5.01 ANIFROLUMAB, Solution concentrate for I.V. infusion 300 mg in 2 mL, Saphnelo®, AstraZeneca Pty Ltd.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drug Program) Authority Required (Written) listing of anifrolumab for the treatment of patients with systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard of care (SOC).

1.2 The basis of the requested listing was cost-utility analyses versus SOC. Table 1 summarises the components of the overall clinical claim addressed by the submission.

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

Component	Description
Population	Adult patients with SLE with a high degree of disease activity despite standard 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, Adverse events.
Clinical claim	In patients with SLE and a high degree of disease activity despite SOC comprising of an antimalarial, immunosuppressant (MTX, AZA, or mycophenolate) and 7.5 mg/day prednisone (or equivalent), anifrolumab added to SOC has superior effectiveness and non-inferior safety compared to SOC alone.

Source: Table 1.1-1, p19 of the submission.
AZA=azathioprine; BICLA=BILAG–Based Composite Lupus Assessment; BILAG=British Isles Lupus Assessment Group; 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; SLEDIA-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SOC=standard of care; SRI(4)=4-point reduction on the SLE Responder Index.

2 Background

Registration status

2.1 Anifrolumab was listed on the ARTG on 29 March 2022. The TGA indication is:

> "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 Anifrolumab is currently being evaluated for funding by the Canadian Agency for Drugs and Technologies in Health (CADTH)[1]. National Institute of Clinical Excellence (NICE)

[1] CADTH anifrolumab, available from: https://www.cadth.ca/anifrolumab, accessed 21/7/2022.

was unable to make a recommendation on anifrolumab because the sponsor did not provide an evidence submission[2].

Previous PBAC consideration

2.3 This was the first consideration of anifrolumab by the PBAC.

2.4 Currently, belimumab is the only other biologic therapy that is TGA registered for SLE, however it is not listed on the PBS. Belimumab was considered by the PBAC in November 2019 and July 2020, but was not recommended on both occasions.

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.

Initial treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty (packs)	Max. qty (units)	№. of repeats
ANIFROLUMAB Injection	NEW (Public) NEW (Private)	1	1	~~7~~*6*
Available brands				
Saphnelo *anifrolumab 300 mg/2 mL injection, 2 mL vial)*				

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☒*Medical Practitioners*
Restriction Level / Method: ~~Section 100 highly specialised drug program (S100 HSD public)~~ ~~Section 100 highly specialised drug program (S100 HSD private)~~ ☒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 *Alternatively* *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 A*merican College of* R*heumatology (ACR)*/E*uropean* L*eague* A*gainst* R*heumatism (EULAR)* SLE Classification Criteria 2019~~)~~
AND
Clinical criteria:

[2] NICE anifrolumab, available from: https://www.nice.org.uk/guidance/ta793, accessed 21/7/2022.

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 ~~renal~~ active lupus nephritis or severe active central nervous system systemic lupus erythematosus
Population criteria:
Patient must be aged 18 years or older.
~~**Prescriber**~~ ***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.* ~~(a) a completed authority prescription form; and~~ ~~(b) details of current therapy used (dosage, date of commencement and duration of therapy); and~~ ~~(c) a completed SLEDAI-2K score sheet, including the date of assessment,~~ ~~AND~~ 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)*
~~**Prescriber**~~ ***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:

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: *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. ~~EST~~ 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*
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.*

Continuing treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty (packs)	Max. qty (units)	№. of repeats
ANIFROLUMAB Injection	NEW	1	1	~~5~~6
Available brands				
Saphnelo *anifrolumab 300 mg/2 mL injection, 2 mL vial*				

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☒*Medical Practitioners*
Restriction Level / Method: ~~Section 100 highly specialised drug program (S100 HSD public)~~ ~~Section 100 highly specialised drug program (S100 HSD private)~~ ☒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 *Alternatively* *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.
~~**Population criteria:**~~
~~Patient must be aged 18 years or older.~~
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: *Note* *[Complex Authority Required flag] Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*

3.2 The submission stated that a Section 100 listing on the Highly Specialised Drugs (HSD) Program was necessary given anifrolumab is administered by intravenous (IV) infusion every 4 weeks.

3.3 The PSCR updated the number of repeats to be six in the initial and continuing settings, which was consistent with the submission's proposal to assess response at 24 weeks and to provide six months of treatment with each continuing prescription.

3.4 The submission did not propose a separate grandfather restriction, despite stating that a patient access program (PAP) was planned to commence post TGA approval, with the final numbers in the PAP to be confirmed. The sponsor was requested to propose a grandfather restriction; the PSCR agreed with the evaluation (p2) to include a grandfather restriction to expire 12 months after PBS-listing but did not propose the wording for the restriction.

3.5 In its July 2020 consideration of belimumab for the treatment of SLE, the PBAC had considered that the restriction for belimumab should target use in patients who have the greatest clinical need and are most likely to respond to treatment. The requested PBS restriction for anifrolumab was generally consistent with this intent. Differences compared with the wording proposed by the PBAC for belimumab (paragraph 3.1, belimumab Public Summary Document (PSD) July 2020 PBAC meeting) included:

- The restriction does not limit access to patients based on laboratory evidence of serological activity (i.e. elevated anti-double-stranded DNA (anti-dsDNA), and low complement (C3 or C4) levels). The inclusion of serological activity in the proposed belimumab restriction was based on the European League Against Rheumatism

and the American College of Rheumatology (EULAR/ACR) 2019 recommendations and the belimumab studies (paragraphs 2.8 and 7.4, belimumab PSD November 2019 PBAC meeting). Eligibility criteria in the key anifrolumab trials were similar to the belimumab trials (based on anti-dsDNA positivity and/or antinuclear antibodies (ANA) titre). For example, in the TULIP trials, 44-45% of the patients tested positive for anti-dsDNA antibodies and 34-39% and 21-26% had low/abnormal complement levels, respectively. However, given no subgroup analyses were presented in the anifrolumab trials by serological activity, it was unknown if patients with positive anti-dsDNA or low complement levels would have greater response to anifrolumab treatment. The pre-PBAC response stated (p3) that, unlike belimumab, anifrolumab targets the innate immune system; in contrast, belimumab targets B-cells. It stated that serological activity is a characteristic of the adaptive immune system driven by B-cells and not the innate immune system driven by Type I interferon, and therefore it is not relevant to include laboratory evidence of serological activity in the anifrolumab restriction.

- 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 (paragraph 3.6, belimumab PSD July 2020 PBAC meeting); however, the evaluation considered that the word 'renal' could be removed to align more closely with the TGA approved indication. The PSCR agreed with the evaluation (p2) to remove the word 'renal' in severe lupus nephritis in the initial treatment phase.
- The restriction did not include a criterion to prevent patients from re-trialling anifrolumab. The proposed initial restriction for belimumab included: "Patient must not have previously received PBS-subsidised treatment with this drug for this condition" (paragraph 3.1, belimumab PSD July 2020 PBAC meeting). The PSCR agreed with the evaluation (p2) to include this criterion in the initial treatment phase. However, the ESC considered that, similar to other rheumatic autoimmune diseases such as rheumatoid arthritis and psoriatic arthritis, this should not be an absolute exclusion for future re-initiation of treatments. Further, SLE patients can have a fluctuating disease course over many years, and an initial course of treatment may have been discontinued due to control of disease and resolution of flare. 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), and the pre-PBAC response agreed with this approach (p3).

3.6 Given only a small subset of SLE patients are expected to meet the proposed eligibility criteria due to the requirements of disease severity and current SOC, the evaluation and the ESC considered there is potential for use outside of the requested restrictions.

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, and no two patients experience the same disease journey. Clinical manifestations include musculoskeletal, dermatologic/cutaneous, gastrointestinal, renal, neuropsychiatric, cardiac and vascular and obstetric manifestation. Constitutional symptoms include fatigue, fever, malaise, arthralgias, myalgias, headaches and weight loss. The exact cause of SLE is unknown, however evidence indicates that the aetiology is multifactorial with genetic, immunological, endocrine/hormonal and environmental factors having a role in the cause and development of the disease. The risk of SLE is 10 times higher in women than in men due to genetic and hormonal factors with onset usually between 20-40 years old. There is also higher prevalence among certain ethnic groups. In Australia, SLE is more common and more severe in Aboriginal and Torres Strait Islander peoples and Asian patients. ANA are present in 98% of SLE patients. Serological (immunological) findings are important in suggesting the possibility of SLE, with some antibodies such as anti-dsDNA or low complement (C3, C4) levels highly associated with SLE (Gordon et al., 2018[3]).

4.2 Diagnosis of SLE is based on assessment of clinical manifestations and laboratory findings with histology of affected organs (usually skin and kidneys). Diagnosis is challenging due to the clinical heterogeneity of SLE; however, the presence of ANA provides an entry criterion under the current diagnosis criteria by the EULAR/ACR (2019). The EULAR/ACR 2019 SLE classification criteria requires a positive ANA test at least once as an obligatory entry criterion, followed by scoring of weighted criteria across seven clinical (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and three immunologic (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) domains; patients scoring ≥10 points are classified as having SLE.

