupus erythematosus</p>
<p>Population criteria: Patient must be aged 18 years or older.</p>
<p>Prescribing Instructions: The authority application must be made via the Online PBS Authorities (real time assessment), or in writing via HPOS form upload or mail and must include: (a) details of the ACR/EULAR SLE Classification Criteria 2019 confirming diagnosis of SLE (b) details (date and score) of the completed SLEDAI-2K score sheet (c) details of current systemic therapy used (dosage, date of commencement and duration of therapy). All the reports must be documented in the patient's medical records. The name of the specialist consulted must be provided at the time of application for initial supply.</p>
<p>Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)</p>
<p>Prescribing Instructions: History of systemic lupus erythematosus medication therapy should be based on documented use of treatment prescribed by a physician. 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. 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. If treatment with standard of care therapy is contraindicated according to the relevant TGA approved Product Information, details of the contraindication must be provided at the time of application.</p>
<p>Administrative Advice: SLEDAI-2K can be accessed via Gladman 2002 J. Rheumatol. 29 (2) 288-291 or from AstraZeneca Medical Information on 1800 805 342.</p>
<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>

Continuing treatment

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities immediate assessment
Episodicity: Active
Condition: Systemic lupus erythematosus
PBS Indication: Active systemic lupus erythematosus
Treatment Phase: Continuing or recommencement of treatment after a break
Treatment criteria: Must be treated by a rheumatologist; or Must be treated by a clinical immunologist; or <i>Alternatively</i> Must be treated by a specialist physician experienced in the management of this condition
Clinical criteria: Patient must have previously been issued with an authority prescription for this drug for this condition. [phase out 18091, 19469, 23815 draft]
AND
Clinical criteria: Patient must have demonstrated or maintained at least a 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, compared to the baseline assessment, or Patient must have demonstrated or maintained at least a 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, compared to the baseline assessment prior to having a treatment break for clinical reasons.
Administrative Advice: SLEDAI-2K can be accessed via Gladman 2002 J. Rheumatol. 29 (2) 288-291 or from AstraZeneca Medical Information on 1800 805 342.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: <u>Note</u> [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. Monday to Friday).

Grandfather initial treatment

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – In Writing/HPOS upload or Online PBS Authorities immediate assessment
Episodicity: Active
Condition: Systemic lupus erythematosus
PBS Indication: Active systemic lupus erythematosus
Treatment Phase: Initial (grandfather patients) – transitioning from non-PBS to PBS subsidised supply
Treatment criteria: Must be treated by a rheumatologist; or Must be treated by a clinical immunologist; or <i>Alternatively</i>

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Must be treated by a specialist physician experienced in the management of this condition
Clinical criteria:
Patient must have received prior non-PBS-subsidised treatment with this drug for this condition in this treatment cycle prior to [date of PBS listing]
AND
Clinical criteria:
Patient must have a confirmed and documented diagnosis of systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) SLE Classification Criteria 2019
AND
Clinical criteria:
Patient must have persistent disease activity as supported by a SLE Disease Activity Index 2000 (SLEDAI-2K) score of at least 10 points
AND
Clinical criteria:
Patient must be currently receiving hydroxychloroquine and must have received this for at least 12 weeks
AND
Clinical criteria:
Patient must be currently receiving immunosuppressant medication and must have received this for at least 12 weeks (minimum dose of methotrexate 20 mg per week, azathioprine 100 mg per day, or mycophenolate 1,000 mg per day)
AND
Clinical criteria:
Patient must be currently receiving prednisolone or equivalent ≥ 7.5 mg per day and must have received this for at least 4 weeks
AND
Clinical criteria:
Patient must not have severe active lupus nephritis or severe active central nervous system systemic lupus erythematosus
Population criteria:
Patient must be aged 18 years or older.
Prescribing Instructions:
The authority application must be made via the Online PBS Authorities (real time assessment), or in writing via HPOS form upload or mail and must include: (a) details of the ACR/EULAR SLE Classification Criteria 2019 confirming diagnosis of SLE (b) details (date and score) of the completed SLEDAI-2K score sheet (c) details of current systemic therapy used (dosage, date of commencement and duration of therapy). All the reports must be documented in the patient's medical records. The name of the specialist consulted must be provided at the time of application for initial supply.
Prescribing Instructions:
If the application is submitted through HPOS form upload or mail, it must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)
Prescribing Instructions: History of systemic lupus erythematosus medication therapy should be based on documented use of treatment prescribed by a physician. 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. 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. 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.
Administrative Advice:

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SLEDAI-2K can be accessed via Gladman 2002 J. Rheumatol. 29 (2) 288-291 or from AstraZeneca Medical Information on 1800 805 342.
<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.

Grandfather continuing treatment

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities immediate assessment
Episodicity: Active
Condition: Systemic lupus erythematosus
PBS Indication: Active systemic lupus erythematosus
Treatment Phase: Continuing ('grandfather patients') – transitioning from non-PBS to PBS subsidised supply
Treatment criteria: Must be treated by a rheumatologist; or Must be treated by a clinical immunologist; or <i>Alternatively</i> Must be treated by a specialist physician experienced in the management of this condition
Clinical criteria: Patient must previously been initiated this drug for this condition have received prior non-PBS-subsidised treatment with this drug for this condition in this treatment cycle prior to [date of PBS listing]
AND
Clinical criteria: Patient must have demonstrated or maintained at least a 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, compared to the baseline assessment, or Patient must have demonstrated or maintained at least a 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, compared to the baseline assessment prior to having a treatment break for clinical reasons.
Administrative Advice: SLEDAI-2K can be accessed via Gladman 2002 J. Rheumatol. 29 (2) 288-291 or from AstraZeneca Medical Information on 1800 805 342.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: <u>Note</u>

[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. Monday to Friday).

- 3.2 The requested maximum quantities of an initial script plus 6 repeats allow 24 weeks of treatment and are sufficient for assessment of response at 24 weeks for continuing therapy on PBS. For continuing treatment, the requested maximum quantity of one script and 6 repeats allows for 6 months of continuing treatment.
- 3.3 The resubmission proposed an effective DPMQ of \$ [REDACTED] (public) and \$ [REDACTED] (private) which were lower than the prices (\$ [REDACTED] (public) and \$ [REDACTED] (private)) requested in July 2022 submission and the effective DPMQ of \$ [REDACTED] (public) proposed in the July 2022 pre-PBAC response. The pre-PBAC response offered a lower effective DPMQ of \$ [REDACTED] (public).
- 3.4 In the July 2022 meeting, the sponsor was requested to propose a grandfather restriction (paragraph 3.4, anifrolumab Public Summary Document (PSD), July 2022 PBAC meeting). The resubmission requested initial and continuing grandfather restrictions for patients enrolled in a patient access program (PAP). If listed, the resubmission estimated that < 500 patients will be eligible for anifrolumab on the PBS from the PAP. This estimate was revised to < 500 patients in the Pre-Sub-Committee Response (PSCR).
- 3.5 The requested PBS restriction was slightly amended to be consistent with the wordings proposed by the PBAC in July 2022 (paragraph 3.1, anifrolumab PSD, July 2022 PBAC meeting). The changes included:
- Removing the word 'renal' from the criterion that patients must not have "severe renal active lupus nephritis", to align with the approved TGA indication.
 - Removal of the criterion preventing patients from re-trialling anifrolumab. In July 2022, the PBAC advised that patients should be able to discontinue anifrolumab without excluding them from future treatment for flares (paragraph 7.3, anifrolumab PSD, July 2022 PBAC meeting).
 - The PSCR added statements regarding contraindications or intolerance to hydroxychloroquine and immunosuppressant medications necessitating treatment withdrawal.

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

4 Population and disease

- 4.1 SLE is a complex chronic autoimmune disease with clinical manifestations that are diverse and systemic. The overall goals of treatment are to ensure long-term patient survival, prevention of organ damage and minimise drug side-effects. Management of SLE should aim for remission of disease symptoms and signs (or low disease activity) to improve long-term patient outcomes.

- 4.2 For patients with high disease activity, measured by a score of at least 10 points on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), the preferred treatment is 'triple therapy' comprising hydroxychloroquine (HCQ), oral corticosteroids (OCS) and an immunosuppressive agent (i.e. azathioprine (AZA), methotrexate (MTX) or mycophenolate). This population is reflected by the target population in the proposed restriction: adult patients (aged ≥ 18 years) with diagnosed severe SLE who have a high degree of disease activity (SLEDAI-2K ≥ 10) despite triple therapy SOC (i.e. an antimalarial [HCQ], an immunosuppressant, and 7.5 mg/day prednisone or equivalent).
- 4.3 Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody which is administered by intravenous (IV) infusion as add-on treatment to SOC (triple therapy). The TGA product information (PI) recommended dose of anifrolumab is 300 mg IV over a 30-minute period, every four weeks (Q4W). The treatment should be initiated and supervised by a physician experienced in the treatment of SLE. The PI also recommends discontinuation of treatment with anifrolumab if there is no improvement in disease control after 6 months of treatment.
- 4.4 The key difference between the current and proposed clinical management algorithm in the resubmission was the inclusion of anifrolumab as add-on treatment to SOC for patients with severe SLE (defined as SLEDAI-2K ≥ 10). For a subset of patients in hospital or in the private setting, the resubmission also indicated belimumab and/or rituximab (off-label) to be treatment options. Under the requested restriction, all patients with persistent disease activity despite SOC would be considered refractory and would qualify for anifrolumab.
- 4.5 The resubmission defined the current use of belimumab and/or rituximab as outside SOC and have excluded them from the proposed clinical algorithm, which may not be appropriate. Although their use is limited in Australia^{3 4 5}, belimumab is a TGA approved SLE biologic and rituximab is now openly listed on the PBS. The European League Against Rheumatism and the American College of Rheumatology (EULAR/ACR 2021)⁶ guideline recommend considering belimumab as add-on treatments to SOC in patients with persistently active or flaring disease and rituximab for organ-threatening refractory disease.

³ Centre for Community-Driven Research (CCDR) (2021). Personal Experience Expectations and Knowledge (PEEK) study: People who have experienced lupus. Volume 4, Issue 1.

⁴ Littlejohn G, Ciciriello S and Deakin C (2021). The demographics, burden of disease and real-world treatment patterns of patients with systemic lupus erythematosus and other forms of lupus in Australia: an analysis from the OPAL-QUMI dataset. OPAL Rheumatology Pty Ltd.

⁵ Hoi A, Kandane-Rathnayake R, Koelmeyer R, Bonin J and Morand E (2021). Inadequate disease control and correlates of improved disease activity in Australian SLE patients. Final report 14 December 2021.

⁶ Fanouriakis A, Nikolaos T, Bertsias G and Boumpa DT (2021). Update on the diagnosis and management of systemic lupus erythematosus. *Annals of the Rheumatic Diseases* 80(1):14-25.

4.6 The PBAC previously noted that there were no core outcomes set for SLE (paragraph 7.6, anifrolumab PSD, July 2022 PBAC meeting) and instruments used to assess disease activity include the:

- British Isles Lupus Assessment Group (BILAG) 2004 index, which measures disease activity in individual organ systems. It is generally regarded as complex and time consuming to complete.
- SLEDAI-2K, which is a global measure of disease activity. It is slightly less complex than the BILAG index.
- Physician global assessment (PGA) which is a visual analogue scale (0-3 scale) which is substantially less complex to complete.

4.7 Two composite outcomes are relevant for the submission:

- SLE Responder Index (SRI), which is a composite of SLEDAI-2K, BILAG, PGA; and
- BICLA, which is a different composite of SLEDAI-2K, BILAG, PGA.

Both SLEDAI-2K and BILAG scores correlate with organ damage and mortality risk.

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

5 Comparator

5.1 The resubmission maintained that SOC alone (placebo) was the main comparator comprising triple therapy with: i) HCQ, ii) an immunosuppressant (minimum dose of MTX 20 mg per week, AZA 100 mg per day or mycophenolate 1000 mg per day) for at least 12 weeks, and iii) prednisone ≥ 7.5 mg per day (or equivalent) for at least 4 weeks.

5.2 The PBAC previously considered the nominated comparator was appropriate (paragraph 7.4, anifrolumab PSD, July 2022 PBAC meeting).

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 trial evidence for anifrolumab including the concordance in clinical trial outcome measures based on the analysis published by Bruce et al. (2022). The clinician stated that SLE patients are currently treated with drugs that have been available since the 1950s which can have poor effectiveness and safety. Consequently, patients experience accrual of organ damage, reduced quality of life, low workforce participation and increased mortality. The clinician spoke about the role of steroids in the treatment of SLE and the goal of reducing steroid doses in these patients due to risks associated with long term use. Patients with SLEDAI ≥ 10 have much worse outcomes, with increased organ damage and 5-times higher mortality. The clinician explained that SLE

is a complex disease where any organ can be affected, at any time, and multiple organ damage can occur; treatment needs to be driven by individual patient circumstances, and this makes measurement of outcomes difficult. The clinician stated that a disease flare is not always accompanied by an increase in SLEDAI score, and a flare that resolves may not be accompanied by a decrease in SLEDAI score. This complexity may lead to an individual outcome not reaching statistical significance, as in the TULIP-1 trial.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (11), health care professionals (2) and organisations (5) via the Consumer Comments facility on the PBS website. The PBAC noted that this input was additional to the consumer comments considered during the previous consideration of anifrolumab at the July 2022 meeting which included input from individuals (128), a health care professional (1) and organisations (5).
- 6.3 The PBAC noted the consumer input was consistent with the previously considered comments. Health professionals supported the proposed listing and noted an unmet clinical need due to limited treatment options available for SLE. Individuals described the significant impact of SLE on patient quality of life and noted that anifrolumab treatment would be unavailable to most, in the absence of PBS listing due to cost.
- 6.4 The PBAC noted the advice received from the Australasian Society of Clinical Immunology and Allergy (ASCIA), the Australian Rheumatology Association (ARA), Lupus Victoria, the National Aboriginal Community Controlled Health Organisation (NACCHO), and the National Paediatric Medicines Forum (NPMF). All organisations supported the proposed listing. The ARA noted that benefits of effective therapy would include greater quality of life through better management of symptoms, reduced dependence on corticosteroids, and minimisation of irreversible damage due to poorly controlled disease or excessive use of corticosteroid. The ASCIA stated that current treatments for patients with severe SLE have limitations, including effectiveness in controlling disease and side effects. It was noted by Lupus Victoria that most lupus patients are put on steroids, which is not very effective and causes severe complications in the case of many patients. NACCHO noted that Aboriginal and Torres Strait Islander peoples are known to suffer from SLE at a higher incidence and severity compared to other Australians, and that the impact of SLE may be compounded by effects of other chronic disease. The NPMF group indicated that anifrolumab is relevant to the national paediatric population and would be of benefit as an alternate option for children in the treatment of systemic lupus erythematosus with limited other therapies available. The PBAC noted that the advice from organisations was supportive of the evidence provided in the submission.

Clinical trials

6.5 The clinical data presented in the resubmission was largely unchanged from the July 2022 submission, with the exception of additional results to Week 216 (i.e. 4 years) from TULIP LTE (NCT02794285)), a long-term safety extension study of patients who completed TULIP-1 or TULIP-2 trials.

6.6 The clinical evidence (Table 3) was based on:

- i. three head-to-head randomised controlled trials (RCTs) comparing anifrolumab 300 mg IV Q4W to SOC alone (also referred to as placebo in the submission) in adults with moderate to severe SLE (with SLEDAI-2K \geq 6 and receiving one or more therapy for SLE): TULIP 1, TULIP 2, MUSE; and
- ii. two treatment extension studies (MUSE LTE and TULIP LTE).

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
TULIP-1 (Study 05) NCT02446912	A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Two Doses of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus Furie, R. A., et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial.	20 May 2019 The Lancet Rheumatology 2019; 1(4): e208-e219.
TULIP-2 (Study 04) NCT02446899	A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus. Morand, E. F., et al. Trial of anifrolumab in active systemic lupus erythematosus.	16 December 2019 New England Journal of Medicine 2020; 382(3): 211-221.
MUSE NCT01438489	A Phase 2, Randomized Study to Evaluate the Efficacy and Safety of MEDI-546 in Subjects with Systemic Lupus Erythematosus. Furie, R., et al. Anifrolumab, an Anti-Interferon- α Receptor Monoclonal Antibody, in Moderate to Severe Systemic Lupus Erythematosus.	April 2015. Arthritis and Rheumatology 2017; 69(2): 376-386.
MUSE LTE NCT01753193	A Phase 2, Open-label Extension Study to Evaluate Long-term Safety of MEDI-546 in Adults with Systemic Lupus Erythematosus Chatham, W. W., et al. Long-Term Safety and Efficacy of Anifrolumab in Adults With Systemic Lupus Erythematosus: Results of a Phase II Open-Label Extension Study.	05 December 2018 Arthritis and Rheumatology 2021; 73(5): 816-825.
TULIP LTE NCT02794285	A Multicentre, Randomised, Double-blind, Placebo-Controlled Phase 3 Extension Study to Characterise the Long-term Safety and Tolerability of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus. Study D3461C00009 Clinical Study Protocol v2.0 Kalunian K, et al. Long-term Safety and Efficacy of Anifrolumab in Adult Patients with Systemic Lupus Erythematosus: A Multicenter, Randomized, Double-blind, Placebo-controlled 3-year TULIP Extension Study [abstract].	6th May 2016 Arthritis and Rheumatology 2022; 74 (suppl 9).

Blue shading represents information previously considered by the PBAC.

Source: Table 2.2-1, p33-34 of the resubmission.

6.7 Table 4 presents the key features of the included trials.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	Modelled evaluation
Anifrolumab vs SOC (placebo)							
TULIP-1	457 ^a	R, MC, DB, PBO 52 weeks / f-up 12 weeks [^]	Unclear	ANI 150 mg IV Q4W ANI 300 mg IV Q4W SOC (PBO) ^e	18-70, SLEDAI-2K ≥6, autoantibody positive	1°: SRI(4) (Wk 52) 2°: OCS dose, flare rate Other: BICLA	SLEDAI- 2K, flare rates, OCS dose
TULIP-2	362	R, MC, DB, PBO 52 weeks / f-up 12 weeks [^]	Unclear	ANI 300 mg IV Q4W SOC (PBO) ^e	18-70, SLEDAI-2K ≥6, autoantibody positive	1°: BICLA (Wk 52) 2°: OCS dose, flare rate, Other: SRI(4)	
MUSE	305 ^b	R, MC, DB, PBO 52 weeks / f-up 12 weeks [#]	Low	ANI 1000 mg IV Q4W ANI 300 mg IV Q4W SOC (PBO) ^e	18-65, SLEDAI-2K ≥6, autoantibody positive	1°: SRI(4) (Wk 24) 2°: OCS dose, AEs Other: BICLA, flares	-
MUSE LTE	246 ^c	MC, OL 156 weeks	High	ANI 300 mg IV Q4W ^{d f}		1°: Safety Other: SLEDAI-2K	-
TULIP LTE	547 ^g	R, MC, DB, PBO 156 weeks / f-up 12 weeks [#]	Low	ANI 300 mg IV Q4W SOC (PBO)	Completed 52 weeks of TULIP-1 or TULIP-2	1°: Safety Other: SLEDAI-2K, OCS dose, SDI	Safety, SLEDAI- 2K, OCS dose

Blue shading represents information previously considered by the PBAC.

Italics indicate results extracted during the evaluation.

Source: Furie 2019 (TULIP-1), Morand 2020 (TULIP-2), Furie 2017 (MUSE), Chatham 2020 (MUSE LTE), Kalunian 2022 (TULIP LTE).

ANI=anifrolumab; AE=adverse event; AZA=azathioprine; BICLA=British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG=British Isles Lupus Assessment Group; DB=double blind; f-up =follow up, MC=multi-centre; MTX=methotrexate; NSAIDs=nonsteroidal anti-inflammatory drugs; OCS=oral corticosteroids; OL=open label; PBO=placebo; R=randomised; SDI=SLICC/ACR (Systemic Lupus International Collaborating Clinics/American College of Rheumatology) Damage Index; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4)=4-point reduction on the SLE Responder Index; SOC=standard of care; Q4W=every 4 weeks; Wk=week.

[^] At week 52, if eligible, patients were enrolled in a separate long-term extension study (TULIP LTE), or they continued the study for another 8 weeks to complete a 12-week safety follow-up after the last dose of study medication (given at Week 48)

[#] All patients were required to complete a 12-week follow-up period after administration of the final dose of the study drug.

^a Eligible patients randomized in 1:2:2 ratio to receive a fixed IV dose of anifrolumab, (150 or 300 mg) or placebo Q4W for a total of 13 doses (Week 0 to Week 48).

^b Eligible patients randomised in a 1:1:1 ratio to receive a fixed IV dose of anifrolumab (300 or 1000 mg) or placebo Q4W for a total of 13 doses over 48 weeks.

^c Patients were eligible for the OL extension if they completed RCT treatment (MUSE) and follow-up, met the open-label extension inclusion criteria, and had no safety issues that led to exclusion. The start of OLE study (Day 1 the subject received their first dose of open-label anifrolumab) was to occur within 28 days of the Day 422 visit of MUSE.

^d Prior to implementation of Protocol Amendment dated 12 February 2015, all patients received IV anifrolumab 1000 mg fixed dose administered as infusion over at least 60 minutes Q4W starting at Day 1 (Week 0). After Amendment, all patients received IV anifrolumab as a 300 mg fixed dose infusion over at least 30 minutes Q4W starting at Day 1 (Week 0) for a total 40 doses or up to 3 years.

^e Permitted medications for SOC included OCS (≤40 mg/day prednisone or equivalent), antimalarials, immunosuppressants (AZA, MTX, mycophenolate) and NSAIDs.

^f SOC treatments for SLE were allowed throughout the open-label extension and were modified at the discretion of the investigator within protocol-defined limits. Permitted SLE medication included OCS (up to 40 mg/day of prednisone or equivalent), immunosuppressants (MTX, AZA, mycophenolate) and NSAIDs.

^g TULIP LTE enrolled 547 patients who completed 52-week treatment in TULIP-1 or TULIP-2 and at least 1 dose in LTE study. Of these, 257 patients in the TULIP trials treated with anifrolumab 300 mg continued LTE anifrolumab 300 mg. Of the 223 placebo patients in the TULIP trials, 112 were re-randomised to LTE placebo and 111 to LTE anifrolumab 300 mg. In addition, 67 patients switched from anifrolumab 150 mg in TULIP-1 to LTE anifrolumab 300 mg.

6.8 Details of TULIP-1, TULIP-2, MUSE and MUSE LTE were unchanged from the July 2022 submission. TULIP LTE was a 3-year multicentre, randomised, double blind placebo-controlled long-term safety extension study. The enrolled population comprised of patients who completed 52-week double-blind treatment in TULIP-1 or TULIP-2. In total, 85.6% (547/639) patients who completed 52 weeks of treatment in TULIP-1 or

TULIP-2 enrolled in TULIP LTE and received at least one dose of study drug. Of these, 257 patients treated with anifrolumab 300 mg in the TULIP trials continued treatment with anifrolumab 300 mg (LTE anifrolumab 300 mg group). Of the 223 patients treated with placebo in the TULIP trials, 112 patients were re-randomised to continue placebo (LTE placebo group) and 111 patients were re-randomised to anifrolumab 300 mg. In addition, 67 patients treated with anifrolumab 150 mg in TULIP-1 switched to anifrolumab 300 mg in TULIP LTE. The proportion of patients who completed 156 weeks of LTE treatment across the treatment arms was 62.3% (68.9% in LTE anifrolumab 300 mg group and 46.4% in LTE placebo group).

- 6.9 It was noted that less stringent steroid rules were applied in TULIP LTE, as there was no requirement for steroid tapering and steroid burst was permitted. Patients with increased SLE disease activity could receive one steroid burst within the first 12 weeks of the LTE study. After this time point, one steroid burst was allowed every 6 months. An increase in the regular OCS dose was also allowed if needed to control the disease. In contrast, SOC must have remained stable throughout the TULIP-1 and TULIP-2 trials, and there was a mandatory attempt to taper OCS to ≤ 7.5 mg/day in patients receiving ≥ 10 mg at baseline.
- 6.10 Among the RCTs, the risk of bias associated with MUSE and TULIP LTE trial was considered low. However, there was unclear risk of bias with the TULIP trials due to two amendments for outcome assessment that likely favoured anifrolumab (paragraph 6.10, anifrolumab PSD, July 2022 PBAC meeting):
- TULIP-1 was unblinded first and detected no difference between anifrolumab and placebo in terms of response on the SLE response index (SRI(4)), however a larger nominally significant difference was detected using the British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA). Based on this, the primary outcome of TULIP-2 was amended to BICLA response (with the trial investigators arguing that SRI(4) lacked sensitivity). While the trial amendment had occurred prior to data lock and unblinding in TULIP-2, the amended analysis was akin to a post-hoc analysis given the trial was already nearing completion at the time of the change.
 - Following the unblinding of the TULIP-1 trial and data review, investigators decided that the restricted medication rules were not appropriate and were overly restrictive compared to clinical practice, particularly with regard to the use of NSAIDs and limited OCS for mild flares. TULIP-1 therefore performed post-hoc analyses with the revised restricted medication rules that allowed patients with NSAID use before Week 50 of the 52-week trial to be classified as responders. The new medication rule was also adopted for TULIP-2 and was referred to as the pre-specified analysis in the publications. The rule change occurred after significant data collection, thus, for much of the trial, investigators had followed the original medication rules. Based on results of TULIP-1, the new medication rule appeared to favour anifrolumab.

- 6.11 Baseline demographics and disease characteristics were reasonably balanced between treatment arms and across the included trials. The baseline characteristics of patients continuing in TULIP LTE were generally consistent with the overall patient population in the TULIP trials.
- 6.12 In July 2022, the PBAC had considered that the proportion of patients in the trials who would meet the proposed PBS criteria was likely to be small, and as such the included trials may not present direct evidence for the requested PBS population. However, the PBAC acknowledged that the purpose of restricting use to this narrow population was to target patients with the greatest clinical need (paragraph 6.11, anifrolumab PSD, July 2022 PBAC meeting).

Comparative effectiveness

- 6.13 Table 5 presents the key outcomes of SRI(4) and BICLA response plus its component indexes at Week 52 from the TULIP-1, TULIP-2 and MUSE trials.

Table 5: SRI(4) and BICLA and their component indexes plus medication rules at Week 52 from the TULIP-1, TULIP-2 and MUSE trials

	Anifrolumab 300 mg IV n/N (%)	Placebo (SOC) n/N (%)	RD (95%CI)
SRI(4) response			
TULIP-1 (pre-specified) ^{# a}	65/180 (36.2)	74/184 (40.4)	-4.2 (-14.2, 5.8) ^b
TULIP-1 (post-hoc) ^{# c}	84/180 (46.9)	79/184 (43.0)	3.9 (-6.3, 14.1) ^b
TULIP-2 [#]	100/180 (55.5)	68/182 (37.3)	18.2 (8.1, 28.3)^b
TULIP 1 & 2 pooled ^d	184/360 (52.2)	147/366 (40.2)	12.1 (4.9, 19.3)^e
MUSE (incl. OCS taper)	51/99 (51.5)	26/102 (25.5)	26 (13, 39)^f
MUSE (excl. OCS taper)	62/99 (62.6)	41/102 (40.2)	22 (9, 36)^f
≥4 point reduction from baseline in SLEDAI-2K			
TULIP-1 (pre-specified) ^a	66/180 (36.7)	75/184 (40.8)	-4 (-14, 6)
TULIP-1 (post-hoc) ^c	85/180 (47.2)	80/184 (43.5)	4 (-6, 14)
TULIP-2	101/180 (56.1)	71/182 (39.0)	17 (7, 27)
TULIP 1 & 2 pooled ^d	186/360 (51.7)	151/366 (41.3)	10 (3, 18)
MUSE	62/99 (62.6)	40/102 (40.2)	23 (10, 37)
No worsening (increase of <0.30 points from baseline) in PGA			
TULIP-1 (pre-specified) ^a	94/180 (52.2)	96/184 (52.2)	0 (-10, 10)
TULIP-1 (post-hoc) ^c	114/180 (63.3)	104/184 (56.5)	7 (-3, 17)
TULIP-2	122/180 (67.8)	95/182 (52.2)	16 (6, 26)
TULIP 1 & 2 pooled ^d	236/360 (65.6)	199/366 (54.4)	11 (4, 18)
MUSE	76/99 (76.8)	62/102 (60.8)	16 (3, 29)
No new 1A/2B BILAG domain scores			
TULIP-1 (pre-specified) ^a	96/180 (53.3)	96/184 (52.2)	1 (-9, 11)
TULIP-1 (post-hoc) ^c	116/180 (64.4)	104/184 (56.5)	8 (-2, 18)
TULIP-2	125/180 (69.4)	94/182 (51.6)	18 (8, 28)
TULIP 1 & 2 pooled ^d	241/360 (66.9)	198/366 (54.1)	13 (6, 20)
MUSE	75/99 (75.8)	61/102 (59.8)	16 (3, 29)
BICLA response			
TULIP-1 (pre-specified) ^{# a}	67/180 (37.1)	49/184 (27.0)	10.1 (0.6, 19.7)
TULIP-1 (post-hoc) ^{# c}	83/180 (46.1)	54/184 (29.6)	16.4 (6.7, 26.2)
TULIP-2 [#]	86/180 (47.8)	57/182 (31.5)	16.3 (6.3, 26.3)^b
TULIP 1 & 2 pooled ^d	169/360 (46.9)	111/366 (30.3)	16.8 (9.8, 23.8)^b
MUSE (incl. OCS taper)	43/99 (43.4%)	17/102 (16.8%)	27 (15, 39)^f
MUSE (excl. OCS taper)	53/99 (53.5)	26/102 (25.7)	28 (15, 41)^f
Reduction of baseline BILAG A and B scores and no new 1A/2B BILAG domain scores			
TULIP-1 (pre-specified) ^a	67/180 (37.2)	51/184 (27.7)	10 (-0, 19)
TULIP-1 (post-hoc) ^c	83/180 (46.1)	57/184 (31.0)	15 (5, 25)
TULIP-2	88/180 (48.9)	59/182 (32.4)	16 (6, 26)
TULIP 1 & 2 pooled ^d	171/360 (47.5)	116/366 (31.7)	16 (9, 23)
MUSE	NR	NR	-
No worsening (increase >0 points) from baseline in the SLEDAI-2K score			
TULIP-1 (pre-specified) ^a	98/180 (54.4)	96/184 (52.2)	2 (-8, 13)
TULIP-1 (post-hoc) ^c	118/180 (65.6)	103/184 (56.0)	10 (-0, 20)
TULIP-2	122/180 (67.8)	94/182 (51.6)	16 (6, 26)
TULIP 1 & 2 pooled ^d	240/360 (66.7)	197/366 (53.8)	13 (6, 20)
MUSE	NR	NR	-
No discontinuation of study drugs			
TULIP-1 (pre-specified) ^a	144/180 (80.0)	146/184 (79.3)	1 (-8, 9)
TULIP-1 (post-hoc) ^c	144/180 (80.0)	146/184 (79.3)	1 (-8, 9)
TULIP-2	153/180 (85.0)	130/182 (71.4)	14 (5, 22)
TULIP 1 & 2 pooled ^d	297/360 (82.5)	276/366 (75.4)	7 (1, 13)
MUSE	NR	NR	-

	Anifrolumab 300 mg IV n/N (%)	Placebo (SOC) n/N (%)	RD (95%CI)
No use of medication beyond protocol allowed thresholds			
TULIP-1 (pre-specified) ^a	114/180 (63.3)	113/184 (61.4)	2 (-8, 12)
TULIP-1 (post-hoc) ^c	138/180 (76.7)	127/184 (69.0)	8 (-1, 17)
TULIP-2	144/180 (80.0)	123/182 (67.6)	12 (3, 21)
TULIP 1 & 2 pooled ^d	282/360 (78.3)	250/366 (68.3)	10 (4, 16)
MUSE	NR	NR	-

Blue shading represents information previously considered by the PBAC.