4.3 There is no one 'gold standard' instrument to assess disease activity in SLE, due to heterogeneity of the disease and clinical manifestations. The 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.
- Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), which is a global measure of disease activity. It is slightly less complex than the BILAG index.

[3] Gordon C, Amissah-Arthur MB, Gayed M, Brown S, Bruce IN, D'Cruz D, Empson B, Griffiths B, Jayne D, Khamashta M, Lightstone L, Norton P, Norton Y, Schreiber K, Isenberg D; British Society for Rheumatology Standards, Audit and Guidelines Working Group. 2018. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford). 57(1):e1-e45. doi: 10.1093/rheumatology/kex286.

- Physician global assessment (PGA) which is a visual analogue scale (0-3 scale) which is substantially less complex to complete.

4.4 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.

4.5 Both SLEDAI-2K and BILAG scores correlate with organ damage and mortality risk. SLEDAI-2K differs from BILAG in that it is binary (presence/absence of a symptom), whereas BILAG assesses the presence of a symptom (whether new, improved, same or worse) to evaluate the activity for each organ. While the SLEDAI is a simple global index and the BILAG is comprehensive organ-specific index, the limitations of these instruments are that SLEDAI cannot evaluate improvement and the BILAG does not contain serological evaluation.

4.6 The overall goals of treatment are to ensure long-term patient survival, prevention of organ damage, minimise drug side-effects and improve patient outcome. Management of SLE should aim for remission of disease symptoms and signs (or low disease activity) to improve long-term patient outcomes.

4.7 For patients with high disease activity (SLEDAI-2K ≥10), current treatments are: non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials (i.e. hydroxychloroquine (HCQ)), oral corticosteroids (OCS), non-biologic immunosuppressants (i.e. azathioprine (AZA), methotrexate (MTX) and mycophenolate), and/or biologic therapies (i.e. belimumab and off-label rituximab). The preferred treatment is 'triple therapy' comprising HCQ, OCS and an immunosuppressive agent, unless contraindicated or not tolerated. This population is reflected by the target population in the submission: patients with diagnosed severe SLE who have a high degree of disease activity (measured by SLEDAI-2K ≥10 points disease activity score) despite triple therapy SOC (i.e. an antimalarial [HCQ], an immunosuppressant, and 7.5 mg/day prednisone or equivalent).

4.8 Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody that binds to Type I interferon receptor (IFNA1), inducing the internalisation of IFNAR1 (reducing the cell surface levels) and blocking the activity of Type I IFNs. Type I IFNs play an important role in the pathogenesis of SLE. By blocking Type I signalling, anifrolumab inhibits IFN responsive gene expression and downstream inflammatory and immunological processes. Anifrolumab is able to target IFN signalling that is dysregulated in SLE and therefore blocks plasma cell differentiation and normalises peripheral T-cells subsets, restoring balance between adaptive and innate immunity that is dysregulated in multiple autoimmune disorders.

5 Comparator

5.1 The submission nominated SOC alone (placebo) as 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 submission did not consider belimumab a near market comparator, given that it was not recommended by the PBAC and the sponsor of belimumab stated that it will not be resubmitting to the PBAC for the subset of patients with severe SLE (paragraph 9, belimumab PSD July 2020 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 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. 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 with SLE or family members (128), a health care professional (HCP) (1) and organisations (5) via the Consumer Comments facility on the PBS website.

6.3 The majority of the consumer contributors (101) were individuals who have SLE. Consumers outlined that SLE affects every aspect of their life including their physical, mental and emotional health. Many patients discussed their current condition without anifrolumab: painful joints, sleep difficulties, inflamed gums, headaches, low energy, depression, stress, anxiety, nose and mouth ulcers, rashes, and the effect that this has on their schooling and work, as well as social and family lives. Consumers outlined the importance of having another treatment option available, particularly for those whose condition is not adequately managed with current treatments. Consumers expressed hope that anifrolumab will improve their quality of life and allow them to live pain free and productive lives.

6.4 The HCP commented that anifrolumab is effective across the spectrum of lupus manifestations and has an early onset of benefit. The HCP noted the steroid sparing effect of anifrolumab, whereby patients have been able to taper their steroid dose

and avoid an associated disease flare. The HCP stated that the reduction in active disease observed with anifrolumab treatment was expected to reduce or prevent long-term damage such as permanent organ damage and death.

6.5 The PBAC noted the advice received from Musculoskeletal Australia (MSK), Lupus Victoria, Lupus Australia, the National Aboriginal Community Controlled Health Organisation (NACCHO), and the Australian Rheumatology Association (ARA) clarifying the likely benefit of anifrolumab in clinical practice. The organisations raised many of the points detailed in paragraphs 6.3 and 6.4, and provided the following additional information. MSK stated that young people often suffer from SLE, and emphasised the importance of achieving symptom control early in life to improve long term outcomes, as well as the capacity to return to work/increase hours as health improves. NACCHO noted that Aboriginal and Torres Strait Islander peoples are known to suffer from SLE at greater rates and severity compared to other Australians, and stated that, if cost effectiveness is a concern across the whole Australian population, listing could be considered on the Schedule for Aboriginal and Torres Strait Islander people. Lupus Victoria similarly noted the disproportionate burden of SLE disease among Indigenous Australians, as well as among African and Asian populations. The PBAC noted that this advice from the organisations was supportive of the evidence provided in the submission.

Clinical trials

6.6 The clinical evidence in the submission (Table 2) was based on three head-to-head randomised controlled trials (RCTs) comparing anifrolumab to placebo in adults with moderate to severe SLE (with SLEDAI-2K ≥6 and receiving one or more therapy for SLE) which were: TULIP 1, TULIP 2, MUSE, and an open-label treatment extension study (MUSE LTE).

Table 2: Trials and associated reports presented in the submission

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.

Source: Table 2.2-1, p47 of the submission.

6.7 A potentially relevant safety study in Japanese patients with SLE (Tanaka 2020, NCT01559090) was excluded on the grounds it was not conducted in the PBS population. This may not be appropriate, studies conducted in Asian patients are relevant to the requested restriction, as it is one of the predominant ethnic groups affected by SLE in Australia and are associated with more severe phenotypes (Connelly et al., 2013[4]). Thirty-eight percent of patients in the Australian Lupus Registry and Biobank (ALRB) are of Asian ethnicity (ALRB 2021).

6.8 Table 3 presents the key features of the included trials.

[4] Connelly K, Morand EF, Hoi AY, 2013. Asian ethnicity in systemic lupus erythematosus: an Australian perspective. Internal Medicine Journal. 43(6):618-624.

Table 3: 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[g]	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[g]	Low	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[h]	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	-

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

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 implementation of 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 At week 52, if eligible, patients were enrolled in a separate long-term extension study (TULIP SLE 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).

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

6.9 The TULIP-1, TULIP-2 and MUSE trials were all multicentre (TULIP-1 also included 2 study sites in Australia), randomised, double blind placebo-controlled trials where patients received either anifrolumab or placebo in addition to SOC for 52 weeks. MUSE LTE was an open-label extension (to 156 weeks) of the Phase 2 dose-finding MUSE trial. In all trials, SRI or BICLA response were assessed as either the primary or secondary endpoints at time points between Week 24 and 52.

6.10 Among the RCTs, the risk of bias associated with the MUSE trial was considered low. However, there was an unclear risk of bias with the TULIP trials due to two amendments to outcome assessment that likely favoured anifrolumab:

- The pre-specified primary endpoint in both TULIP-1 and TULIP-2 trials was a 4-point reduction on the SRI, primarily based on ≥4 point improvement on the SLEDAI-2K.

TULIP-1 was unblinded first and detected no difference between anifrolumab and placebo in terms of SRI(4) response, however a larger nominally significant difference was detected using the 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.

- The primary and several secondary outcomes in TULIP-1 included the condition "no use of restricted medications beyond the protocol-allowed threshold before assessment." Following the unblinding of the TULIP-1 trial and data review, investigators decided that the restricted medication rules were not appropriate and overly restrictive in 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 Broadly, patients enrolled in the trials had less severe SLE compared to the requested PBS population. The requested PBS eligibility criteria requires patients to have SLEDAI-2K ≥10 and be on triple therapy including OCS ≥7.5 mg/day, while the trials only required patients to have SLEDAI-2K ≥6 and be on one of the triple therapy agents. The evaluation considered that it was likely that less than 16% of the trial population would meet the PBS eligibility criteria, given only 16% of patients in the TULIP trials were on triple therapy (including OCS ≥7.5 mg/day) and had SLEDAI-2K ≥8 at baseline. The evaluation further considered that the actual proportion would likely be lower than 16% due to: (a) the requested PBS eligibility criteria requires patients to have SLEDAI-2K ≥10; and (b) differences in diagnostic criteria used, ACR 1982 (trial populations) and the EULAR/ACR 2019 (requested PBS population). Overall, the PBAC agreed with the ESC 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 ESC and PBAC acknowledged that the purpose of restricting use to this narrow population was to target patients with the greatest clinical need.

Comparative effectiveness

6.12 Under the proposed PBS restriction for continuing therapy with anifrolumab, patients must demonstrate response to therapy, defined as a reduction in SLEDAI-2K of at least four points from baseline after 24 weeks of initial treatment. Response in the included trials was assessed using composite outcomes (either BICLA and SRI(4)). However, the

SLEDAI-2K results fed into both composite scales and were also reported separately as an exploratory outcome.

6.13 Table 4 presents the trial results for SRI(4) and BICLA response plus its component indexes at Week 52.

Table 4: SRI(4) and BICLA and their component indexes plus medication rules at Week 52

	Anifrolumab 300 mg IV n/N (%)	Placebo (SOC) n/N (%)	RD (95% CI)
SRI(4) response			
TULIP-1 (pre-specified) [a,i]	65/180 (36.2)	74/184 (40.4)	–4·2 (–14·2, 5·8)[b]
TULIP-1 (post-hoc) [c,i]	84/180 (46.9)	79/184 (43.0)	3·9 (–6·3, 14·1)[b]
TULIP-2 [i]	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,i]	67/180 (37.1)	49/184 (27.0)	**10.1 (0.6, 19.7)**
TULIP-1 (post-hoc) [c,i]	83/180 (46.1)	54/184 (29.6)	**16.4 (6.7, 26.2)**
TULIP-2 [i]	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)[h]**
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)

	Anifrolumab 300 mg IV n/N (%)	Placebo (SOC) n/N (%)	RD (95% CI)
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	-
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	-

Difference in response rate was calculated using Review Manager (version 5.4.1). **Bold** text designates statistical significance.
Source: Table 2.5-1, p81, Table 2.5-2, pp83-84 of the submission, 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; NR=not reported; OCS=oral corticosteroids; 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 in SLE Responder Index.

a Original pre-specified 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).
i 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]).

6.14 The results shown in Table 4 are for responses at Week 52; data are not shown for Week 24, however the results at this timepoint are discussed below. The results demonstrated:

- In the TULIP-1 trial, there were no significant differences between anifrolumab and placebo for SRI(4) at either Week 24 or Week 52, with results favouring placebo in the pre-specified analysis. In contrast, numerically more patients achieved a BICLA response at Week 52 in the anifrolumab arm, reaching nominal significance. However, as BICLA response at Week 52 in TULIP-1 and MUSE were not included in the testing strategy for multiplicity, they should be considered exploratory and cannot be interpreted in terms of statistical significance. On the other hand, in the TULIP-2 and MUSE trials, both SRI(4) and BICLA responses at Week 24 and Week 52 were significantly higher in the anifrolumab 300 mg group compared to placebo.
- Placebo response was high (approximately 40%) in all trials. In the consideration of belimumab for SLE, the PBAC considered the high placebo response was likely due

to reasons such as the optimisation and adherence to SOC in the clinical trial setting, as well as regression to the mean as some patients may have commenced therapy during a disease flare (paragraphs 6.14 and 7.7, belimumab PSD November 2019 PBAC meeting).

- Differences in the proportion of SRI(4) and BICLA responders between the anifrolumab and placebo arms also appeared to fluctuate over time; even when the differences reached statistical significance at Weeks 24 and 52, the differences were not statistically significant just peripheral to these time points (e.g. TULIP-2 SRI(4) response at Week 48 and TULIP-2 BICLA response at Weeks 44, 48, as indicated by overlapping 95% CI bars; error bars were not reported for MUSE).
- In TULIP-1, the post-hoc analyses based on the revised restricted medication rules resulted in numerically greater differences for SRI(4) and BICLA responses compared to the pre-specified analyses, favouring anifrolumab (i.e. resulted in disproportionately more responders in the anifrolumab arm). Results using the original medication rules were not reported for TULIP-2. Trial investigators (Furie et al., 2019) for the TULIP-1 trial considered that the change in the restricted medication rules was clinically appropriate, arguing that use of NSAIDs in the trial were not as important as changes to the use of immunosuppressants, antimalarials or corticosteroids. However, the change in NSAID use could potentially affect the arthritis scores of SLEDAI and BILAG, which were components of SRI(4) and BICLA, and attributable to the higher number of responders observed in TULIP-1 for both measures with the revised medication rules (Koh et al,. 2020).

6.15 The results of the trials differed despite seemingly similar trial designs (particularly the TULIP trials which had almost identical designs) and broadly similar reported patient disease characteristics. Because concordance between the SLEDAI (driver of SRI(4) results) and the BILAG index (driver of BICLA results) has been demonstrated[5], it would be expected that the SRI(4) and the BICLA should provide similar results. The submission and PSCR stated that retrospective review of patient data showed there were more patients with arthritis in the placebo group of TULIP-1 that resolved with standard steroid use, which meets the criteria for improvement in SLEDAI-2K ≥4 points (i.e. SRI(4) responder). These patients were classified as complete responders even if there was no response in other affected organs. This argument was further re-iterated in the PSCR, which referred to a publication by Bruce et al (2022) that suggested the discordance was primarily driven by the sensitivity of SRI(4) to single organ (arthritis) improvement, as the discordant placebo group in TULIP-1 was enriched for patients with lower baseline joint counts. However, the evaluation considered such explanation is unlikely to fully account for the differences in trial results given there were similar proportions of patients achieving an SLEDAI-2K ≥4 response in the

[5] Ward MM, Marx AS, Barry NN. 2000. Comparison of the validity and sensitivity to change of 5 activity indices in systemic lupus erythematosus. J Rheumatol; 27: 664-70.

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 is unclear, the ESC acknowledged it is likely to be impacted by patient heterogeneity, including unobserved and yet unknown characteristics that drive the disease, and further considered that it may be an issue with the response indexes.

6.16 The submission presented results of other outcomes such as OCS dose and annualised flare rate, which showed reductions from baseline to Week 52 in all treatment groups. A larger proportion of patients with baseline OCS ≥10 mg/day were able to taper OCS dose to ≤7.5 mg/day at Week 52 in the anifrolumab arm compared to placebo, and the differences were statistically significant in the TULIP-2 and MUSE trials. In TULIP-2, the reduction in the annualised flare rate at Week 52 was also statistically significantly greater in the anifrolumab group than placebo.

6.17 However, there were no significant differences between anifrolumab and placebo groups in terms of improvement in fatigue (FACIT-F) or quality of life (EQ-5D) at Week 52.

6.18 The clinical trial reports also reported no difference between anifrolumab and placebo in the mean change from baseline in the SLE damage index (SDI) – a measure of non-reversible chronic organ damage – at Weeks 24 or 52 in any of the included trials. Organ damage in the model was based on a separate parametric survival distribution developed using data from the John Hopkins Lupus Cohort (JHLC) with patient characteristics (e.g., age) and disease history (e.g., SLEDAI-2K score and SDI) as predictors.

6.19 The results from open-label extension study MUSE LTE showed that improvement in disease activity as assessed on the SLEDAI-2K was maintained for up to three years. Health related quality of life (HRQoL) and organ damage (SDI score) were generally stable.

Subgroup analyses

6.20 The submission presented post-hoc subgroup analyses to estimate response in the requested PBS population. However, the submission claimed that, in the trials, the numbers of patients meeting all three PBS eligibility criteria (i.e. SLEDAI-2K ≥10 and receiving triple therapy, consisting of HCQ, an immunosuppressant and OCS ≥7.5 mg/day) were too small for any meaningful and robust analyses. Instead, it argued that patients with SLEDAI-2K ≥10 would be a reasonable proxy given these patients have high disease activity (Table 5). Results were also presented for patients taking triple therapy with OCS ≥10 mg/day, and the combined SLEDAI-2K ≥8 plus triple therapy (including prednisone ≥7.5 mg/day) (Table 5).

Table 5: SRI(4) and BICLA response by subgroups[g] in TULIP-1 and TULIP-2 (post-hoc)

	Anifrolumab 300 mg IV n/N (%)	Placebo (SOC) n/N (%)	Risk Difference (95% CI)
SRI(4) response at Week 24			
SLEDAI-2K ≥10			
TULIP-1 (pre-specified)[a]	55/125 (44.1)	57/130 (43.9)	0.2 (-12.0, 12.3)
TULIP-2	74/129 (57.4)	-60/131 (45.8)	12 (-1, 24)
TULIP 1 & 2 pooled	NE	NE	NE[b]
SRI(4) response at Week 52			
SLEDAI-2K ≥10			
TULIP-1	62/129 (48.1)	58/135 (43.0)	5.2 (-6.8, 17.2)
TULIP-2	76/129 (58.9)	52/131 (39.7)	**19.2 (7.3, 31.1)**
TULIP-1 & 2 pooled	138/258 (53.5)	110/266 (41.4)	**12.1 (3.6, 20.6)**
SLEDAI-2K ≥8, triple therapy[h] including prednisone ≥7.5 mg/day			
TULIP-1	13/26 (50.0)	10/35 (28.6)	**27.6 (0.4, 54.8)[c]**
TULIP-2	19/30 (63.3)	12/27 (44.4)	**24.3 (0.0, 48.6)[c]**
TULIP-1 & 2 pooled	32/56 (57.1)	22/62 (35.5)	**22.8 (5.2, 40.4)[c]**
BICLA response at Week 52			
SLEDAI-2K ≥10			
TULIP-1	57/129 (44.2)	35/135 (25.9)	**18.6 (7.4, 29.8)**
TULIP-2	60/129 (46.5)	36/131 (27.5)	**19.0 (7.5, 30.5)**
TULIP-1 & 2 pooled	117/258 (45.3)	71/266 (26.7)	**18.7 (10.7, 26.8)**
SLEDAI-2K ≥8, triple therapy[h] including prednisone ≥7.5 mg/day			
TULIP-1	13/26 (50.0)	8/35 (22.9)	**30.5 (7.2, 53.8)[f]**
TULIP-2	17/30 (56.7)	11/27 (40.7)	Not calculated[f]
TULIP-1 & 2 pooled	30/56 (53.6)	19/62 (30.6)	**25.6 (9.0, 42.3)[f]**

Bold text designates statistical significance

Source: Tables 2.6-3 and 2.6-4, pp95-97 of the submission and Anifrolumab versus Placebo for SLE.rm5 (*submission* Attachment 2_5).