Italics indicate results estimated during the evaluation. Difference in response rate was calculated using Review Manager (version 5.4.1).

Bold text designates statistical significance.

Source: Table 2.5-1, pp80-81, Table 2.5-2, p84 of the resubmission, Table 11.2.3.2.2 and 11.2.3.2.2a, pp315-322, Tables 11.2.3.2.3 and 11.2.3.2.4, pp327-328 of TULIP-1 CSR Section 11 Tables, Table 11.2.1.1, pp199-201, Table 11.2.1.3, p203 and Table 11.2.3.1.2, pp291-292, Table 11.2.3.1.4, p294 of TULIP-2 CSR Section 11 Tables, Table 14.2.2.3.4, pp283-285, Table 14.2.2.4.17, pp374-376, Table 14.2.2.5.5, pp395-397 of MUSE CSR Errata List

BICLA=BILAG-Based Composite Lupus Assessment; BILAG=British Isles Lupus Assessment Group; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; FAS=full analysis set; OCS=oral corticosteroids; NR=not reported; PGA=physician's global assessment; RD=risk difference; SLE=Systemic Lupus Erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SOC=standard of care; SRI(4)=4-point reduction on SLE Responder Index.

The responder/non-responder rates (percentages), the difference in estimates and associated 95% CI are weighted and calculated using a stratified CMH approach, with stratification factors (SLEDAI-2K score at screening [<10 vs ≥ 10 points], Week 0 OCS dose [<10 vs ≥ 10 mg/day prednisone or equivalent] and type I IFN gene signature test result at screening [high vs low]).

a Original prespecified restricted medication rules.

b Unadjusted p-value.

c Post-hoc revised restricted medication rules.

d Pooled analysis excluded the 150 mg group from TULIP-1. Results are based on the revised restricted medication rules.

e The submission reported pooled TULIP-1 and TULIP-2 result based on SRI(4) response of 188/360 (52.2%) on anifrolumab, which could not be verified. Correcting for the pooled response on anifrolumab group, the analysis conducted during the evaluation resulted in pooled response difference of 11 (4, 18).

f MUSE presented odds ratio (90% CI) and p-values based on a logistic regression model for comparisons of each anifrolumab group versus placebo adjusted for randomization stratification factors.

h The submission reported pooled TULIP-1 and TULIP-2 result based on BICLA response of 171/360 (47.5%) on anifrolumab vs 112/366 (30.6%) on placebo, which could not be verified. Correcting for the pooled response on anifrolumab and placebo group, the analysis conducted during the evaluation showed minimal change in the pooled response difference of 17 (10, 24).

- 6.14 The results of SRI(4) and BICLA response at Weeks 52 and 24 were unchanged from the July 2022 submission. The results demonstrated that there was improved disease activity in both anifrolumab and placebo treated patients based on SRI(4) and BICLA responses and their component indexes (including reduction in SLEDAI-2K ≥ 4) at Weeks 24 and 52. In TULIP-1 there were no significant differences between anifrolumab and placebo treated patients for SRI(4) at either Week 24 or Week 52, with results favouring placebo in the prespecified analysis. In contrast, numerically more patients achieved a BICLA response at Week 52 in the anifrolumab arm, reaching nominal significance. In TULIP-2 and MUSE, the SRI(4) and BICLA responses at Week 24 and Week 52 were significantly higher in the anifrolumab 300 mg group compared to placebo. However, placebo response was high (approximately 40%) in all trials.
- 6.15 At the July 2022 meeting, the PBAC considered that anifrolumab likely conferred a small reduction in disease activity, with a risk difference in SRI(4) response of 12.1% (95% CI: 4.9%, 19.3%) pooled across the TULIP-1 and TULIP-2 trials, noting the large placebo response (SRI(4) response rate of 40.2% in the placebo arm, compared with 52.5% in the anifrolumab arm, pooled results). However, the PBAC also considered the magnitude of benefit was uncertain (paragraph 7.5, anifrolumab PSD, July 2022

PBAC meeting) due to:

- differing results between TULIP-1 and TULIP-2 with respect to SRI(4), despite similar trial designs and patient characteristics.
- changes in trial design which likely biased results in favour of anifrolumab. The PBAC noted that two amendments to outcome assessment occurred during the TULIP trials. These amendments were introduced following unblinding of TULIP-1, in which no difference in terms of SRI(4) response between anifrolumab and placebo was observed (see paragraph 6.6).

- 6.16 Of note, in its considerations of belimumab for a similar SLE population in November 2019 and July 2022 (both submissions were not recommended), the PBAC considered that belimumab demonstrated a modest clinical benefit compared with placebo, based on a 13% increase in the proportion of SRI responders at Week 52 in the belimumab group compared with placebo plus SOC (0.13; 95% CI: 0.06, 0.20) (paragraph 7.7, belimumab PSD, November 2019 PBAC meeting and paragraph 7.4, belimumab PSD, July 2020 PBAC meeting).
- 6.17 The resubmission reiterated from the July 2022 PSCR that the reason that there was no significant difference in SRI(4) in TULIP-1 was that there were fewer arthritis responders in the anifrolumab arm compared to placebo (50% vs 78.6%). The subgroup with discordant BICLA/SRI(4) response was larger in TULIP-1. Bruce et al 2022⁷ suggested the discordance was primarily driven by the sensitivity of SRI(4) to single organ (arthritis) improvement as the discordant placebo group had more patients with lower baseline joint counts. Therefore, SLEDAI-2K arthritis responses (hence SRI(4) responses) may be more easily achieved in the placebo group of TULIP-1. The study reported that across the trials, most patients had concordant BICLA/SRI(4) outcomes and dual BICLA/SRI(4) responses favoured anifrolumab. A BICLA non-responder/SRI(4) responder subgroup was identified where imbalances of key factors driving the BICLA/SRI(4) discordance (disease activity, glucocorticoid taper) disproportionately favoured the TULIP-1 placebo group. Improvement in arthritis was sufficient to achieve individual SRI(4) response, but insufficient for BICLA response unless there was improvement from baseline in the BILAG-2004 A and B organ activity.
- 6.18 However, at the July 2022 meeting, the PBAC considered this explanation was unlikely to fully account for the differences in trial results (paragraph 7.5, anifrolumab PSD, July 2022 PBAC meeting). It was noted there were similar proportions of patients achieving a SLEDAI-2K ≥ 4 response in the placebo arms of TULIP-1 and TULIP-2 (43.5% in TULIP-1 and 39.0% in TULIP-2). While the reason for the discrepancy was unclear, it was likely to be impacted by patient heterogeneity, including unobserved and yet

⁷ Bruce IN, Furie RA, Morand EF, Manzi S, Tanaka Y, Kalunian KC, Merrill JT, Puzio P, Maho E, Kleoudis C, Albuлесcu M, Hultquist M and Tummala R (2022a). Concordance and discordance in SLE clinical trial outcome measures: Analysis of three anifrolumab phase 2/3 trials. *Annals of the Rheumatic Diseases* 81(7):962-969.

unknown characteristics that drive the disease, and it may have been an issue with the response indexes (paragraph 6.15, anifrolumab PSD, July 2022 PBAC meeting).

- 6.19 Table 6 presents the mean change from baseline in SLEDAI-2K, reduction in annual OCS use (excluding patients with >40 mg/day at baseline), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score in TULIP LTE to Week 216 (4.15 years).

Table 6: mean change from baseline in SLEDAI-2K, reduction in annual OCS use and SDI score in TULIP LTE to Week 216.

Exploratory outcomes	Combined anifrolumab 300 mg N=358 ^a		Combined placebo (SOC) N=360 ^b		Difference
	n	mean change (SD)	n	mean change (SD)	
SLEDAI-2K					Difference (SE), p-value
1 year (Wk 52)	293	-6.1 (4.12)	284	-5.2 (4.33)	-0.9 (0.4), p=0.01
2-years (Week 104)	198	-7.4 (4.33)	85	-6.1 (4.22)	-1.3 (0.6), p=0.02
3-years (Week 156)	173	-7.5 (4.02)	55	-5.7 (4.69)	-1.8 (0.7), p=0.01
4-years (Week 208)	139	-7.7 (4.00)	44	-6.4 (3.60)	-1.3 (0.6), p=0.04
Safety FU (week 216)	142	-7.0 (4.12)	40	-5.5 (4.44)	-1.5 (0.8), p=0.05
Annual OCS use (standardised AUC)^c	n	mean dose, mg (SD)	n	mean dose, mg (SD)	Difference, mg
1 year (Wk 52)	355	2,445 (1,948)	359	2,835 (2,163)	-390
2-years (Week 104)	254	1,717 (1,619)	112	2,303 (2,133)	-586
3-years (Week 156)	233	1,633 (1,708)	94	2,249 (1,705)	-616
4-years (Week 208)	208	1,538 (1,567)	72	2,238 (1,799)	-700
SDI score	n	mean change (SD)	n	mean change (SD)	Difference (SE), p-value
1 year (Wk 52)	292	0.1 (0.29)	278	0 (0.21)	ND
2-years (Week 104)	221	0.2 (0.43)	89	0.2 (0.44)	ND
3-years (Week 156)	199	0.2 (0.50)	63	0.2 (0.46)	ND
4-years (Week 208)	184	0.3 (0.62)	59	0.3 (0.58)	ND

Source: Table 2.5-5, p87 of the resubmission, AZ_TULIP LTE HLR presentation – May 2022.pdf and TULIP LTE – SLEDAI-2K p-value calculation v1.0.xlsx.

AUC=area under the curve; ND=no difference; OCS=oral corticosteroid; SDI=SLICC/ACR (Systemic Lupus International Collaborating Clinics/American College of Rheumatology) Damage Index; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000

a Total patients randomised to anifrolumab 300mg at the start of TULIP studies.

b Total patients randomised to placebo at the start of TULIP studies who continued to receive placebo in TULIP LTE.

c Excluded patients with baseline OCS dose >40mg/day at baseline. The AUC for each single dose was derived by the daily dose (mg/day) multiplied with the duration (days). The yearly AUC was the sum of the AUCs of the single doses within the respective period.

- 6.20 The results from TULIP LTE demonstrated that patients treated with anifrolumab 300 mg had a small but significant improvement from baseline in the SLEDAI-2K and reduction in annual OCS use compared to placebo, which was maintained from Week 52 to Week 208. The difference between anifrolumab and placebo arms in mean annualised OCS dose for those who remained on treatment until Year 4 was - 700 mg (approximately 1.9 mg per day). The clinical significance of this difference was not discussed in the resubmission. Additional analyses showed that a higher proportion of patients in the anifrolumab group achieved ≥4 points reduction from baseline in SLEDAI-2K at Week 52 and maintained to Week 208 for those who continued treatment (76.1% and 90%, respectively) compared to the placebo group (69.5% and 81.8%, respectively).

- 6.21 The mean SDI global score and the annualised flare rate (0.1 flares per patient year in the combined anifrolumab group vs 0.2 flares per patient year in the combined placebo group) were similar between groups for the duration of TULIP LTE; all flares were mild to moderate in severity. There were no significant differences between the anifrolumab group and placebo in terms of improvement in quality of life (EQ-5D-5L) at Week 208.

Meta-analysis

- 6.22 The meta-analysis performed on the three anifrolumab trials (TULIP-1, TULIP-2 and MUSE) was unchanged from the previous submission. The results of the meta-analysis showed that anifrolumab improved disease activity in terms of SRI(4) and BICLA response at Weeks 24 and 52. It was also associated with significant reductions in OCS dose and cutaneous manifestation (as measured on the CLASI activity score) at Week 52.
- 6.23 The resubmission identified nine published meta-analyses of TULIP-1, TULIP-2 and/or MUSE. The results in terms of disease activity (SRI(4) and BICLA response), OCS dose and CLASI at Week 52 were generally consistent between the resubmission and the published meta-analyses. The published meta-analyses found that patients treated with anifrolumab had significantly longer median time to first flare, time spent flare free and greater reduction in annualised flare rate compared to placebo (Furie et al 2021b⁸ and Vital et al 2022⁹). However, in contrast, the results from the longer term follow up from TULIP LTE suggest no significant difference in annualised flare rates between anifrolumab and placebo for those who continued treatment.
- 6.24 Given that the management of SLE should aim for remission of disease symptoms (or low disease activity) to improve long-term patient outcomes, the resubmission presented further post-hoc analysis of attainment of Low Lupus Disease Activity State (LLDAS, defined as SLEDAI-2K \leq 4 without major organ activity, no new disease activity, PGA \leq 1, prednisone or equivalent \leq 7.5 mg/day, and well-tolerated standard immunosuppressant) by Morand et al 2021 (abstract)¹⁰. The results demonstrated LLDAS attainment increased over 52 weeks and was achieved earlier in patients treated with anifrolumab 300 mg compared to placebo (time to first LLDAS, HR = 1.76,

⁸ Furie R, Morand EF, Askanase AD, Vital EM, Merrill JT, Kalyani RN, Abreu G, Pineda L and Tummala R (2021b). Anifrolumab reduces flare rates in patients with moderate to severe systemic lupus erythematosus. *Lupus* 30(8):1254-1263.

⁹ Vital EM, Merrill JT, Morand EF, Furie RA, Bruce IN, Tanaka Y, Manzi S, Kalunian KC, Kalyani RN, Streicher K, Abreu G and Tummala R (2022). Anifrolumab efficacy and safety by type I interferon gene signature and clinical subgroups in patients with SLE: post hoc analysis of pooled data from two phase III trials. *Annals of the Rheumatic Diseases* 81(7):951-961.

¹⁰ Morand EF, Abreu G, Furie R and Tummala R (2021). Attainment of the Lupus Low Disease Activity State in Response to Anifrolumab in 2 Phase 3 Trials [abstract no. 1459]. American College of Rheumatology Conference November 8 2021.

95% CI: 1.35, 2.30, $p < 0.001$). Patients treated with anifrolumab also had significantly more cumulative time ($p < 0.001$) and percentage of time ($p < 0.001$) spent in LLDAS compared to placebo. There was also a significant difference in the proportion of patients in LLDAS at Week 52 between the anifrolumab group compared to placebo (17.5% vs 10.6%, OR = 1.8, 95% CI: 1.2, 2.8, $p = 0.008$). Morand et al 2021 evaluated LLDAS as a potential treat-to-target endpoint for SLE clinical trials, given that attainment of LLDAS is a treatment goal of SLE. Based on EULAR/ACR 2019 guidelines the goal of treatment is remission (SLEDAI-2K=0) or low disease activity states based on a SLEDAI score ≤ 3 on antimalarials, or alternatively SLEDAI ≤ 4 , PGA ≤ 1 with glucocorticoids ≤ 7.5 mg of prednisone and well tolerated immunosuppressants.

Comparative harms

6.25 A summary of the key adverse events (AEs) across the included trials to Week 52 (TULIP-1, TULIP-2 and MUSE) and Week 216 (MUSE LTE and TULIP LTE) is presented in Table 7.

Table 7: Summary of key adverse events (AEs) across the included trials.