BICLA=BILAG–Based Composite Lupus Assessment; CI=confidence interval; NE=not estimable; RD=risk difference; SLEDIA-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SOC=standard of care; SRI(4)=4-point reduction on SLE Responder Index.

Analysis was based on the TULIP-2 rules for restricted medications. The responder rate, difference estimate and associated 95% CIs are calculated using a binomial model with an identify link, with covariates for SLEDAI-2K score at screening, Day 1 OCS dose, type I IFN gene signature test result at screening, treatment, subgroup and treatment by subgroup interaction. In the pooled analysis, an additional covariate is added for study (TULIP-1 vs TULIP-2). The p-values presented was based on this binomial model

a Original pre-specified restricted medication rules.

b Pooled TULIP-1 and TULIP-2 response was not evaluated due to outcomes reported using inconsistent restricted medication rules. SRI(4) response by subgroup in TULIP-1 was a pre-specified analyses based on original medication rules and in TULIP-2 was based on the revised medication rules.

c The response difference in TULIP-1, TULIP-2 and pooled TULIP-1 and TULIP-2 could not be verified. Analysis conducted during the evaluation showed non-significant response difference of 21 (-3, 46) for TULIP-1, 19 (-7, 44) for TULIP-2 and a pooled response difference of 20 (3, 38).

f The response difference in TULIP-1, TULIP-2 and pooled TULIP-1 and TULIP-2 could not be verified. Analysis conducted during the evaluation showed response difference of 27 (3, 51) for TULIP-1, 16 (-10, 42) for TULIP-2 and a pooled response difference of 22 (4, 39).

g The N of the subgroups was based on characteristic at baseline, not screening as presented in the CSR figures. The submission reported that in TULIP-1, patients with SLEDAI-2K ≥10 at baseline and screening was n=125, however the subgroup analysis was based on n=129, which could not be verified. Analysis conducted during the evaluation showed that this difference had minor impact on the treatment effect.

h Triple therapy defined as antimalarials, immunosuppressant and OCS at baseline.

6.21 The results of the subgroup analyses from TULIP-1 and TULIP-2 showed a higher proportion of additional responders for anifrolumab versus placebo for SRI(4) and BICLA compared to the ITT trial populations. The differences were mostly driven by poorer response rates from the placebo arms in the subgroups. Given these were not

a priori defined subgroups, all statistically significant differences are considered exploratory and should be interpreted with caution.

6.22 The PSCR provided additional subgroup analyses which it stated were in the target PBS population of patients with SLEDAI-2K ≥ 10 and triple therapy including prednisone ≥7.5 mg/day. However, as outlined in Paragraph 6.11, it was unclear whether the additional data accounted for baseline OCS dose of ≥7.5 mg/day given discrepancies between the patient numbers in the PSCR and Section 2.6 of the submission.

Meta-analysis

6.23 The submission performed a meta-analysis on the three anifrolumab trials (TULIP-1, TULIP-2 and MUSE). The results 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 CLASI at Week 52. These results were generally consistent with the results of the published meta-analysis by Koh et al., 2020, which was referred to in the PSCR. The evaluation noted that while the results were statistically significant, they should be interpreted with caution noting they were post-hoc analyses.

Comparative harms

6.24 Table 6 summarises the key adverse events (AEs) across the included trials.

Table 6: Summary of key adverse events (AEs) across the included trials

	Anifrolumab 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, 0.0)]
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)**
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, 0.0)]
MUSE LTE				
≥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)	-	-	-

Bold text designates statistical significance.

Source: Tables 2.5-11 and 2.5-12, pp92-93 of the submission.

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 randomised 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.

6.25 In all trials, the incidence of any AEs was higher in the anifrolumab group compared to placebo during treatment to Week 52. The majority of AEs were non-serious, mild or moderate in intensity and did not lead to discontinuation of study drugs. There were no significant differences between groups in the incidence of serious AEs (SAEs), discontinuations due to AEs and AEs of special interest with the exception of TULIP-2, which showed significantly higher incidence of serious AEs in the placebo group.

Serious AEs included pneumonia, radial fracture, chest pain, asthma, urinary tract infection and gastroenteritis.

6.26 The most frequent AE of special interest across the trials was herpes zoster, which was higher in the anifrolumab group than placebo. The herpes zoster infections were generally cutaneous in manifestation, non-serious, mild to moderate (one event in TULIP-1 was severe and one patient in MUSE discontinued treatment due to transverse myelitis with a positive test for herpes zoster in the cerebrospinal fluid) and resolved with antiviral treatment.

6.27 There was a higher incidence of infusion-related events in the anifrolumab group across the TULIP trials.

6.28 The long-term safety data up to 3 years was consistent with the included trials to 52 weeks, with no new safety signals.

Benefits/harms

6.29 The comparative benefits and harms for anifrolumab versus placebo (i.e. SOC) in patients with SLE can be drawn from Table 4 and Table 6 above. On the basis of direct evidence presented in the submission, for every 100 patients treated with anifrolumab in comparison with placebo (SOC):

- Approximately 4 fewer patients to 22 additional patients will achieve SRI(4) response at Week 52 depending on the trial and analysis used.
- Approximately 10-28 more patients will achieve BICLA response at Week 52 depending on the trial and analysis used.
- Approximately 5 to 11 more patients will experience any AEs over 52 weeks.
- Approximately 2 to 9 fewer patients will experience SAEs over 52 weeks.
- Approximately 3 to 6 more patients will experience herpes zoster.

The above statements are based on the total trial populations, whereas the submission has targeted a patient group that the PBAC previously considered to have the greatest clinical need.

Clinical claim

6.30 The submission described anifrolumab added to SOC (comprising triple therapy, unless contraindicated or not tolerated) in patients with severe SLE as:

- superior to SOC alone in terms of effectiveness.
- non-inferior to SOC alone in terms of safety, however the PSCR (p2) revised this to a claim of inferior, but manageable safety.

6.31 The PBAC agreed with the ESC that anifrolumab has a clinical benefit over standard of care, but the magnitude of the benefit in the requested PBS population is uncertain. The discussion around these issues from the ESC and the PBAC is as follows:

Efficacy

- There were inconsistent results in the two key anifrolumab trials between disease activity indices. Anifrolumab was not associated with a beneficial response in the primary outcome of SRI(4) in the TULIP-1 trial, however a positive response was demonstrated using the BICLA. In contrast, the TULIP-2 trial showed favourable improvements with anifrolumab for both SRI(4) and BICLA. These inconsistencies arose despite near identical trial designs and reasonably similar reported patient characteristics. While the reason for the discrepancy is unclear, the ESC acknowledged it is likely to be impacted by patient heterogeneity, including unobserved and yet unknown characteristics that drive the disease, and further considered that it may be an issue with the response indexes.
- There were no significant differences in change between Week 52 and baseline of patient reported outcomes such as fatigue or quality of life for anifrolumab versus placebo in the trials. Further, while treatment with anifrolumab resulted in less OCS use, there was no change in quality of life reported in the trials.
- In TULIP-2 the restricted medication rules (around use of NSAIDs and OCS for mild flares) were changed after significant data collection had already occurred. This was likely to confound results in favour of anifrolumab.
- The trial population was not representative of patients likely to be treated on PBS, who are expected to have more severe disease. However, the ESC noted that the purpose of restricting use to this narrow population was to target patients with the greatest clinical need. Further, the ESC considered the presented subgroup analyses, while exploratory, did not raise concerns of potentially lower efficacy in the proposed PBS population.
- Overall, the the PBAC acknowledged that the issues associated with clinical efficacy of anifrolumab reflect the challenges associated with SLE and its measurement given the complex and variable nature of the disease. The PBAC considered the claim of superiority to SOC alone in terms of effectiveness was supported based on the small improvement in disease activity for some patients.

Safety

- Anifrolumab was associated with more adverse events (AEs) than placebo in TULIP-1 (RD 0.11, 95% CI: 0.04, 0.19), but not in TULIP-2 or MUSE. TULIP-2 reported fewer SAEs for anifrolumab (RD: -0.09; 95% CI: -0.15, -0.02). As these safety results reflected trial conditions where patients were administered sham infusions in the placebo arm, additional infusions reactions are to be expected for anifrolumab in clinical practice versus placebo. Anifrolumab treatment was associated with greater numbers of herpes zoster infections in all 3 trials, including one case of likely central nervous system infection. The PBAC agreed with the ESC that a claim of inferior but likely manageable safety was reasonable.

Economic analysis

6.32 The submission presented a stepped economic evaluation comparing anifrolumab to SOC. The economic evaluation was based on direct evidence from the TULIP trials and extrapolations using evidence from the MUSE LTE and the John Hopkins Lupus cohort (JHLC), which is a SLE registry based in the US. The type of economic evaluation presented was a cost-utility analysis across a 30-year time horizon, using patient level microsimulation.

6.33 The key components of the economic evaluation are summarised in Table 7.

Table 7: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-utility.
Outcomes	Quality adjusted life years.
Time horizon	• 30 years in the model base case vs. 52 weeks in the TULIP trials. SLE is a life-long chronic condition, therefore the evaluation considered that a lifetime model would be appropriate to capture all the costs and benefits associated with the disease. The PBAC agreed with the evaluation that the comparatively short trial follow-up (52 weeks vs 30-year time horizon) and the lack of direct evidence on organ damage and mortality results in an uncertain ICER.
Population	• Based on TULIP trials for the subgroup with SLEDAI-2K ≥10. • Longer term data were based on JHLC (n = 1,354) which had 6.9 years follow-up. The evaluation noted that limited information was provided about the JHLC registry. Neither the TULIP nor the JHLC populations were fully representative of the requested population, considering PBS eligibility also required patients to be on triple therapy and OCS ≥7.5 mg/day at baseline; the evaluation estimated that less than 16% of TULIP trial patients would qualify for PBS treatment. The ESC noted that the TULIP trials did not provide directly comparable data for the requested PBS population. Compared to Australian patients in the ALRB, patients with SLEDAI-2K ≥10 in the TULIP trials were older (mean age 40 years vs 34.5 years in ALRB) and with less baseline organ damage (38.6% (TULIP ITT data) vs 61.3% in ALRB). There were also far fewer patients of Asian ethnicity in the TULIP trials (9.7% versus 45.2%). Asian ethnicity is associated with more severe disease, and the PSCR claimed that subgroup analyses found that placebo-adjusted response rates were nominally higher in Asian patients indicating that the benefit of anifrolumab to the requested PBS population is potentially greater.
Methods used to generate results	• Individual patient microsimulation to allow patient characteristics/history to influence future disease events. The evaluation and ESC considered that there were issues with how this approach was implemented, including: summary level data was 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. 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.

Component	Description
Cycle length	• 6 months. The evaluation considered this to be reasonable. 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 probabilities	• Treatment discontinuation rates from the TULIP trials and MUSE LTE. • Mortality rates derived from a survival model based on JHLC adjusted by standardised mortality ratios for SLE patients. • Cycle dependent event regression models were based on evidence from the TULIP trials and JHLC. The evaluation noted that 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. 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 or less than 0 (which have no clinical interpretation), and assumed a change in SLEDAI-2K is constant across the scale (e.g. a reduction from score 6 to 2 is the same as the reduction from 13 to 9). The ICER was not very sensitive to rounding SLEDAI-2K to the nearest integer greater than or equal to 0, increasing to $[redacted][1] per QALY gained when this and other linear regressions for SDI score, OCS dose, hospital length of stay and utility were restricted to be non-negative.
Software package	• Excel 2010 with @RISK. The evaluation considered this to be reasonable, though @RISK was not utilised as expected: the distributions of the regression models were not included in the simulations.

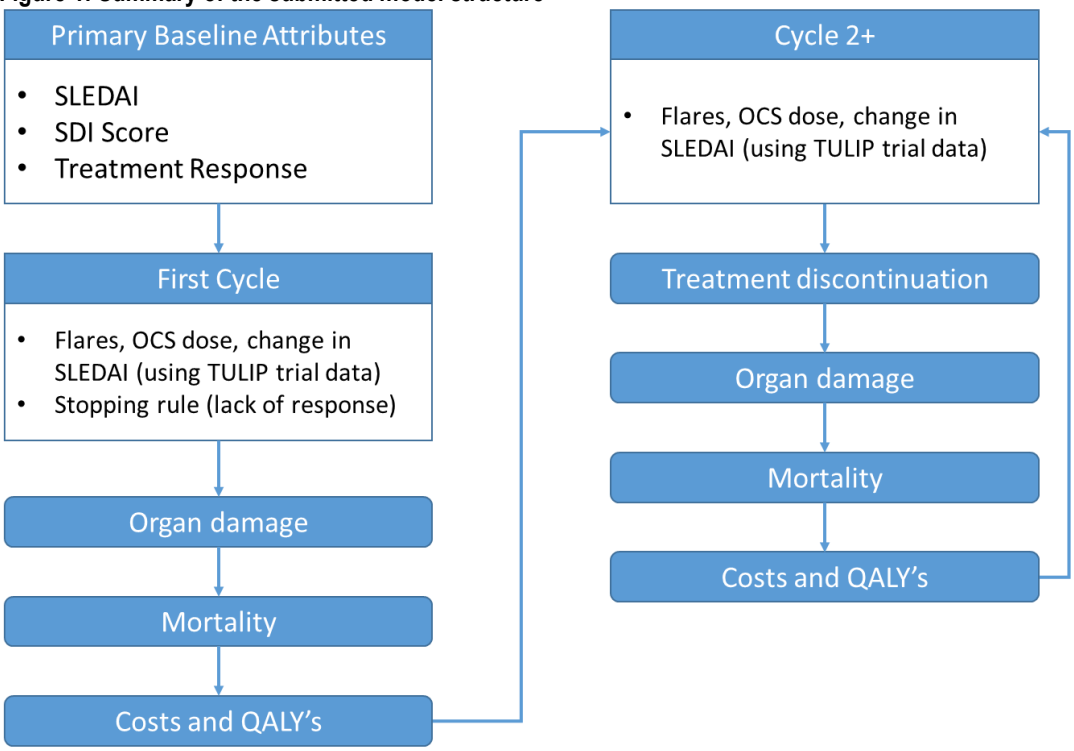
Source: Table 3.1-1, pp107-108 of the submission
ALRB=Australian Lupus Registry and Biobank; AR-DRG= Australian Refined Diagnosis Related Groups, ICER=incremental cost-effectiveness ratio, JHLC=John Hopkins Lupus cohort, NHCDC=National Hospital Cost Data Collection, OCS=oral corticosteroids, PSCR=Pre-Sub-Committee Response, QALYs=quality adjusted life years, SLE=systemic lupus erythematosus, SLEDAI-2K= Systemic Lupus Erythematosus Disease Activity Index 2000, SOC = standard of care.

The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*

6.34 The submission presented a microsimulation model to allow patient characteristics/history to influence future disease events. The ESC considered that this approach may not be reasonable, as there were limited data to populate the model particularly for longer term events such as organ damage and mortality. However, the PBAC noted that the microsimulation approach did allow for the model to reflect variability across the patient population.

6.35 A summary of the microsimulation model structure is presented in Figure 1.

Figure 1: Summary of the submitted model structure

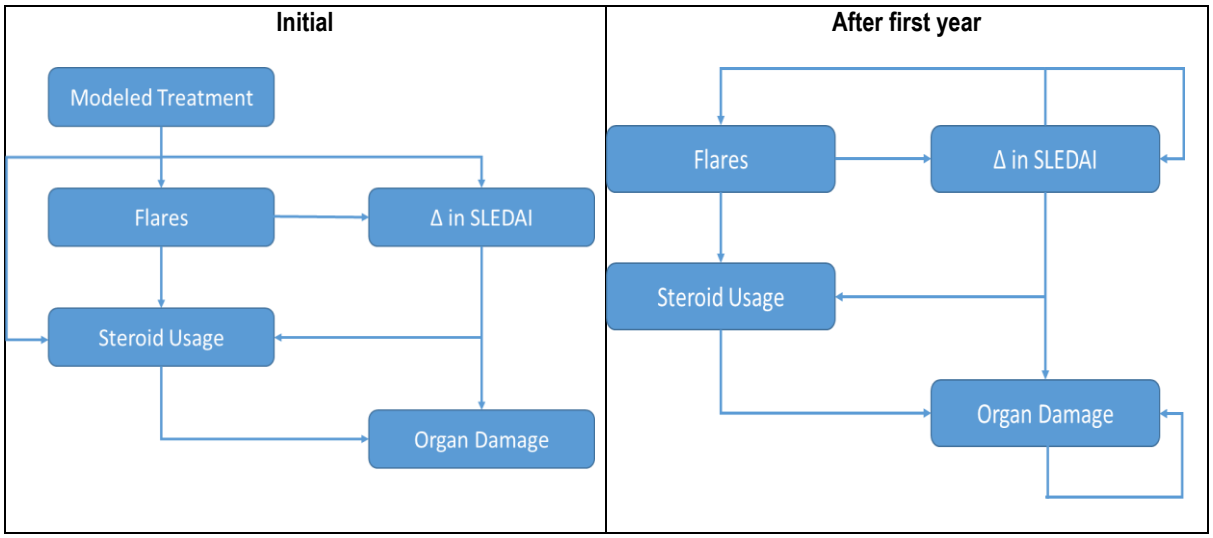


Source: Figure 3.2-3 of the submission
OCS=oral corticosteroids; QALYs=quality-adjust life year; SDI=Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index.