	Anifrolumab 300 mg n/N (%)	Placebo n/N (%)	RR (95%CI)	RD (95%CI)
TULIP-1				
Any AEs	161/180 (89.4)	144/184 (78.3)	1.14 (1.04, 1.25)	0.11 (0.04, 0.19)
SAE	25/180 (13.9)	30/184 (16.3)	0.85 (0.52, 1.39)	-0.02 (-0.10, 0.05)
Death due to AEs	1/180 (0.6) ^a	0	3.07 (0.13, 74.78)	0.01 (-0.01, 0.02)
Discontinuation of study drugs due to AEs	11/180 (6.1)	5/184 (2.7)	2.25 (0.80, 6.34)	0.03 (-0.01, 0.08)
AEs of interest	22/180 (12.2)	15/184 (8.2)	1.50 (0.80, 2.80)	0.04 (-0.02, 0.10)
Non-opportunistic serious infections	9/180 (5.0)	8/184 (4.3)	1.15 (0.45, 2.91)	0.01 (-0.04, 0.05)
Herpes Zoster	10/180 (5.6)	3/184 (1.6)	3.41 (0.95, 12.18)	0.04 (0.00, 0.08)
Infusion-related reaction	16/180 (8.9)	13/184 (7.1)	1.26 (0.62, 2.54)	0.02 (-0.04, 0.07)
TULIP-2				
Any AEs	159/180 (88.3)	153/182 (84.1)	1.06 (0.98, 1.16)	0.05 (-0.02, 0.12)
SAE	15/180 (8.3)	31/182 (17.0)	0.49 (0.28, 0.88)	-0.09 (-0.15, -0.02)
Death due to AEs	1/180 (0.6) ^b	0	3.07 (0.13, 74.78)	0.01 (-0.01, 0.02)
Discontinuation of study drugs due to AEs	5/180 (2.8)	13/182 (7.1)	0.39 (0.14, 1.08)	-0.04 (-0.09, 0.00)
AEs of interest	25/180 (13.9)	18/182 (9.9)	1.42 (0.80, 2.51)	0.04 (-0.03, 0.11)
Non-opportunistic infections	5/180 (2.8)	10/182 (5.5)	0.51 (0.18, 1.47)	-0.03 (-0.07, 0.00)
Herpes Zoster	13/180 (7.2)	2/182 (1.1)	6.64 (1.52, 29.03)	0.06 (0.02, 0.10)
Infusion-related reaction	25/180 (13.9)	14/182 (7.7)	1.83 (0.98, 3.40)	0.06 (-0.00, 0.13)
TULIP LTE (Weeks 52-216)				
Any AEs	226/257 (87.9)	94/112 (83.9)	1.05 (0.95, 1.15)	0.04 (-0.04, 0.12)
SAE	58/257 (22.6)	28/112 (25.0)	0.90 (0.61, 1.34)	-0.02 (-0.12, 0.07)
Death due to AEs	3/257 (1.2)	1/112 (0.9)	1.31 (0.14, 12.43)	0.00 (-0.02, 0.02)
Discontinuation of study drugs due to AEs	17/257 (6.6)	8/112 (7.1)	0.93 (0.41, 2.08)	-0.01 (-0.06, 0.05)
AEs of interest	75/257 (29.2)	24/112 (21.4)	1.36 (0.91, 2.04)	0.08 (-0.02, 0.17)
Non-opportunistic infections	25/257 (9.7)	9/112 (8.0)	1.21 (0.58, 2.51)	0.02 (-0.05, 0.08)
Herpes Zoster	23/257 (8.9)	7/112 (6.3)	1.43 (0.63, 3.24)	0.03 (-0.03, 0.08)
Major acute cardiovascular event	5/257 (1.9)	3/112 (2.7)	0.73 (0.18, 2.99)	-0.01 (-0.04, 0.03)
Infusion-related reaction	17/257 (6.6)	6/112 (5.4)	1.23 (0.50, 3.05)	0.01 (-0.04, 0.06)

	Anifrolumab 300 mg n/N (%)	Placebo n/N (%)	RR (95%CI)	RD (95%CI)
MUSE^c				
Any AEs	84/99 (84.8)	78/101 (77.2)	1.10 (0.96, 1.26)	0.08 (-0.03, 0.18)
SAE	16/99 (16.2)	19/101 (18.8)	0.86 (0.47, 1.57)	-0.03 (-0.13, 0.08)
Death due to AEs	0	0	-	-
Discontinuation of study drugs due to AEs	3/99 (3.0)	8/101 (7.9)	0.38 (0.10, 1.40)	-0.05 (-0.11, 0.01)
AEs of interest	10/99 (10.1)	12/101 (11.9)	0.85 (0.39, 1.88)	-0.02 (-0.10, 0.07)
Non-opportunistic infections	NR	NR	-	-
Herpes Zoster	5/99 (5.1) ^d	2/101 (2.0)	2.55 (0.51, 12.84)	0.03 (-0.02, 0.08)
Infusion-related reaction	2/99 (2.0)	6/101 (5.9)	0.34 (0.07, 1.64)	-0.04 (-0.09, 0.01)
MUSE LTE (Weeks 52-216)				
≥1 SAE	50/218 (22.9)	-	-	-
Death	1/218 (0.5)	-	-	-
Discontinuation of study drugs due to AEs	17/218 (7.8)	-	-	-
AEs of interest	24/218 (11.0)	-	-	-
Non-opportunistic infections	NR	NR	-	-
Herpes Zoster	11/218 (5.0)	-	-	-
Infusion-related reaction	4/218 (1.8)	-	-	-

Blue shading represents information previously considered by the PBAC.

Bold text designates statistical significance. *Italics* indicate results estimated during the evaluation using Review Manager (version 5.4.1).

Source: Tables 2.5-14 to 2.5-16, pp98-102 of the resubmission.

AE=adverse event; SAE=serious AE; RR=relative risk; RD=risk difference; NR=not reported; CI=confidence interval.

a Death due to pneumonia; patient received two doses of anifrolumab 300 mg.

b Death due to pneumonia.

c The safety population consisted of patients who received at least 1 dose of study drug. One patient randomized to the placebo group mistakenly received a single dose of anifrolumab 1000 mg and was included in anifrolumab 1000 mg group for the safety analyses.

d One patient also had transverse myelitis with a quantitatively positive test result for varicella-zoster virus in the cerebrospinal fluid.

6.26 The long-term safety data from TULIP LTE and MUSE LTE (from 52 weeks to approximately 4 years) was consistent with the included trials to 52 weeks, with no new safety signals. Long term safety data from TULIP LTE also demonstrated no significant difference between groups in the incidence of AEs, serious AEs, discontinuations due to AEs and AEs of special interest during the LTE treatment and follow-up to Week 216. However, the rates of serious AEs and non-opportunistic infections decreased over time and were lower during TULIP LTE than in the first year of treatment in the TULIP trials. In patients treated with anifrolumab there was also a reduction in the rates of herpes zoster over time during TULIP LTE. There were 3 deaths (1 due to COVID-19 and 2 to pneumonia) in the anifrolumab group and 1 death (from major acute cardiovascular event) in the placebo group during TULIP LTE.

Benefits/harms

6.27 The comparative benefits and harms for anifrolumab versus placebo (i.e. SOC alone) in patients with SLE can be drawn from Table 5, Table 6 and Table 7 above. On the basis of direct evidence presented in the submission, for every 100 patients treated with anifrolumab in comparison with placebo (SOC alone):

- Approximately 4 fewer patients to 26 additional patients will achieve SRI(4) response at Week 52 depending on the trial and analysis used.
- Approximately 10 to 28 additional patients will achieve BICLA response at Week 52 depending on the trial and analysis used.
- An approximate -0.9 and -1.5 change from baseline in mean SLEDAI-2K score at Week 52 and Week 216, respectively.
- Approximately 5 to 11 additional patients will experience any AEs at Week 52, and 4 additional patients will experience any AEs between Weeks 52-216.
- Approximately 2 to 9 fewer patients will experience SAEs at Week 52, and 2 fewer patients will experience SAEs between Weeks 52-216.
- Approximately 3 to 6 additional patients will experience herpes zoster at Week 52, and 3 additional patients will experience herpes zoster between Weeks 52-216.

The above statements are based on the total trial populations, whereas the resubmission has targeted a patient group that the PBAC previously considered to have the greatest clinical need and were most likely to respond.

Clinical claim

- 6.28 In patients with severe SLE (SLEDAI-2K ≥ 10) and on SOC (triple therapy), the resubmission maintained that anifrolumab added to SOC was superior in terms of effectiveness and non-inferior in terms of safety compared to SOC alone. The PSCR updated the safety claim to inferior compared to SOC alone.
- 6.29 At the July 2022 meeting, the PBAC considered the claim of superiority to SOC alone in terms of effectiveness was supported based on the small improvement in disease activity observed for some patients (paragraph 6.31, anifrolumab PSD, July 2022 PBAC meeting). The PBAC previously considered that a claim of inferior but manageable safety was reasonable (paragraph 7.7, anifrolumab PSD, July 2022 PBAC meeting).
- 6.30 While it was noted that anifrolumab has a clinical benefit over SOC, the PBAC had previously considered the magnitude of the benefit to the requested PBS population was uncertain (paragraphs 6.31 and 7.5, anifrolumab PSD, July 2022 PBAC meeting). The ESC noted that the resubmission presented additional clinical data up to 4 years (TULIP LTE), but the clinical benefit for anifrolumab in the requested PBS population remained uncertain. The ESC considered that although the sustained benefit of continued anifrolumab treatment for reductions in SLEDAI-2K and reduction in OCS dose to Week 216 in TULIP-LTE demonstrated some persistence of effect, the lack of measured benefits in mean change from baseline in SDI, flare rates or quality of life versus SOC alone despite the longer follow up were indicative of the uncertainty associated with determining clinical efficacy.
- 6.31 Consistent with its July 2022 consideration, the PBAC considered the claim of superiority to SOC alone in terms of effectiveness was supported based on

improvement in disease activity for some patients; however, the magnitude of benefit was modest and uncertain. The PBAC considered the claim of inferior safety to SOC alone was reasonable.

Economic analysis

- 6.32 The resubmission presented an updated stepped economic evaluation starting with a trial-based cost per responder analysis informed by TULIP 1 and 2 and then implemented a modelled cost-utility analysis using evidence from TULIP LTE, the Australian cohort of the Asia-Pacific Lupus Collaboration (APLC), the Australian Lupus Registry and Biobank (ALRB), and the John Hopkins Lupus cohort (JHLC). The type of economic evaluation was a patient level microsimulation with a 30-year time horizon.
- 6.33 The PBAC had previously expressed concern about the model and considered the ICER (\$55,000 to <\$75,000 per additional QALY gained) was highly uncertain and favourable to anifrolumab (paragraph 7.11, anifrolumab PSD, July 2022 PBAC meeting).
- 6.34 The PBAC's key concerns of the July 2022 economic evaluation (paragraphs 7.9, 7.10 anifrolumab PSD, July 2022 PBAC meeting) and how the resubmission addressed them are provided below:
- **Trial follow-up was short (52 weeks) relative to the model time horizon (30 years).** The resubmission included additional data from the TULIP LTE (with up to 4 years of follow up). This was still short compared to the 30-year time horizon of the model. Inclusion of the TULIP LTE data increased the ICER from \$55,000 to <\$75,000 per QALY gained in the July 2022 submission to \$95,000 to <\$115,000 per QALY gained.
 - **Lack of direct evidence on longer term clinical outcomes.** The PBAC considered there was a lack of direct evidence on organ damage and mortality and limited clinical evidence of the relationship between SLEDAI-2K and the long-term outcomes to which it contributed. The resubmission removed the effect of SLEDAI-2K on hospitalisation rates but maintained its effect on all other long term outcomes including organ damage. The resubmission also highlighted literature linking SLEDAI-2K to long term outcomes; however, it remained unclear whether SLEDAI-2K had been a sole contributor of these outcomes.
 - **Multicollinearity of regressors, appropriateness of model fit and the extrapolation of the regression coefficients across the time horizon and the high chance of double counting.** Not addressed in the resubmission. Similar regressions were used to estimate transition probabilities, utilities and resource use in the model. Some of the changes to the regressions resulted in very different outcomes compared to those presented in the July 2022 submission, e.g., average utility in the absence of organ damage was <0.3 when previously this was >0.8; however, these changes were not adequately discussed in the resubmission. The PSCR stated that there was no multicollinearity in the economic model as it did not rely on

matrix algebra operations for which multicollinearity impedes stable estimations and as the statistical models in the economic analysis did not demonstrate convergence issues (which would indicate multicollinearity). The ESC considered that appropriateness of model fit was not properly addressed in the resubmission, with models displaying considerable lack of fit being used in predictions. The ESC also considered that reverse causality, induced by using likelihood of flares to predict SLEDAI-2K scores and vice versa, was a more specific description of the continuing problems with the regression models used.

- **Plausibility of the model's results: Survival.** The PBAC previously noted there was a 10% difference in survival between the arms at Year 30 despite fewer than 10% of patients still being on treatment at Year 15. ESC considered that it was also not clinically plausible for incremental survival in the anifrolumab arm to be increasing toward the end of the modelled time horizon (paragraph 6.46, anifrolumab PSD, July 2022 PBAC meeting). This was partially addressed in the resubmission. There remained a 7% difference in survival at Year 30, with 10% patients on anifrolumab at Year 15. Furthermore, incremental survival in the anifrolumab arm continued to increase towards the end of the time horizon (though it mostly stabilised from Year 20). Incremental survival was no longer a key driver of the model results.
- **Longer term benefit for non-responders.** The PBAC considered that some outputs of the economic model did not appear to be clinically plausible including long term benefits for non-responders, and that some linear regressions inappropriately fell below 0. The resubmission addressed this by restricting linear regressions from falling below 0 and removing long-term benefits for non-responders. Limiting the linear regressions increased the July 2022 submission ICER by 1.4%; however, removing the long-term benefit for non-responders in the flare rates increased the ICER from \$55,000 to < \$75,000 in the July 2022 submission to \$115,000 to < \$135,000 per QALY gained.
- **Modelled SLEDAI-2K.** The PBAC was concerned that compared with data from the ALRB, the model appeared to overestimate the adjusted mean SLEDAI-2K for patients receiving only SOC. The resubmission appropriately stated that Figure 6 of the July 2022 PSD did not adequately adjust for mortality, resulting in inflated SLEDAI-2K scores. The resubmission instead compared: i) modelled SLEDAI-2K to TULIP LTE data and ii) modelled adjusted mean SLEDAI-2K to APLC Australian cohort, which appeared closer to the modelled estimates for the SOC arm. However, ALRB data were still included in the model and the modelled SOC arm consistently exceeded SLEDAI-2K reported from the ALRB.
- **Large impact of flares on ICER.** The PBAC noted that small changes in flare duration had very large impacts on the ICER, which may not have been plausible. Further, the PBAC considered that flare duration (3.9 months) was likely overestimated in the model. Flare duration was amended to be based on APLC data, increasing flare duration to 5.3 months for non-severe flares and reducing it to 2.5 months for

severe flares. The resubmission also updated the change in SLEDAI-2K resulting from flares to reflect the APLC data (non-severe flares resulted in an increase to the SLEDAI-2K score of 4.3 points as compared to an increase of 3 points in July 2022 and an increase of 9.7 for severe flares as compared to an increase of 7 in July 2022). The inclusion of the APLC data reduced the July 2022 base case from \$55,000 to < \$75,000 to \$5,000 to < \$15,000 per QALY gained. The ICER remained very sensitive to changes in flare duration.

- **Price reduction required.** The PBAC considered a price reduction would be required to achieve acceptable cost effectiveness. The resubmission reduced the effective DPMQ of anifrolumab to \$|, from \$| in the July 2022 submission and \$| in the pre-PBAC response. The July 2022 base case ICER \$55,000 to < \$75,000 per QALY (based on anifrolumab price of \$|) decreased to \$35,000 to < \$45,000 per QALY gained with the effective DPMQ of \$|.

6.35 A summary of the key components of the economic evaluation is presented in Table 8. The structure of the model was unchanged from the July 2022 submission.