6.36 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. 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 data (for the SLEDAI-2K ≥10 subgroup), and predictive models for longer-term outcomes (mortality and organ damage) were based on JHLC registry data. Organ damage frequency was based on data from the Australian Lupus Registry and Biobank (ALRB).

6.37 The interdependencies of the disease progression predictive models are presented in Figure 2.

Figure 2: Dependencies among predictive models of disease progression



Source: Figure 3.2-1 and Figure 3.2-2 of the submission
SLEDAI= Systemic Lupus Erythematosus Disease Activity Index.

6.38 In the SLEDAI-2K ≥10 subgroup of the TULIP trials, the percentage of responders at Week 24 (i.e., patients whose SLEDAI-2K decreased by at least 4 points consistent with the criteria for response in the proposed PBS restriction) was 55.4% in the anifrolumab arm versus 47.4% in the placebo arm.

6.39 Many of the regression models resulted in circular estimations 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 regressor and regressand). This was particularly important given the limited clinical evidence of the relationship between SLEDAI-2K and the long-term outcomes it contributed to. The PSCR stated (p3) that a flare is a sudden large increase in disease activity combined with the need to change treatment; as such, it was appropriate for SLEDAI-2K scores to be impacted by flares and vice versa. The PSCR further argued that anifrolumab does not have a direct impact on SLEDAI-2K in the model beyond the trial period. However, the evaluation and the ESC considered there was a high chance of double counting the SLEDAI-2K effect, given it was used in predictions of other model components. The pre-PBAC response removed the effect of SLEDAI-2K on utility and the number of hospitalisations, however its effect on mortality, organ damage and OCS use remained unchanged, likely leading to some double-counting of the effect of SLEDAI on mortality.

6.40 The ESC considered that the relationship between SLEDAI-2K and clinical outcomes was not well justified in the submission, particularly the long-term outcomes to which it contributed.

6.41 Mortality was not captured in the TULIP data and organ damage was only presented as an exploratory outcome that showed no difference between the anifrolumab and

placebo arms. Instead, the model used SLEDAI-2K scores to estimate flares, OCS use, organ damage, and mortality. 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 a 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).

6.42 The evaluation considered that the chosen regression models were not justified, neither the choice of the distribution nor the covariates, and much of the underlying data and methodology could not be verified. Further, some of the regressions resulted in potentially spurious results, for example, the flare regression coefficients suggested that from Cycle 2 onwards anifrolumab non-responders had fewer non-severe flares than responders and fewer flares than SOC patients. Even if non-responders from Cycle 2 had some ongoing protection from anifrolumab over SOC, that this would continue to the end of the time horizon was not justified, especially compared to SOC responders. The ESC considered that this example demonstrated the uncertainty with the model (e.g. lack of data to inform microsimulation approach and issues with how different outcomes are predicted in the model).

6.43 Duration of flares was assumed to be 3.9 months both for patients in the SOC arm and for patients who discontinued anifrolumab in the anifrolumab arm (based on Nikpour 2009[6]). A hazard ratio (HR) of 1.76 was applied to patients receiving anifrolumab, resulting in a flare duration of 2.2 months. The value from Nikpour 2009 appeared to refer to the mean time interval between visits used to diagnose flares, rather than actual flare duration, and thus flare duration was likely overestimated in the model. A recent US cost study (Hammond et al. 2021[7]) estimated the cost of flares over a one month duration. The ICER was very sensitive to flare duration. When the duration was reduced to 3 months (1.7 months for patients receiving anifrolumab), the ICER increased to $155,000 to < $255,000 per QALY gained. Flare duration was not reported in the included trials.

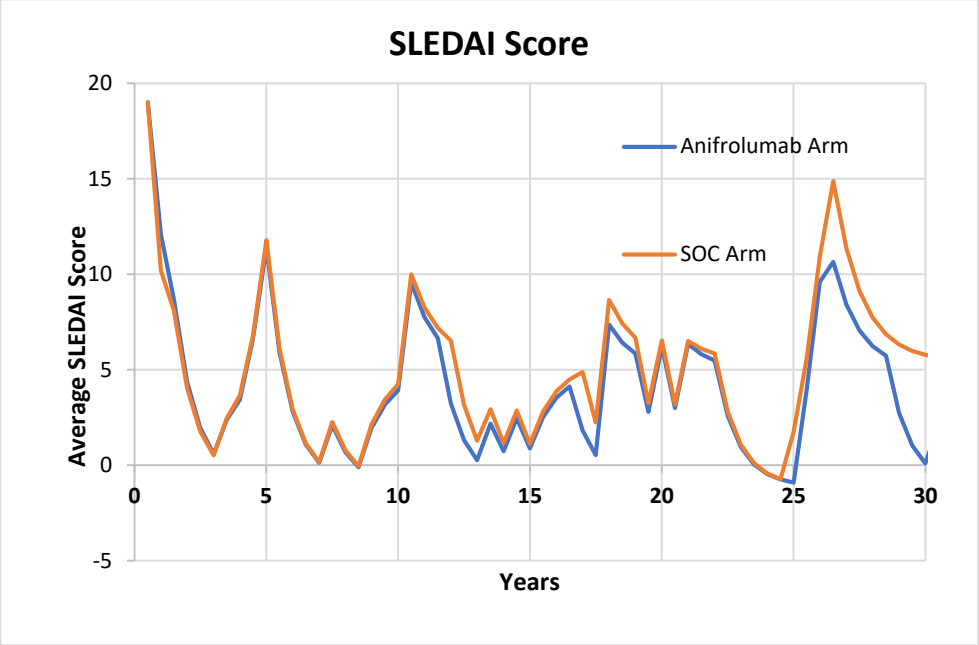
6.44 While the overall results were based on the average of 5,000 simulations, it is important to consider how reasonable the model predictions were for individual simulated patients. Figure 3 presents a single patient's SLEDAI-2K score over time,

[6] Nikpour M, Urowitz MB, Ibañez D, Gladman DD. Frequency and determinants of flare and persistently active disease in systemic lupus erythematosus. Arthritis Rheum. 2009 Sep 15;61(9):1152-8. doi: 10.1002/art.24741. PMID: 19714602.

[7] Hammond ER, Desta B, Near AM, et al Frequency, severity and costs of flares increase with disease severity in newly diagnosed systemic lupus erythematosus: a real-world cohort study, United States, 2004–2015 Lupus Science & Medicine 2021;8:e000504. doi: 10.1136/lupus-2021-000504

based on one iteration of the fixed seed 1111 used for the base case @RISK model. This patient discontinued anifrolumab at Year 1, but the greatest difference between the arms did not occur until after Year 10, and was likely driven by a reduction in flares predicted for anifrolumab non-responders compared to SOC. This example also demonstrates how the model could predict a SLEDAI-2K score less than 0.

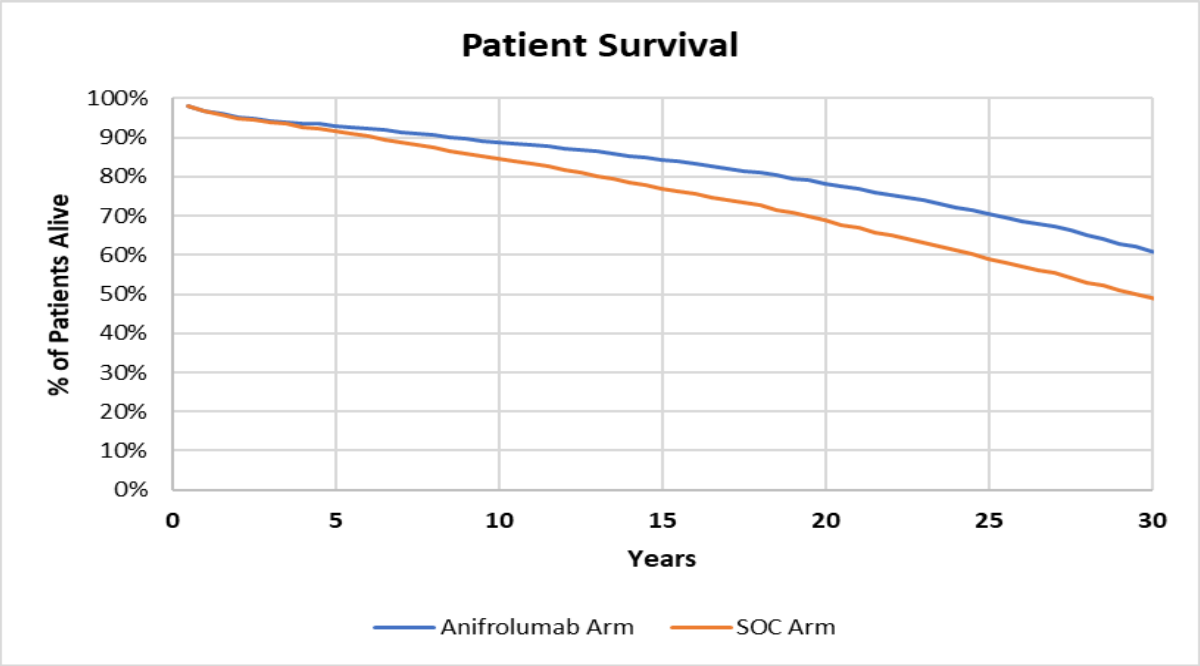
Figure 3: Modelled changes in SLEDAI-2K for 1 patient



Source: *compiled from sheet 'Summary' of the Excel workbook 'CE model_anifrolumab_SLE_March2022_circ.xlsx'*

6.45 Figure 4 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 10% difference at Year 30). The ICER was sensitive to mortality assumptions. As with other model inputs, mortality was largely driven by SLEDAI-2K estimates. If the coefficient for SLEDAI-2K in the survival distribution was set to 0, the incremental undiscounted life years gained reduced to 0.239 from 0.770 in the base case.