Table 8: Key components of the economic evaluation

Component	July 2022 submission	Resubmission Justification/comments
Type of analysis	Cost-utility	Unchanged. Appropriate.
Outcomes	Quality adjusted life years (QALYs)	Unchanged. While QALYs were a reasonable outcome, organ damage, adverse events avoided or reduction in OCS use would also have been informative.
Time horizon	30 years in the model base case vs. 52 weeks in the TULIP trials.	Added data from TULIP LTE (total 4 years of follow up). Remained short relative to the 30-year time horizon of the model.
Methods used to generate results	Individual patient microsimulation.	Unchanged. The approach may not be reasonable due to how it was implemented, including that: summary level data were used to model each patient (rather than individual patient data based on the trials, in particular, SOC patients were modelled as an average of responders and non-responders), many model inputs were treated independently, and parameter uncertainty was not captured for many inputs since most treatment effect inputs were modelled using uniform distributions assuming a constant value.
Health states	- Anifrolumab arm: alive on treatment, alive off treatment, dead. - SOC arm: alive, dead. Each cycle patients could also experience events such as flares, organ damage, OCS use, and change in SLEDAI-2K. Some events were associated with ongoing costs and disutilities, effectively making these a different health state.	Unchanged. Health states and events were reasonable, but allocation, particularly to events appeared circular (see Transition Probabilities below). Response in the economic model was equivalent to a 4-point reduction in SLEDAI-2K by Week 24 and anifrolumab non-responders discontinued treatment beyond this point. Patients who discontinued anifrolumab treatment after Week 24 (for any given reason) were referred to as non-responders in the model.
Cycle length	6 months.	Unchanged. Appropriate. However, it was unclear if some transition probabilities were adjusted correctly for cycle length- the model referred to "annual rates" and "during current year" regressions which were implemented per 6 monthly cycles.
Transition	- Treatment discontinuation rates	- TULIP LTE data was used instead of MUSE LTE data for

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Component	July 2022 submission	Resubmission Justification/comments
probabilities	<p>from the TULIP trials and MUSE LTE.</p> <ul style="list-style-type: none"> - Mortality rates derived from survival model based on JHLC adjusted by standardised mortality ratios for SLE patients. - Cycle dependent event regression models based on evidence from the TULIP-1 and 2 trials and JHLC. 	<p>discontinuations from Cycle 3.</p> <ul style="list-style-type: none"> - Mortality rates were unchanged. - Cycle dependent event regression models based on evidence from the TULIP trials (including TULIP LTE) and JHLC. <p>QALYs, SLEDAI-2K and OCS use were restricted to not fall below 0.</p> <p>Mortality and event probabilities were dependent on patient characteristics and other events, resulting in circular estimates: e.g., SLEDAI-2K was an input for risk of flares and flares were an input for change in SLEDAI-2K and both were inputs for steroid use.</p> <p>Choice of regression may also not adequately capture events. For example, change in SLEDAI-2K was modelled as linear regression, resulting in SLEDAI-2K estimates that could be non-integer and assumed change in SLEDAI-2K was constant across the scale (e.g. a reduction from score 6 to 2 was the same as a reduction from 13 to 9).</p>
Software package	Excel 2010 with @RISK.	Unchanged. Appropriate, though @RISK was not utilised as expected: the distributions of the regression models were not included in the simulations.

Blue shading represents information previously considered by the PBAC.

Source: Table 3.1-1, pp107-108 of the July 2022 submission, Table 3.1-1, pp146 of the resubmission

ICER = incremental cost-effectiveness ratio, JHLC=John Hopkins Lupus cohort, OCS = oral corticosteroids, QALYs = quality adjusted life years, SLEDAI-2K= Systemic Lupus Erythematosus Disease Activity Index 2000, SOC = standard of care

6.36 The model mechanics were unchanged from the July 2022 submission. At the beginning of the simulations, a set of baseline patient characteristics were sampled for each patient, including response to treatment based on pooled TULIP-1 and TULIP-2 data for the SLEDAI-2K ≥ 10 subgroup. The ESC noted that although the TULIP-1 and -2 SLEDAI-2K ≥ 10 subgroup population was not representative of the requested population, as the proposed PBS restriction also requires patients to be on triple therapy and an OCS dose ≥ 7.5 mg/day, the ESC recalled that the PBAC had previously considered that, based on subgroup analyses presented, there were no concerns regarding potentially lower efficacy in the proposed PBS population (paragraph 7.8, anifrolumab PSD, July 2022 PBAC meeting). The ESC did note however, that compared to ALRB data, patients with a SLEDAI-2K ≥ 10 in the TULIP trials were older (mean age of 40 years compared to 34.5 years in the ALRB data) and with less baseline organ damage (38.6% compared to 61.3% in the ALRB data).

6.37 Patients who did not respond to treatment at Week 24 discontinued from anifrolumab at the end of the first cycle. Events each cycle were based on predictive models of disease progression, with each element informed by disease history. Predictive models for clinical outcomes (flares, change in SLEDAI-2K and OCS dose) were based on pooled TULIP-1 and -2 data and TULIP LTE, with flare duration and impact on SLEDAI-2K for SOC based on the APLC Australian data. Predictive models for longer-term outcomes (mortality and organ damage) were based on data from the John Hopkins Lupus Cohort (JHLC) registry and organ damage frequency was based on data from the ALRB, these were unchanged from the July 2022 submission. Direct data from JHLC registry was not used to inform organ damage or mortality. Instead, previously estimated regressions for organ damage by system and overall mortality based on the

JHLC were taken from NICE TA397¹¹, though the details of the regressions and covariates chosen were not detailed.

- 6.38 Many of the regression models continued to result in circular estimations/reverse causality and had the potential for double counting, particularly flares and SLEDAI-2K scores (i.e. SLEDAI-2K affected the likelihood of flares and flares affected the change in SLEDAI-2K, so each had acted as both predictor and outcome). The PSCR stated that the relationship between disease activity and model outcomes was reasonable and that the inclusion of both SLEDAI-2K scores and flares was justified because high disease activity can be episodic in the form of flares or patients can experience persistently active disease. The PSCR stated that SLEDAI-2K is a significant predictor of flare rates in the TULIP trials and the published literature and, thus, the model reflects the best available evidence that flare rates do increase with SLEDAI-2K. The ESC remained concerned that reverse causality was present as a result of using the likelihood of flares and SLEDAI-2K scores to predict one another, as well as other outcomes, and that regression analyses potentially double counted the treatment effect, adding additional uncertainty to the modelled outcomes.
- 6.39 The resubmission identified literature relating to SLEDAI-2K and long-term outcomes, but direct evidence from TULIP LTE did not demonstrate a difference in mortality or organ damage across the two treatment arms by end of the 4 year follow up, despite identifying a modest difference in SLEDAI-2K. SLEDAI-2K scores were used to estimate flares, OCS use, organ damage, and mortality, which remained unchanged from the July 2022 submission. In the consideration of belimumab for SLE, the PBAC noted while it was clinically plausible to expect a benefit in organ damage with belimumab (and consequently reduction in mortality), the magnitude of the effect was uncertain. The PBAC noted reasons for the uncertainty included the lack of statistically significant differences for most measures of organ damage progression in the clinical trials (but acknowledged the short duration of the studies and that the studies were not powered for this outcome) and uncertain reliability, applicability and external validity of estimates derived from secondary data sources (paragraphs 7.5 and 7.7, Belimumab PSD, July 2020 PBAC meeting).
- 6.40 The resubmission provided more justifications for the choice of regression models, but the covariates were often not well justified, and much of the underlying data and methodology could not be verified.
- 6.41 Operational errors and spurious regression outcomes identified in the July 2022 submission were corrected in this resubmission, including restricting linear regressions from falling below 0, correcting OCS cost calculations to use cycle length

¹¹ National Institute for Health and Care Excellence. Belimumab for treating active autoantibody-positive systemic lupus erythematosus Appraisal Consultation Document. Technology appraisal guidance [TA397]. July 2013.

rather than year, and removing the long-term reduction in flares for anifrolumab non-responders. However, the ESC noted that the resubmission again did not appear to have checked the regressions for consistency or clinical plausibility. For example, OCS dose was predicted to be higher in the anifrolumab arm than the SOC arm from Year 4, which was inconsistent with the modelled reduction in SLEDAI-2K and flare, and contradicted the TULIP LTE data which demonstrated a reduction in OCS for anifrolumab patients versus SOC. Utility regressions also resulted in low quality of life in the absence of organ damage (average utility <0.3) and patients could have a utility of 0 many times in their simulated life (see Figure 3). In comparison, utility in the TULIP LTE was ~0.7 at Year 4 compared to ~0.4 predicted by the model.

6.42 Duration of flares and impact of flares on SLEDAI-2K scores were updated in the resubmission based on Australian patient data collected from the APLC. Details are provided in the following table. The duration of flares in the APLC data remained highly uncertain (they ranged from 1 month to 1 year). It was noted that a flare was not considered resolved in the APLC data unless the SLEDAI-2K had decreased by at least 4 points, though the resubmission stated that flare resolution may depend upon the organ system involved and that “the literature around an ‘end’ of a flare is not clear”. For patients with mild to moderate flares on the APLC (defined as an increase in SLEDAI-2K of 3-6 points) their SLEDAI-2K score needed to return to almost pre-flare or better to be considered resolved. This may explain why non-severe flares took considerably longer than severe flares (SLEDAI-2K increase of at least 7) to resolve.

Table 9: Flare duration and impact upon SLEDAI-2K

	Non-severe		Severe		Source
	Anifrolumab	SOC ^a	Anifrolumab	SOC ^a	
Effect on SLEDAI-2K per flare^b					
July 2022	+3		+7		Minimum definition
Resubmission	+4.3 ^c *		+9.7 ^d *		Mean APLC-AU*
Flare duration					
July 2022	2.2 months ^h	3.9 months	2.2 months ^h	3.9 months	Nikpour 2009, Anifrolumab HR Morand 2021
Resubmission ^e	3.0 months ^h *	5.3 months ^f *	1.4 months ^h *	2.5 months ^g *	Median APLC-AU, Anifrolumab HR Morand 2021*
Effect on SLEDAI-2K per flare per cycle from Cycle 3ⁱ = effect on SLEDAI-2K per flare x flare duration / 6 months					
July 2022	+1.11	+1.95	+2.59	+4.55	As modelled
Resubmission	+2.16	+3.80	+2.33	+4.09	As modelled

Blue shading represents information previously considered by the PBAC.

Source: compiled during the evaluation

APLC-AU= Asia Pacific Lupus Collaboration- Australian subgroup, SOC=standard of care, HR=hazard ratio

a including patients who discontinued anifrolumab

b Mild/moderate flare definition SLEDAI-2K increase 3-6 points, severe flare definition SLEDAI-2K increase at least 7 points

c Standard deviation 0.9

d Standard deviation 3.0

e Flare resolved if SLEDAI-2K reduced by at least 4 points

f IQR 2.8 to 11.5 months

g IQR 1.1 to 5.3 months

h SOC/1.76 based on HR 1.76 (95%CI 1.35, 2.30) from Morand et al. 2021

i Cycles 1 and 2 used regression coefficients to estimate flare impact upon SLEDAI-2K

* Note that the results presented in Table 9 are derived from ad-hoc/post-hoc analyses conducted by the applicant to input into the economic model specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the APLC. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.43 Flare duration was used to estimate the change in SLEDAI-2K from Cycle 3 (after Year 1). The increase in SLEDAI-2K as a result of flares was also updated for the resubmission based on APLC data (see Table 9). The effect of non-severe flares on SLEDAI-2K score per cycle was greatly increased compared to the July 2022 submission, primarily a result of the longer flare duration. Each non-severe flare had a similar effect on the SLEDAI-2K score as a severe flare per model cycle, which may not be clinically plausible.
- 6.44 The duration of flares did not directly affect OCS use, resource use or utility, which did not appear appropriate. It may also not be reasonable to assume the same hazard ratio for anifrolumab versus SOC in reduction of flare duration for both non-severe and severe flares.
- 6.45 The ESC noted that the changes to flare duration and impact of flares on SLEDAI-2K were key drivers in the model and greatly favoured anifrolumab. If duration and effect on SLEDAI-2K were returned to the July 2022 submission inputs (all other changes kept), the ICER increased to \$115,000 to < \$135,000 per QALY gained, compared to \$75,000 to < \$95,000 in the base case. The PSCR stated that anifrolumab resulted in a significant decrease in flare rates and a significantly faster return to low disease activity and, that as these were the main treatment effects modelled in the economic analysis, then it was reasonable that the ICER was sensitive to changes in these outcomes.
- 6.46 Organ damage incidence was unchanged from the July 2022 submission but was a key driver of the incremental costs in the resubmission. The model used parametric survival distributions to estimate organ damage each cycle, based on data from the JHLC, the coefficients and distribution of organ damage types based on ALRB. The PSCR stated that as the 4 years of follow-up in TULIP LTE was insufficient to capture organ damage rates JHLC data, which followed patients for over 20 years, was used. The ESC noted that several concerns with the organ damage modelling remained unaddressed by the resubmission:
- The time horizon of the JHLC data in NICE TA397 was not described, and therefore it was unclear if organ damage estimates had been adjusted to 6-month cycles. The JHLC demographics also differed from the Australian population, e.g., regressions of the JHLC population were derived from a population that was majority Caucasian with approximately 40% of Black African Ancestry (Hill et al. 2021¹²), compared to majority Asian (44%) in the APLC Australian HDAS subgroup, with 38.7% Caucasian.

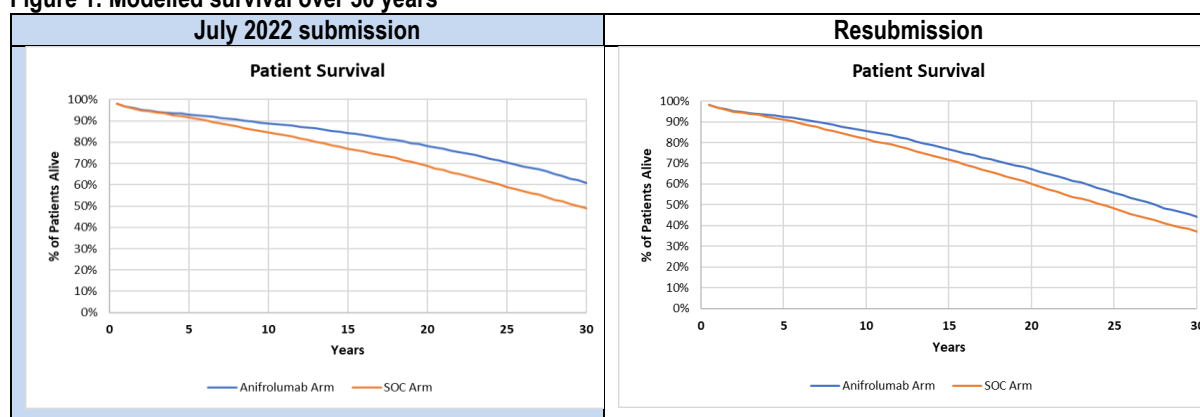
¹² Hill DD, Eudy AM, Egger PJ, et al. Impact of systemic lupus erythematosus disease activity, hydroxychloroquine and NSAID on the risk of subsequent organ system damage and death: analysis in a single US medical centre. *Lupus Science & Medicine* 2021;8:e000446. doi:10.1136/lupus-2020-000446

- Organ damage regression models were not dependent on existing organ damage within a particular system and very few were dependent upon damage in other systems or prior SDI score. In particular, patient history of specific organ damage was not modelled at baseline which did not seem clinically reasonable. The PSCR stated that the JHLC data showed cumulative disease activity was predictive of damage in most of the organ systems evaluated in the SDI.
- OCS use and SLEDAI-2K were included in several of the regressions, therefore any uncertainty in these estimates would be exaggerated in the organ damage estimates.