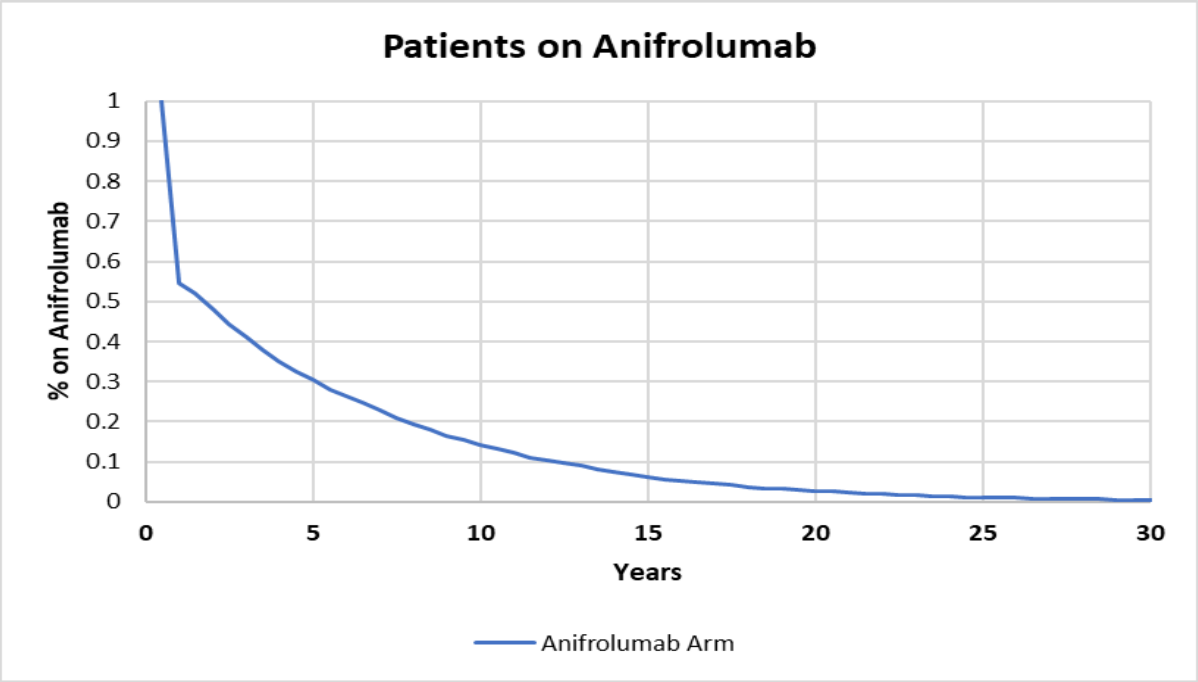
Figure 4: Modelled survival over 30 years, 5,000 patients (base case)



Source: Figure 3.7-8 of the submission

6.46 Anifrolumab treatment discontinuation was estimated as 44.6% and 7.6% in Cycles 1 and 2 respectively, based on pooled TULIP SLEDAI-2K≥ 10 subgroup data at Weeks 24 to 52, and 7.2% from Cycle 3 onwards based on MUSE LTE. As shown in Figure 5, the constant discontinuation of anifrolumab resulted in <10% patients still on treatment at Year 15, though benefits persisted to Year 30, including survival benefits, per Figure 4. The ESC considered that it was not clinically plausible for incremental survival in the anifrolumab arm to be increasing toward the end of the modelled time horizon despite few patients remaining on treatment.

Figure 5: Modelled proportion of patients on treatment

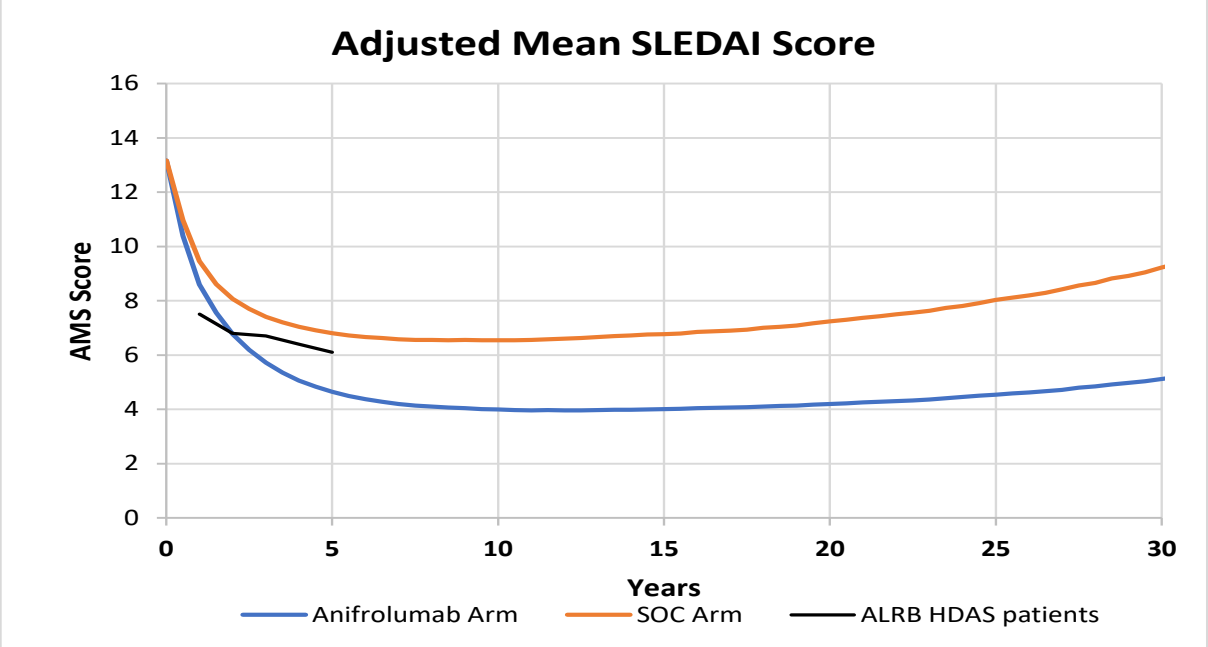


Source: Figure 3.7-1 of the submission.

6.47 The submission estimated utilities for each cycle based on a linear regression of patient characteristics, and response to treatment from the pooled ITT data from the TULIP trials. The linear regressions for utility could fall below 0 and exceed 1, (as did occur in individual patient simulations), which the ESC and the PBAC considered was not reasonable. Mean utility in the absence of organ damage was relatively high once adjusted for mortality, averaging 0.875 across the time horizon in the anifrolumab arm, and 0.874 in the SOC arm. In comparison, the mean EQ-5D scores in the pooled TULIP data were 0.566 for the anifrolumab arm and 0.555 for the placebo arm. As with many of the other regressions in the model, utility was very sensitive to the SLEDAI-2K coefficient. If the SLEDAI-2K coefficient was set to 0, the ICER increased to $75,000 to < $95,000per QALY gained, compared to $55,000 to < $75,000 in the base case. Furthermore, in the submission base case, the effect of the SLEDAI-2K score may have been double counted in the utility estimates, contributing both directly as a covariate in the utility regression and indirectly in the prediction of organ damage, and consequently organ damage associated disutility. The PBAC noted that the revised base case in the pre-PBAC response had changed the SLEDAI-2K coefficient in the utility regression to zero.

6.48 The submission compared the SLEDAI-2K scores over time to the belimumab NICE submission and the ALRB, but it was hard to draw conclusions based on the shorter follow up, and the differences between the data sources. With adjustment for mortality, the model appeared to overestimate the average mean SLEDAI-2K for patients receiving only SOC (Figure 6).

Figure 6: Modelled SLEDAI-2K score compared to ALRB data, adjusted for mortality



Source: Compiled from Sheet 'Summary' of the Excel workbook 'CE model_anifrolumab_SLE_March2022_circ.xlsx' SLEDAI-2K score adjusted for mortality. ALRB = Australian Lupus Registry and Biobank; HDAS = high disease activity score; SOC = standard of care

6.49 The key drivers of the model are summarised in Table 8.

Table 8: Key drivers of the model

Description	Method/Value in submission base case	Impact Submission base case: $[1]/QALY gained.
Time horizon	30 years in base case.	• High, favoured anifrolumab. If the time horizon was reduced to 20 years, the ICER increased to $[2]/QALY gained (incremental costs similar to 30 years, but incremental QALYs reduced from 0.844 in base case to 0.609).
Flare duration	3.9 months for SOC arm and anifrolumab non-responders. HR 1.76 applied for anifrolumab responders.	• High, favoured anifrolumab. If flare duration reduced to 3 months in SOC arm, the ICER increased to $[3]/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 hospitalisation rates and LOS. 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 equal across arms, anifrolumab was dominated by SOC (more costly and less effective). If SLEDAI-2K was assumed to only impact utility, mortality and hospital visits via the impact on flares, OCS use and organ damage, the ICER increased to $[3]/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 constant from cycle 3 onwards.	• High, favoured anifrolumab. If treatment effect was assumed to converge from Year 5, the ICER increase to $[4]/QALY gained.