6.47 As noted in the Comparative effectiveness section, no difference in SDI score was identified between the anifrolumab and placebo arms of the TULIP LTE after a maximum of 4 years of follow up.

6.48 Figure 1 presents the modelled survival in the base case. The anifrolumab arm resulted in greater survival compared to SOC, and this survival benefit appeared to increase over the time horizon (at Year 5 survival was similar between the arms, compared to a 7% difference at Year 30). Unlike the 2022 submission, the ICER was not sensitive to mortality assumptions in the resubmission.

Figure 1: Modelled survival over 30 years



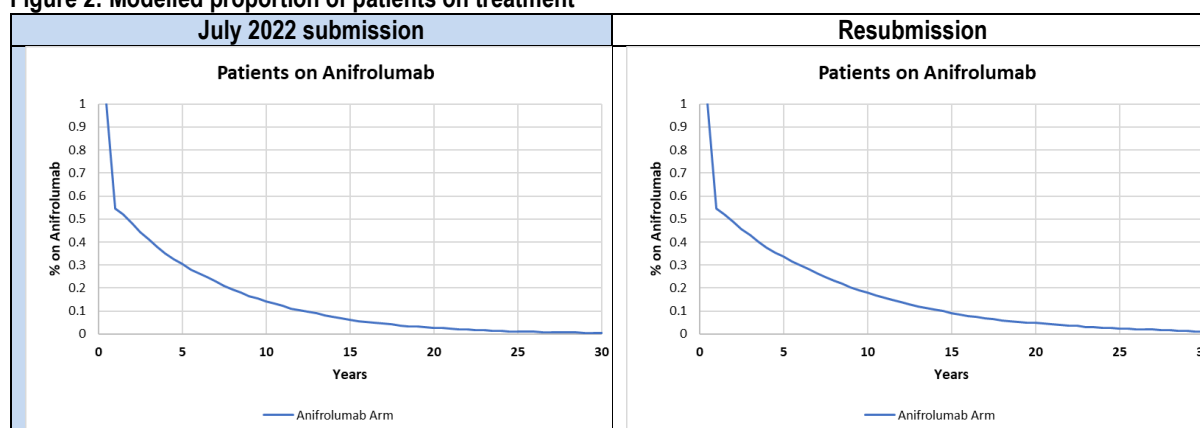
Blue shading indicates data previously seen by the PBAC

Source: Figure 3.7-8 of the July 2022 submission, Figure 3.7-8 of the resubmission

SOC=standard of care

6.49 Anifrolumab treatment discontinuation was estimated as 44.6% and 7.6% in Cycles 1 and 2 respectively, based on pooled TULIP 1 and 2 SLEDAI-2K ≥ 10 subgroup results at Weeks 24 and 52 unchanged from the July 2022 submission, and 6% from Cycle 3 onwards based on TULIP LTE (as compared to 7.2% from MUSE LTE in July 2022 submission). No discontinuation was assumed for SOC therapy (aside from adjustment of OCS use over time). As shown in Figure 2, the constant discontinuation of anifrolumab resulted in 10% of patients still on treatment at Year 15, although benefits persisted to Year 30.

Figure 2: Modelled proportion of patients on treatment



Blue shading indicates data previously seen by the PBAC

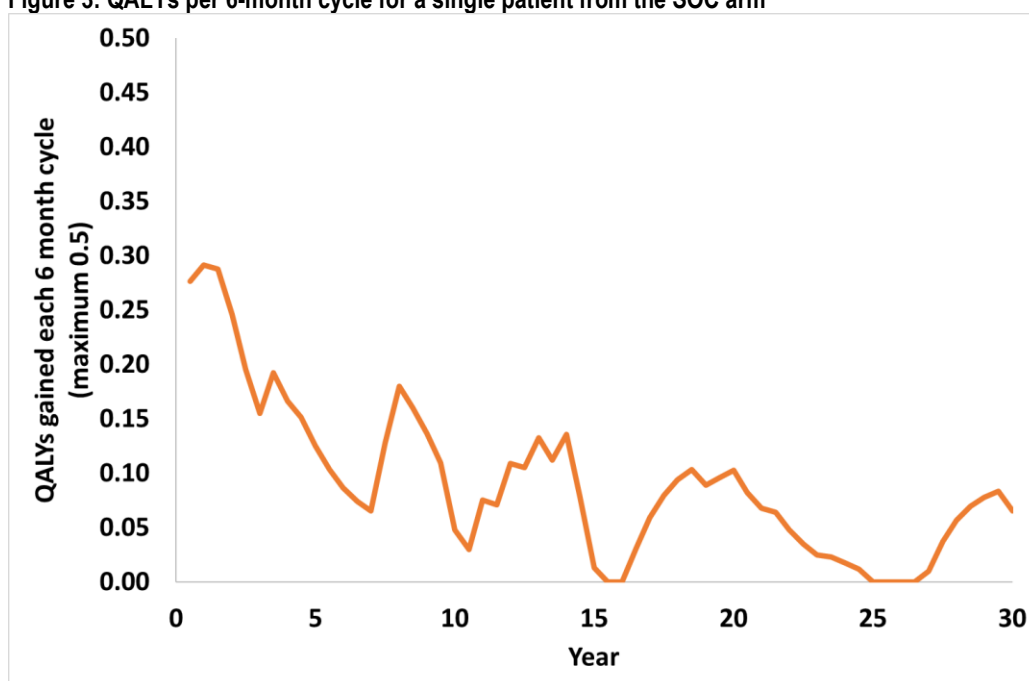
Source: Figure 3.7-1 of the July 2022 submission and Sheet 'Summary' of the Excel workbook 'CE model_anifrolumab_SLE_Nov2022.xlsm' resubmission.

Figure 3.7-1 of the resubmission did not appear to have been updated and was identical to the July 2022 submission

- 6.50 The submission estimated utilities each cycle based on a linear regression of patient characteristics and response to treatment from the pooled ITT data from the TULIP trials and TULIP LTE. This was reasonable as utilities predicted from patients with SLEDAI-2K ≥ 10 would likely not be representative of patients with a lower score (which patients in the model were likely to move to). However, this resulted in the utility estimates being inconsistent with the transition probability estimates.
- 6.51 The resubmission corrected an error in the July 2022 submission where the coefficient for $\log(\text{age})$ was omitted from the utility estimates. Unlike the transition probabilities where the same covariates were chosen for the pooled TULIP 1 and 2 analysis and the TULIP LTE analysis, different covariates were chosen for Cycle 3 onwards. It was unclear if a consistent approach to choosing covariates had been conducted across the regression analyses presented in the model, and therefore it was unclear whether this was appropriate. Organ damage disutility was derived separately and unchanged from the July 2022 submission.
- 6.52 In comparison to the July 2022 submission where utilities in the absence of organ damage were high (average >0.87 across the time horizon), utilities in the absence of organ damage in the resubmission were low (average 0.281 for the anifrolumab arm, 0.252 for the SOC arm across the time horizon), but the difference in mean utility across arms was larger than the July 2022 submission (0.030 versus 0.001). The resubmission did not validate the utilities with external data or with the TULIP LTE data, and the modelled mean utility did not appear to reflect the TULIP LTE utility estimates of 0.614-0.615 at baseline, increasing at the end of 4 years of follow-up by 0.088 in the anifrolumab arm and 0.017 in the SOC arm (p116, TULIP LTE CSR). In comparison, average utility in the absence of organ damage decreased from baseline and was predicted to be 0.401 in the anifrolumab arm and 0.316 in the SOC arm at 4 years. Example QALYs per cycle over the time horizon for a single SOC patient are presented in Figure 3 and demonstrate that patients could have very low quality of

life, even 0, for multiple cycles of the model. The PSCR stated that TULIP LTE provided the best available quality of life data. The PSCR noted that although the TULIP LTE and TULIP 1 and 2 datasets underwent the same mapping and model selection processes, the TULIP LTE utilities were derived from using the EQ-5D-3L questionnaire, whereas the TULIP 1 and 2 utilities were derived using the EQ-5D-5L questionnaire. The ESC noted that the PSCR did not address the concern that patients could have zero utility in multiple cycles (see Figure 3) and did not adequately justify why the utility was estimated to be significantly lower than predicted in July 2022, particularly considering the utility at Year 4 for patients in TULIP LTE was approximately 0.7.

Figure 3: QALYs per 6-month cycle for a single patient from the SOC arm



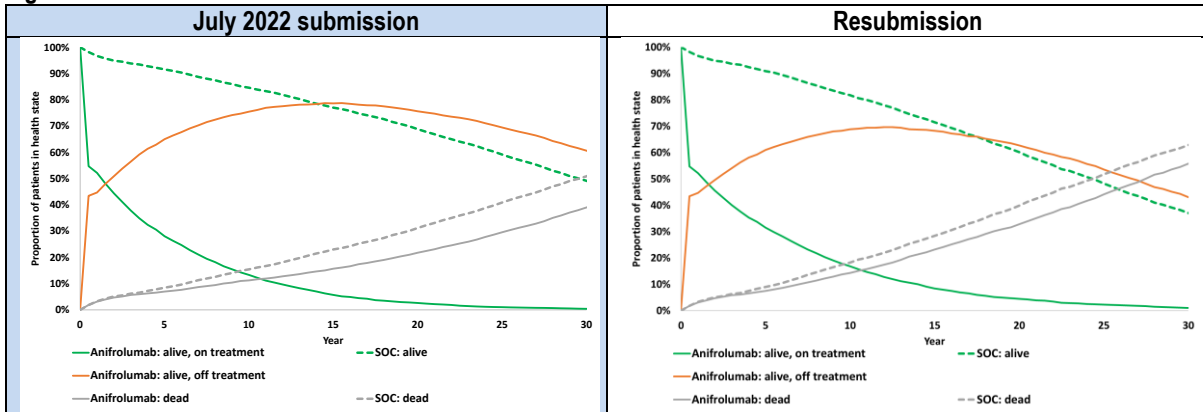
Source: compiled during the evaluation.

QALY=quality adjusted life year, SOC=standard of care

As each cycle length=0.5 years, there is a maximum of 0.5 QALYs per cycle (i.e. full health utility =1 x 0.5LYs = 0.5 QALYs)

6.53 The resubmission did not present health state allocation plots. The figure below was constructed during the evaluation. In the anifrolumab arm, the majority of patients were alive and off-treatment by Year 2. The health state allocation plots demonstrate the reduced survival compared to July 2022 submission in both arms, plus the reduced survival benefit of anifrolumab over SOC and the slight increase in time on treatment for anifrolumab.

Figure 4: Health state allocation in the economic evaluation



Blue shading indicates data previously seen by the PBAC

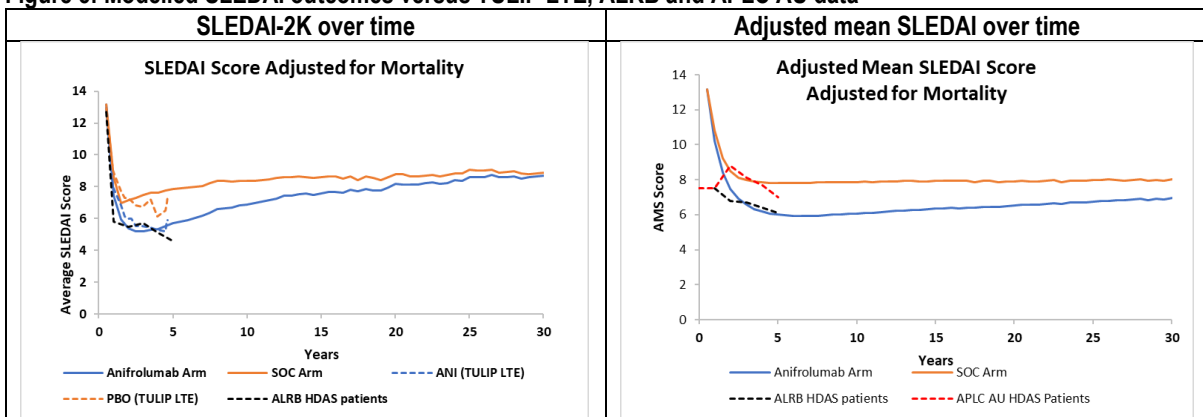
Source: compiled during the evaluation

Anifrolumab = anifrolumab arm; SOC = standard of care arm

On and off treatment only refers to whether patients were receiving anifrolumab. Patients in the anifrolumab arm received treatment with SOC for the entirety of the modelled time horizon.

6.54 The resubmission also compared the modelled SLEDAI-2K to the TULIP LTE (reproduced below), along with the SLEDAI-2K score from ALRB data. A further comparison is presented of the modelled adjusted mean SLEDAI versus ALRB and APLC data. Adjusted mean SLEDAI was calculated as the average SLEDAI-2K score from baseline to each cycle. In the presented figures it was further adjusted for mortality. Generally, the modelled SOC SLEDAI-2K scores and adjusted mean SLEDAI-2K were overestimated compared to the TULIP LTE data and the ALRB data, though the APLC data was similar to modelled estimates. The difference between the ALRB and APLC also demonstrated that even amongst similar patients from the same country there may be heterogeneity in disease activity. Modelled SLEDAI-2K for the anifrolumab arm was similar to the TULIP LTE data, but the TULIP LTE data for the anifrolumab arm did not appear to include patients who discontinued anifrolumab.

Figure 5: Modelled SLEDAI outcomes versus TULIP LTE, ALRB and APLC AU data



Source: Compiled from Sheet 'Summary' of the Excel workbook 'CE model_anifrolumab_SLE_Nov2022.xlsx'

ALRB = Australian Lupus Registry and Biobank; ANI = anifrolumab; APLC = Asia-Pacific Lupus; AU=Australian; LTE=long term extension; HDAS = high disease activity score; SOC = standard of care, SLEDAI-2K= Systemic Lupus Erythematosus Disease Activity Index 2000

6.55 Despite potentially overestimating the SLEDAI-2K score in the SOC arm, the model appeared to underestimate the SDI score compared to ALRB data. This suggested that

the model predictions did not fully reflect the relationship between SLEDAI-2K and organ damage that might be expected in the Australian population. Change in SDI score reported from the TULIP LTE was identical across arms at Year 4, and it appeared that the arms of the model did not begin to diverge until after this point.

6.56 The key drivers of the model are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: \$ ¹ /QALY gained.
Flare duration	5.3 months for non-severe and 2.5 months for severe flares in the SOC arm and anifrolumab non-responders. HR of 1.76 applied for anifrolumab responders.	High, favoured anifrolumab. If flare duration was reduced to the lower bound of the IQR from the APLC data (2.8 months non-severe, 1.1 months severe) in the SOC arm, the ICER increased to \$ ² /QALY gained.
SLEDAI-2K estimates	Change in SLEDAI-2K was estimated each cycle through linear regressions, with covariates for treatment effect, previous SLEDAI-2K score, TULIP-2 indicator and flares. SLEDAI-2K estimates contributed to estimates of flares (circular calculation), OCS, organ damage, mortality, utility, and medical resource utilisation (excluding hospitalisations). As many of these estimates were correlated there was a high likelihood of double counting the effect of SLEDAI-2K.	High, favoured anifrolumab. If SLEDAI-2K was assumed to be equal across the arms, the ICER increased to \$ ³ /QALY gained. However, the anifrolumab arm accrued fewer life years than the SOC arm in this analysis, a result of life years accruing more QALYs in the anifrolumab arm than in the SOC arm. If the effect of flares on SLEDAI-2K (+4.3 for non-severe, +9.7 for severe in the base case) was returned to those assumed in the July 2022 submission (+3 for non-severe, +7 for severe), the ICER increased to \$ ⁴ /QALY gained.
Extrapolation of treatment effect	Treatment effect was included in regressions for flares, SLEDAI-2K, OCS use and utility and the effects were assumed to be constant from Cycle 3 onwards.	High, favoured anifrolumab. If treatment effect was assumed to converge from Year 5, the ICER increased to \$ ⁵ /QALY gained.
Utility	Linear regressions for utility (excluding organ damage disutility) included covariates for treatment effect, SLEDAI-2K, TULIP-2 indicator and patient characteristics.	High, favoured anifrolumab. If no mortality benefit (i.e. 0 incremental LYG) was assumed for anifrolumab, the incremental discounted QALYs were still 0.537 vs 0.664 in the base case, and the ICER increased only slightly to \$ ¹ /QALY gained.
Organ damage incidence	Regressions for organ damage incidence taken from published estimates based on JHLC and several included covariates such as AMS, OCS use and patient characteristics.	Moderate, favoured anifrolumab. If AMS coefficients were set to 0 (affecting 9 out of 12 organ system regressions), the ICER increased to \$ ¹ /QALY gained.

Source: compiled during the evaluation

AMS=adjusted mean SLEDAI; ICER=incremental cost-effectiveness ratio; OCS=oral corticosteroids; LOS=length of stay; QALY=quality adjusted life year; SLE=Systemic Lupus Erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SOC=standard of care, HR=hazard ratio

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$135,000 to < \$155,000

³ \$255,000 to < \$355,000

⁴ \$115,000 to < \$135,000

⁵ \$95,000 to < \$115,000

6.57 Table 11 summarises the stepped economic evaluation. The base case ICER was \$75,000 to < \$95,000 per QALY gained compared to \$55,000 to < \$75,000 per QALY gained once the OCS costs were corrected in the July 2022 submission. An additional step was included in the resubmission to consider the cost per QALY at 4 years (i.e. to the end of the TULIP LTE data). For completeness, cost per life year gained for Steps 3

to 5 were calculated during the evaluation. The results showed significantly higher quality of life benefits than survival with anifrolumab versus SOC in the first 4 years of treatment, with the majority of the survival benefits predicted to occur after 4 years (i.e., beyond available clinical data).

Table 11: Results of the stepped economic evaluation

Step and component	July 2022 submission			March 2023 Resubmission		
	Anifrolumab arm	SOC arm	Increment	Anifrolumab arm	SOC arm	Increment
Step 1: Cost per responder at 24 weeks, no discounting						
Costs (at 6 months) (\$)		\$0			\$0	
Responders ^a	55.4%	47.4%	8.0%	55.4%	47.4%	8.0%
Incremental cost/extra responder			1			2
Step 2: Cost per QALY at 1 year, anifrolumab costs, no discounting						
Costs (\$)		\$0			\$0	
QALYs gained	0.818	0.785	0.033	0.597	0.564	0.033
Incremental cost/extra QALY gained			3			6
Step 3: ICER at 1 year, all costs, no discounting						
Costs ^{b,c} (\$)		\$5,530			\$3,907	
LYG	-	-	-	0.983	0.983	0.0003
Incremental cost/LYG			-			7
QALYs gained	0.818	0.785	0.033	0.597	0.564	0.033
Incremental cost/extra QALY gained			3			6
Step 4: ICER at 4 years, all costs, 5% discounting for costs and benefits						
Costs ^{b,c} (\$)	-	-	-		\$15,103 ^d	
LYG	-	-	-	3.474	3.463	0.011
Incremental cost/LYG			-			7
QALYs gained	-	-	-	1.694	1.481	0.213
Incremental cost/extra QALY gained			-			1
Step 5: ICER at 30 years, 5% discounting for costs and benefits (base case)						
Costs ^c (\$)		\$98,456			\$90,363	
LYG	13.491	12.721	0.770	12.667	12.082	0.585
Incremental cost/LYG			4			4
QALYs gained	10.219	9.375	0.844	3.853	3.189	0.664
Incremental cost/extra QALY gained (base case)			5			4

Blue shading indicates data previously seen by the PBAC

Source: Table 3.8-1 of the submission, Table 3.8-1 of the resubmission and compiled during the evaluation. LYG have been included in Steps 3-5.

ICER=incremental cost-effectiveness ratio, QALY- quality adjusted life year, LYG=life-years gained, SOC=standard of care

^a Responders were hard coded into the model based on trial results. Response in the SOC arm was not modelled. Costs were based on 6 month estimates in the model.

^b Step 3 costs were incorrectly hardcoded in the July 2022 model, and were corrected during the evaluation

^c OCS costs corrected from those reported in Table 3.8-1 of the July 2022 submission

^d SOC costs were reported at 1 year in the resubmission, corrected to 4 years here.

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$95,000 to < \$115,000

³ \$455,000 to < \$555,000

⁴ \$75,000 to < \$95,000

⁵ \$55,000 to < \$75,000

⁶ \$355,000 to < \$455,000

⁷ > \$1,055,000

- 6.58 While low utility affected both arms similarly, (undiscounted incremental QALYs gained were similar to the undiscounted incremental life years gained (1.03 versus 1.45)), when survival was assumed the same in both arms (i.e. incremental life years gained were 0) the undiscounted incremental QALY gained was still 0.76, demonstrating that utilities were a key driver of the results, compared to the July 2022 submission where survival difference was the key driver. Absolute QALYs in each arm were greatly reduced compared to the July 2022 submission (e.g. anifrolumab arm was expected to accrue 18 undiscounted QALYs in the July 2022 submission, but only 5.8 in the resubmission).
- 6.59 The resubmission also presented the SDI organ damage scores, with an expected reduction of 0.31 in the anifrolumab arm versus the SOC arm (slightly larger than the 0.21 reduction estimated in the July 2022 submission). No SDI benefit was observed in the TULIP LTE (see Comparative effectiveness).
- 6.60 Undiscounted and unadjusted for mortality, the resubmission estimated that the anifrolumab arm would experience 0.61 fewer non-severe flares and 1.78 fewer severe flares than the SOC arm, compared to 7.78 fewer non-severe flares and 4.62 fewer severe flares in the July 2022 submission. The annual non-severe flare rates estimated in the first 4 years of the model (adjusted for survival) were 1.46 in the anifrolumab arm and 1.69 in the SOC arm, compared to 0.1 and 0.2 based on the observed data in the TULIP LTE. Similarly, no severe flares were observed in the TULIP LTE, but 2.12 and 2.98 were estimated in the first 4 years of the model (adjusted for survival) for the anifrolumab and SOC arms respectively.
- 6.61 In the previous belimumab submission (Table 14, belimumab PSD, July 2020 PBAC meeting) discounted LYs were estimated as 15.60 for belimumab, 15.39 for SOC (0.20 incremental LYG) and discounted QALYs were estimated as 10.49 in the belimumab arm and 9.95 in the SOC arm (0.54 incremental QALYs gained) were accrued across a 60-year time horizon. The PBAC considered that the resulting ICER was likely underestimated, and the model assumptions likely favoured belimumab (paragraph 7.6, belimumab PSD, July 2020 PBAC meeting). The incremental life years and QALYs presented in this resubmission exceeded the belimumab, despite a shorter time horizon (30 years).
- 6.62 Given the high uncertainty of the ICER at 30 years, Step 4 of the stepped economic evaluation which results in an ICER of \$135,000 to < \$155,000 per QALY is particularly informative as it is based on the duration of the trial follow up (i.e. 4 years). Furthermore, as the 4 year analysis does not use data directly from the trial (rather it uses average patient characteristics to simulate patients and regression analyses to

simulate patient pathways from Time 0), a trial-based cost-effectiveness analysis, using the individual patient data directly from the TULIP trials and TULIP LTE may be more robust.

6.63 Overall, the ESC considered that given the uncertainty within the model, combined with the presence of spurious and clinically implausible findings, a simpler Markov cohort model structure may be more appropriate and would provide greater transparency in the underlying assumptions. Alternatively, noting the 4-year analysis presented in the paragraph above, the ESC considered that a model with a substantially shorter time horizon consistent with the available clinical evidence would reduce the issues associated with extrapolation over a relatively long period of time and hence the results may be more clinically valid. With either approach, the ESC considered that external model validation should be undertaken to demonstrate the relationship between model findings and evidence from trial and/or registry data.

6.64 A summary of sensitivity analyses is presented in Table 12. The ICER was most sensitive to: flare intercept, treatment effect and duration; SLEDAI-2K regression coefficients; extrapolation of treatment effect; the SLEDAI-2K and treatment coefficients for utility estimates; SLEDAI-2K coefficient for mortality; and organ damage incidence.

Table 12: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change
Submitted base case		0.664		
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes		1.031		-15.3%
• 3.5% costs and outcomes		0.748		-4.5%
Mean age (base case 41 years)				
• 34.5 years		0.697		-5.8%
• 45 years		0.647		0.3%
Anifrolumab response rate in first 6 months (base case 55%)				
• 44%		0.472		15.8%
• 66%		0.838		-7.7%
Non-severe flare intercept				
• Lower 95% CI (NR)		0.508		36.4%
• Upper 95% CI (NR)		0.828		-18.8%
Severe flare intercept				
• Lower 95% CI (NR)		0.528		31.5%
• Upper 95% CI (NR)		0.892		-30.4%
Long term SLEDAI-2K intercept (base 0.31)				
• 3.14 (unadjusted parameter)		0.754		-13.5%
• -3.14		0.375		84.6%
Non-severe flare treatment effect				
• Lower 95% CI (NR)		0.782		-14.9%
• Upper 95% CI (NR)		0.505		31.6%
Severe flare treatment effect				
• Lower 95% CI (NR)		0.708		-6.6%
• Upper 95% CI (NR)		0.588		14.0%
Change in SLEDAI-2K treatment effect				

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change
Submitted base case		0.664	█ ¹	
• Assume SLEDAI-2K treatment effect coeffs 0 (anifrolumab affects SLEDAI-2K only through flares)		0.618	█ ¹	7.8%
• Assume SLEDAI-2K equal in both arms (set equal to SOC)		0.186 ^a	█ ⁶	267.3%
Treatment effect on duration of flares (base case HR=1.76)				
• HR=1.35		0.5982	█ ¹	11.2%
• HR=2.30		0.7108	█ ²	-7.1%
Duration of flares (base case 5.3 months non-severe, 2.5 months severe)				
• 20% shorter		0.494	█ ³	39.8%
• 20% longer		0.883	█ ²	-26.4%
• Low IQR of APLC data (2.8 non-severe, 1.1 severe)		0.351	█ ⁵	102.3%
• High IQR of APLC data (11.5 non-severe, 5.3 severe)		0.902	█ ²	-23.5%
• 3.9 months for all flares		0.731	█ ²	-9.6%
Effect of flares on SLEDAI-2K (+4.3 for non-severe, +9.7 for severe)				
• Low 95% CI ^b (+4.2 for non-severe, +9.3 for severe)		0.638	█ ¹	5.2%
• High 95% CI ^b (+4.4 for non-severe, +10.1 for severe)		0.693	█ ²	-3.7%
• Minimum definition (+3 for non-severe, +7 for severe)		0.432	█ ⁷	61.6%
Treatment effect for entire time horizon				
• Remove treatment effect from year 5. Affects flares, OCS, SLEDAI-2K and utility regressions.		0.441	█ ³	51.7%
Assume no mortality benefit for anifrolumab		0.537	█ ¹	4.8%
Utility regression coefficients (base: anifrolumab responder 0.076, anifrolumab non-responder -0.029, AMS -0.009)				
• No treatment effect (anifrolumab responder and non-responder 0)		0.582	█ ¹	14.0%
• No SLEDAI-2K effect (AMS 0)		0.581	█ ¹	14.3%
Mortality regression AMS coefficient (base: 0.214)				
• AMS coefficient 0		0.625	█ ²	-14.8%
Organ damage incidence, set AMS coeffs to 0		0.646	█ ¹	17.2%

Source: Table 3.9-1 of the submission and compiled during the evaluation

AMS = adjusted mean SLEDAI; APLC=Asia-Pacific Lupus Collaboration; OCS = oral corticosteroids; HR = hazard ratio; CI = confidence interval; NR = not reported; IQR=inter-quartile range; LOS = length of stay; LY=life year; yr = year; SOC = standard of care; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000

a due to random mortality estimation each cycle, the anifrolumab arm had fewer LYs than the SOC arm (-0.005), but still had more QALYs.

b 95% CIs estimated from standard errors calculated as standard deviations reported from APLC divided by square root of the number of flares (802 non-severe, 204 severe).

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$55,000 to < \$75,000

³ \$95,000 to < \$115,000

⁴ \$45,000 to < \$55,000

⁵ \$135,000 to < \$155,000

⁶ \$255,000 to < \$355,000

⁷ \$115,000 to < \$135,000

6.65 The pre-PBAC response offered a lower effective DPMQ for anifrolumab of \$█ (public), which corresponded to an ICER of \$55,000 to < \$75,000 per QALY gained compared to \$75,000 to < \$95,000 per QALY gained in the resubmission base case.

Anifrolumab cost/patient/year

6.66 Table 13 presents the drug cost per patient for anifrolumab based on the price proposed in the submission. The pre-PBAC response proposed a lower price.

Table 13: Drug cost per patient for anifrolumab

	Trial dose and duration	Model		Financial estimates	
		July 2022	Resubmission	July 2022	Resubmission
Mean dose anifrolumab	300mg	300mg	300mg	300mg	300mg
Mean number of administrations/year	13.04	13.00	13.00	13.04	12.39*
Mean duration anifrolumab	NR#	4.21 years (30 year time horizon)	4.88 years (30 year time horizon)	3.14 years (6 year time horizon)	NE
Cost/patient/month (\$)	NA				
Cost/patient/year (\$)	NA				

Source: compiled during the evaluation

NA=not applicable, NE=not estimable, NR=not reported

SOC costs not included as anifrolumab used in addition to SOC. In the financial estimates no SOC costs were included. In the model OCS costs differed between the anifrolumab and SOC arms but was not vastly different

Financial estimates used weighted public/private cost.

Mean duration multiplied by per year cost does not give total cost reported in the model as model assumed half a cycle treatment costs for patients who discontinued treatment during that cycle.

The proportion of patients with at least 48 weeks of treatment was 81.1% in TULIP-1, 85.6% in TULIP-2 and 87.9% in MUSE.

* Assuming 95% compliance (13.04 x 0.95).

Estimated PBS usage & financial implications

6.67 This resubmission was not considered by DUSC. As for the July 2022 submission, the resubmission used an epidemiological approach to estimate the financial impact of listing anifrolumab on the PBS. DUSC had considered the July 2022 estimates to be significantly overestimated due to overestimations in the proportion of eligible patients (32.12% was nominated; however, DUSC considered a value of <16% to be more appropriate), and significant double counting in the prevalent population due to inclusion of those treated in previous years. DUSC also considered a static uptake of 50% beyond Year 3 to be unlikely. The resubmission made revisions to the estimates based on the PBAC and DUSC's feedback. Table 14 summarises the sources of data and assumptions used in the financial estimates including changes versus the July 2022 submission.

Table 14: Key inputs for financial estimates

Data	Source	Comment
Eligible population		
Prevalent patients with SLE	Australian adult population estimates (2023-2028) multiplied by prevalence of 94.33 in 100,000 based on Australian estimates.	Unchanged from previous submission. DUSC considered this estimate to be appropriate.
Eligible population: patients with SLEDAI-2K≥10	Prevalent patients multiplied by 15.83% to represent patients with SLEDAI-2K≥ 10 whilst on triple therapy. Adapted from the 2022 IQVIA report commissioned by the sponsor.	DUSC had considered a value of <16% to be more appropriate (Anifrolumab July 2022, DUSC advice).
Grandfathered patients	Estimated number of patients to be enrolled into a patient access program prior to PBS listing.	This was increased from 0 in the previous submission and [REDACTED] in the pre-PBAC response to the July 2022 submission to [REDACTED]. The PAP was yet to enrol any patients at time of the resubmission. As grandfathered patients were not deducted from the prevalent pool of eligible patients, there may be double counting in Year 1. The number of grandfather patients was reduced to [REDACTED] in revised estimates presented in the PSCR.

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Data	Source	Comment
Treatment utilisation		
Uptake rate	Assumption. Increasing from 57% in Yr1, then 10% per year to Yr 3 then increasing to 85%, 95% and 95% in Yrs 4, 5 and 6. This was significantly higher than rates in the July 2022 submission which were 25% in Yr1 to 50% in Yr6 (based on uptake rates suggested in para 6.72, belimumab PSD, July 2020). The new uptake rates however were identical to the rates proposed in the July 2022 pre-PBAC response.	DUSC considered the rates from the July 2022 were likely to rise due to clinical need if recommended. However, given the modest clinical benefit of anifrolumab these estimates may be high, a lower uptake assumption may be more appropriate. The PBAC also considered that the uptake rates applied in the pre-PBAC response (57% in Year 1 increasing to 95% in Year 6) may have been overestimated in the later years (para 7.12, anifrolumab PSD, July 2022). The uptake rate was capped at 77% from Year 3 onwards in revised estimates presented in the PSCR. The pre-PBAC response further revised the uptake rates to 30% in Year 1, increasing by 5% per year to 55% in Year 6.
Initiating patients	Eligible population x uptake rate. Plus [REDACTED] grandfathered patients in Yr 1.	Appropriate calculation.
Continuing patients	The submission assumed a continuation rate of 86.1% for those that initiate anifrolumab each year based on data from MUSE LTE, plus 258 grandfathered continuing patients in Yr 1. This was a revised approach as per DUSC advise (assuming those stopping treatment will do so after 6mth). The submissions' approach doesn't follow patients past the initiation year and implicitly allowed for retrials of anifrolumab, which was reasonable and permitted based on the requested restrictions. In the July 2022 submission the prevalent population each year was not adjusted for the number of prevalent patients in the previous year who had already received/were still receiving anifrolumab. As such some patients were likely double-counted in the financial estimates (para 6.62, anifrolumab PSD, July 2022).	As grandfathered patients were drawn from the prevalent population, they may be double counted in the estimates. The proportions of anifrolumab treated patients achieving SLEDAI-2K reduction ≥ 4 at 24 weeks in the included trials was between 41.1% and 58.3% (See Table 2.5.2 of Anifrolumab July 2022 COM). Using the lower response rate would estimate a lower continuation rate as per DUSC methodology of 70.55% (ie, 41.1% + 58.9%/2 = 70.55%). A continuation rate of 70.55% was applied in revised estimates presented in the PSCR. The continuation rate was reduced to 41% in the pre-PBAC response.
Total number patient-years treated	Calculations assume patients who discontinue treatment did so after 6mth (incl 279 patient years for grandfathered patients in Yr 1).	This was as per methodology outlined in the DUSC advice.
Scripts dispensed	12.39 scripts per patient-year assuming 95% compliance. Previously 100% compliance with 13.04 scripts per year. This differed to the assumed 100% compliance in the model with 13 scripts per patient year.	Notwithstanding comments in relation to double counting, if following the resubmission's methodology, the resubmission erroneously omitted scripts for continuing grandfathered patients (even though they were included in the patient years treated).
Costs		
Anifrolumab	Revised requested price weighted public \$[REDACTED], private \$[REDACTED] based on rituximab weights. Previously requested effective DPMQ was \$[REDACTED] in the July 2022 submission and \$[REDACTED] in its pre-PBAC response.	The pre-PBAC response offered a revised DPMQ of \$[REDACTED] (public).
Patient copayment	Calculation based on rituximab PBS copayment weights using updated PBS copayments.	-
MBS costs	Updated MBS fees for item 14245 (infusion cost for immunotherapy) at 80% rebate (\$103.55 full fee)	Costs of infusions for grandfathered patients were inappropriately omitted.

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Blue shading represents information previously considered by the PBAC.

Source: Tables 4.1-1, 4.1-4, 4.2-1, 4.2-2, 4.2-4, 4.2-5, 4.2-6, 4.2-7, 4.2-9 and Section 4.2.2, p172 of the submission and compiled during the evaluation

ALRB=Australian Lupus Registry and Biobank; PAP=patient access program; RSA=risk share arrangement, SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SOC=standard of care consisting of triple therapy, Yr = year; mth = month

The redacted values correspond to the following range:

¹ <500

- 6.68 A summary of the financial impact of anifrolumab for SLE is presented in Table 15. The total net cost to government over the first six years of use was reduced from the estimated \$600 million to < \$700 million (\$500 million to < \$600million PBS/RPBS costs, \$10 million to < \$20 million MBS costs) in the July 2022 submission to \$200 million to < \$300 million (\$100 million to < \$200 million PBS/RPBS costs, \$10 million to < \$20 million MBS costs) in the resubmission. The resubmission's estimates also did not include MBS infusion fees for grandfathered patients which may not be appropriate.
- 6.69 The PSCR provided updated estimates which, based on paragraph 6.63, assumed a lower continuation rate of 70.55%, capped uptake at 77% from Year 3 onwards and reduced the number of grandfather patients from < 500 to < 500. This resulted in a net cost to the PBS/RPBS of \$30 million to < \$40 million in Year 6 and which totalled \$100 million to < \$200 million over the first 6 years of listing.
- 6.70 Updated estimates were provided in the pre-PBAC response applying the revised price (see paragraph 6.66) and including revised assumptions for the uptake rates (Year 1, 30%; Year 2, 35%; Year 3, 40%; Year 4, 45%; Year 5, 50%; Year 6, 55%) and the continuation rate (41%). These changes resulted in a net cost to the PBS/RPBS of \$10 million to < \$20 million in Year 6 and which totalled \$60 million to < \$70 million over the first 6 years of listing.

Table 15: Estimation of number of treated patients and prescriptions

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Patients							
SLE pop.	1	2	2	2	2	2	3
Eligible pop.	4	4	4	4	4	4	6
	5	5	5	5	5	5	1
Uptake rate	25.00%	30.00%	40.00%	50.00%	50.00%	50.00%	-
	57.00%	67.00%	77.00%	85.00%	90.00%	95.00%	-
Initiating pts	5	5	5	5	5	5	1
	5	5	5	5	5	5	1
Continuing pts	5	5	5	5	4	4	2
	5	5	5	5	5	5	1
Total pt yrs	5	5	5	5	4	4	2
	1.5	5	5	5	5	5	1
Scripts							
Number of anifrolumab scripts							
PBS/RPBS	1	2	7	8	9	10	11
	2	2	2	6	6	6	12
Costs							
Anifrolumab							
PBS/RPBS	13	15	17	18	18	18	19
	13	13	14	14	14	16	20
Less copay	21	21	21	21	21	21	21
	21	21	21	21	21	21	21
Net cost	13	15	17	18	18	18	19
	13	13	14	14	14	16	18
PSCR#	13	13	13	13	13	14	18
MBS item							
Net cost 14245	22	22	22	22	22	22	23
	*.22	22	22	22	22	22	23
Total net cost to gov.	13	15	17	18	18	18	24
	13	13	14	14	16	16	20
PSCR#	13	13	14	14	14	14	18
Pre-PBAC response							
Number of scripts	4	4	1	1	1	1	26
Net cost to PBS/RPBS	22	22	23	23	23	23	25

Blue shading represents information previously considered by the PBAC.

Source: Tables 4.2-1,4.2-6, 4.5-1, 4.5-2, 4.5-4, 4.5-5 of the submission and compiled during the evaluation

pop = population, pt = patient; yr = year, 14245= infusion cost for immunotherapy.

[^] Note despite accounting grandfather patients (n=) in total patient years in Year 1, continuing treatment scripts for these patients after 6mth in Yr 1 have not been included in the submission's estimates.

* The resubmission's estimates did not include MBS infusion costs for grandfather patients.

The PSCR applied a continuation rate of 77.55% following a transcription error in the commentary. The actual rate was 70.55%. Corrected values are presented above. Other changes to the financial estimates were as per the PSCR.

The redacted values correspond to the following ranges:

¹ 10,000 to < 20,000

² 20,000 to < 30,000

³ 100,000 to < 200,000

⁴ 5,000 to < 10,000

⁵ 500 to < 5,000

⁶ 30,000 to < 40,000

⁷ 40,000 to < 50,000

⁸ 60,000 to < 70,000

⁹ 80,000 to < 90,000

¹⁰ 90,000 to < 100,000

¹¹ 300,000 to < 400,000

¹² 100,000 to < 200,000

¹³ \$20 million to < \$30 million

¹⁴ \$30 million to < \$40 million

¹⁵ \$50 million to < \$60 million

¹⁶ \$40 million to < \$50 million

¹⁷ \$80 million to < \$90 million

¹⁸ \$100 million to < \$200 million

¹⁹ \$500 million to < \$600 million

²⁰ \$200 million to < \$300 million

²¹ net cost saving

²² \$0 to < \$10 million

²³ \$10 million to < \$20 million

²⁴ \$600 million to < \$700 million

²⁵ \$60 million to < \$70 million

²⁶ 70,000 to < 80,000

6.71 The financial impact estimated in the pre-PBAC response may still be overestimated as:

- Given grandfather patients were not removed from the prevalent pool of eligible patients, there was potential double counting of patients in Year 1. The PSCR provided revised estimates which reduced the number of grandfather patients from < 500 to < 500.
- Similar to the July 2022 submission, the resubmission's financial estimates did not account for patient mortality, and therefore may overestimate the length of time on treatment.

Quality Use of Medicines

6.72 There were no material changes compared to the July 2022 submission. The resubmission referred to the AstraZeneca Global Patient Safety group which manages pharmacovigilance activities locally. The resubmission stated that there was minimal risk of incorrect administration as anifrolumab is administered by health care professionals with a flat 300 mg dosage.

6.73 The resubmission also mentioned plans to provide educational materials to patients and healthcare professionals including a website and text message reminders for infusions.

Financial Management – Risk Sharing Arrangements

6.74 The resubmission stated that the sponsor was amenable to discussing appropriate risk sharing arrangements to address any areas of uncertainty to the PBS and the Commonwealth. However, no details were provided in the resubmission.

6.75 The PBAC in its evaluation of the July 2022 anifrolumab submission considered a risk share arrangement with a rebate for use over the expenditure caps would be required given the uncertain size of the patient population (paragraph 7.13 anifrolumab PSD, July 2022 PBAC meeting). In the consideration of belimumab, the PBAC also

considered there was a high risk of use outside the restriction given that only a small subset of SLE patients will meet the proposed PBS restriction (paragraph 7.11, belimumab PSD, July 2020 PBAC meeting).

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of anifrolumab for the treatment of systemic lupus erythematosus (SLE) with high disease activity despite standard of care (SOC). The PBAC acknowledged that there is a clinical need for the requested population but remained concerned that the magnitude of benefit associated with anifrolumab was uncertain. The PBAC also considered that the economic model remained highly uncertain and was unreliable for decision making.
- 7.2 The PBAC noted the strong consumer support for this item and agreed that there is a clinical need for effective treatments in the requested population. The PBAC also noted that SLE is an area of significant research interest with numerous therapies in clinical development¹³.
- 7.3 Consistent with its July 2022 advice, the PBAC considered that the proposed clinical place for anifrolumab, which was in patients with persistent disease activity despite receiving SOC, was appropriate. The PBAC noted that the approved TGA indication for anifrolumab excluded two groups with a particularly high clinical need, patients with severe active lupus nephritis and those with severe active central nervous system lupus.
- 7.4 The data to support the clinical claim was again drawn from three head-to-head randomised controlled trials comparing anifrolumab to SOC alone in adults with moderate to severe SLE (TULIP 1, TULIP 2, and MUSE) and an extension study (MUSE LTE), with additional clinical data up to 4 years from the TULIP extension study (TULIP LTE). While TULIP LTE demonstrated a sustained benefit associated with continued anifrolumab treatment in terms of a reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), the results for other outcomes were less certain. For example, the mean time to first Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) worsening (a measure of organ damage) was not statistically significantly different (HR = 0.82; 95% CI: 0.50, 1.39); although oral corticosteroid dose was reduced by an average of 2 mg per day, the clinical significance of this was not discussed in the submission); and there were no statistically significant differences between anifrolumab and placebo in terms of quality of life (EQ-5D-5L) at Week 208. The PBAC

¹³ Tsang-A-Sjoe MWP, Bultink IEM. New developments in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2021 Dec 24;60(Suppl 6):vi21-vi28.

noted that the primary outcomes of TULIP LTE were safety, not efficacy outcomes, and considered that, on balance, the new evidence was not sufficient to alter the clinical conclusions from the previous consideration.

- 7.5 Consistent with its July consideration, the PBAC considered the claim of superiority to SOC alone in terms of effectiveness was supported based on improvement in disease activity for some patients; however, the magnitude of benefit was modest and uncertain. The PBAC considered the claim of inferior safety to SOC alone was reasonable.
- 7.6 The PBAC noted that the economic model was informed by an exploratory subgroup analysis of patients in the TULIP trials with a SLEDAI-2K ≥ 10 which reflected the proposed restriction. The PBAC considered this was reasonable; however, noted that there was low confidence in the magnitude of benefit due to heterogeneity of responses between the trials and by outcome, and because of the amendments to outcome assessment that likely favoured anifrolumab (see paragraph 6.10 regarding potential outcomes selection bias resulting from changes in trial design).
- 7.7 Overall, the PBAC considered that the model did not provide robust estimates for decision making in the Australian context. The PBAC noted that the resubmission presented a largely unchanged microsimulation model and the majority of concerns about the economic model identified at the July PBAC 2022 consideration had not been adequately addressed (see Table 8), including that:
- Although the resubmission included data from TULIP LTE up to a total of 4 years follow up, there remained limited data to populate the model particularly for longer term events such as organ damage and mortality.
 - Events in the model were again based on multiple predictive regression models of disease progression and these remained highly uncertain, with concerns regarding reverse causality within the regression analyses, appropriateness of model fit and the extrapolation of the regression coefficients across the time horizon. SLEDAI-2K remained a significant driver in most of the predictive models. There remained a high chance of double counting the SLEDAI-2K effect, particularly as SLEDAI-2K and flares acted as regressors to each other, and both were used in predictions of other model components.
 - Some of the changes to the regressions in the resubmission resulted in very different, and likely clinically implausible, outcomes compared to those presented in the July 2022 submission, e.g., incremental quality of life gain became a key driver of the ICER in the resubmission instead of survival, such that sensitivity analyses improving survival in the SOC arm would decrease the ICER; and average utility in the absence of organ damage was < 0.3 across the time horizon compared to > 0.8 in the July 2022 submission. The changes to the inputs also demonstrated that the model was not robust and therefore the results were highly uncertain.

- 7.8 The PBAC considered that a revised economic model that addressed the ESC's concerns, along with a price reduction, would be required to achieve acceptable cost-effectiveness.
- 7.9 The PBAC noted that the net cost to the PBS/RPBS over the first 6 years of listing was revised from \$100 million to < \$200 million in the resubmission to \$60 million to < \$70 million in the pre-PBAC response. The PBAC considered that the utilisation estimates for anifrolumab remained high despite the revised inputs in the pre-PBAC response.
- 7.10 The PBAC acknowledged that the low level of certainty in the evidence and the small incremental benefit between anifrolumab and placebo likely reflects, in part, the complex and variable nature of the condition and the challenges associated with assessing outcomes in SLE. The PBAC noted that there is no core outcomes set for SLE (i.e. there is a lack of consensus on core outcomes for use in clinical trials in SLE, unlike in rheumatoid arthritis where the American College of Rheumatology (ACR) response criteria are used, or psoriasis where the Psoriasis Area and Severity Index (PASI) score is used). The PBAC noted that these challenges added considerable uncertainty to the economic evaluation and expressed a desire for a simpler, more robust model for SLE that was based on conservative assumptions and would provide more reliable estimates of cost-effectiveness for this population.
- 7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

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.