Description	Method/Value in submission base case	Impact Submission base case: $[1]/QALY gained.
Mortality	Weibull parametric survival distribution with patient characteristics, SLEDAI-2K, OCS use, organ damage and infection as covariates.	• Moderate, favoured anifrolumab. If the coefficient for SLEDAI-2K was set to 0, survival in SOC was increased similar to anifrolumab arm and the ICER increased to $[4]/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. Though the treatment effect for anifrolumab non-responders was negative, the SLEDAI-2K coefficient (which was driven by treatment effect) favoured the anifrolumab arm. If the SLEDAI-2K coefficient was set to 0, the ICER increased to $[4]/QALY gained.
Treatment discontinuation extrapolation	Treatment discontinuation was assumed to be 7.2% each cycle from cycle 3 onwards	• High, favoured anifrolumab. If long term discontinuation was assumed the same as SOC (i.e. 0%), the ICER increased to $[5]/QALY gained. While this is an unlikely clinical scenario, it is more mathematically consistent with the costing approach of SOC and the assumption of long-term benefit modelling for anifrolumab.
Rate of hospitalisation	Hospital costs were the main driver of costs in the SOC arm and hospitalisation rates were modelled with negative binomial regression with SLEDAI-2K and flares as covariates.	• Moderate, favoured anifrolumab. The flare and SLEDAI-2K coefficients were likely highly correlated (SLEDAI-2K and flares both predicted each other). When the flare coefficients were set to 0, the ICER increased to $[4]/QALY gained. When the SLEDAI-2K coefficient was set to 0, the ICER increased to $[4]/QALY gained.

Source: compiled during the evaluation
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

The redacted values correspond to the following ranges:
[1]$55,000 to < $75,000
[2]$95,000 to < $115,000
[3]$155,000 to < $255,000
[4]$75,000 to < $95,000
[5]$115,000 to < $135,000

6.50 Table 9 summarises the stepped economic evaluation. The base case ICER was $55,000 to < $75,000 per QALY gained once the OCS costs were corrected ($55,000 to < $75,000 per QALY gained in the submitted base case). The majority of the costs and benefits were accrued in the extrapolation period (i.e., after Year 1 until the end of the time horizon) and an increase in survival drove the majority of the benefit of anifrolumab over the SOC arm.

Table 9: Results of the stepped economic evaluation (corrected submission base case)

Step and component	Anifrolumab arm	SOC arm	Increment
Step 1: Cost per responder at 24 weeks, no discounting			
Costs (at 6 months)	$	$0	$
Responders[a]	55.4%	47.4%	8.0%
Incremental cost/extra responder			$
Step 2: Cost per QALY at 1 year, anifrolumab costs, no discounting			
Costs	$	$0	$
QALYs gained	0.818	0.785	0.033
Incremental cost/extra QALY gained			$
Step 3: Cost per QALY at 1 year, all costs, no discounting			
Costs[b,c]	$	$5,530	$
QALYs gained	0.818	0.785	0.033
Incremental cost/extra QALY gained			$
Step 4: Cost per LYG at 30 years, 5% discounting for costs and benefits (base case)			
Costs[c]	$	$98,456	$
LYG	13.491	12.721	0.770
Incremental cost/QALY			**$**
QALYs gained	10.219	9.375	0.844
Incremental cost/extra QALY gained (base case)			**$**

Source: Table 3.8-1 of the submission and compiled during the evaluation. LYG have been included in Step 4.
LYG = life year gained, OS = overall survival, PFS = progression free survival, QALY = quality adjusted life year.
[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 copied from the model, and have been corrected here
[c] OCS costs corrected from those reported in Table 3.8-1 of the submission

6.51 Incremental QALYs were driven by the incremental life years gained for anifrolumab versus SOC. The average SDI organ damage score was 0.20 lower in the anifrolumab arm versus the SOC arm (i.e., average of 3.39 and 3.58 respectively) but a clinical interpretation of this number was not presented. After Year 2, organ damage (as represented by SDI) became increasingly worse over the modelled time horizon for patients in the SOC arm versus the anifrolumab arm (particularly once adjusted for mortality). The total number of flares experienced in each arm was estimated during the evaluation. Undiscounted and unadjusted for mortality, the anifrolumab arm was estimated to have 7.78 fewer non-severe flares and 4.62 fewer severe flares than the SOC arm.

6.52 The economic evaluation that was considered in July 2020 for belimumab estimated there would be 0.2 incremental life years gained with belimumab (Table 14, belimumab PSD July 2020 PBAC meeting). In contrast, the submission's model estimated that there would be 0.77 incremental life years gained with anifrolumab, despite a similar difference in SRI(4) responders at 52 weeks.

6.53 A summary of sensitivity analyses is presented in Table 10. The ICER was most sensitive to: time horizon, flare intercept and duration, SLEDAI-2K regression coefficients, extrapolation of treatment effect, and the SLEDAI-2K coefficient for utility estimates.

Table 10: Results of sensitivity analyses, using the corrected submission base case

Analyses	Incremental cost ($)	Incremental QALY	ICER ($)	%change
Submitted base case	[redacted]	0.844	[redacted][a1]	-
• SLEDAI-2K ≥0 rounded down to nearest integer AND SDI score, OCS dose, hospital LOS cannot ≥0 AND base utility ≥0 and ≤1.	[redacted]	0.517	[redacted][2]	77.4%
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes	[redacted]	1.040	[redacted][3]	-14.7%
• 3.5% costs and outcomes	[redacted]	1.823	[redacted][1]	-44.7%
Time horizon (base case 30 years)				
• 20 years	[redacted]	0.609	[redacted][4]	39.0%
• 40 years	[redacted]	0.979	[redacted][1]	-12.8%
Non severe flare rate				
• Lower 95% CI (NR)	[redacted]	0.546	[redacted][2]	68.4%
• Upper 95% CI (NR)	[redacted]	1.486	[redacted][5]	-62.6%
Severe flare rate				
• Lower 95% CI (NR)	[redacted]	0.457	[redacted][6]	104.9%
• Upper 95% CI (NR)	[redacted]	2.000	[redacted][7]	-79.6%
SLEDAI-2K rate				
• Lower 95% CI (NR)	[redacted]	0.769	[redacted][8]	10.1%
• Upper 95% CI (NR)	[redacted]	0.964	[redacted][1]	-15.8%
Duration of flares (base case 3.9 months)				
• 3 months	[redacted]	0.439	[redacted][9]	116.8%
• 5 months	[redacted]	1.933	[redacted][7]	-77.0%
Long term SLEDAI-2K rate (base case -0.45)				
• 1.28	[redacted]	1.724	[redacted][7]	-67.5%
• -2.18	[redacted]	0.382	[redacted][9]	147.7%
Treatment effect for entire time horizon				
• Remove treatment effect (i.e. transition probabilities for anifrolumab ≡ SOC) from year 5. Affects flares, OCS, SLEDAI-2K and utility regressions.	[redacted]	0.756	[redacted][8]	21.9%
Utility regression coefficients (base: anifrolumab responder 0.076, anifrolumab non-responder -0.029, AMS -0.009)				
• No SLEDAI-2K effect (AMS 0)	[redacted]	0.676	[redacted][8]	24.9%
Number of hospital visits regression coefficients (base: non-severe flares 0.13, severe flares 0.11, SLEDAI-2K 0.09)				
• SLEDAI-2K coefficient 0	[redacted]	0.844	[redacted][8]	13.8%
Mortality regression AMS coefficient (base: 0.214)				
• AMS coefficient 0	[redacted]	0.505	[redacted][8]	7.4%
Multivariate analyses				
• M1: SLEDAI-2K coeff. 0 in mortality and utility regressions	[redacted]	0.289	[redacted][6]	87.6%
• M2: M1 + SLEDAI-2K coeff. 0 in no. of hospital visits regression	[redacted]	0.289	[redacted][9]	157.6%

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

AMS = adjusted mean SLEDAI; OCS = oral corticosteroids; HR = hazard ratio; CI = confidence interval; NR = this value was not reported in the submission; LOS = length of stay; yr = year; SOC = standard of care; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio; SDI = SLICC damage index

a Corrected for OCS costs during the evaluation.

The redacted values correspond to the following ranges:

[1]$55,000 to < $75,000

[2]$115,000 to < $135,000

[3]$35,000 to < $45,000

[4]$95,000 to < $115,000

[5]$25,000 to < $35,000

[6]*$135,000 to < $155,000*
[7]*$15,000 to < $25,000*
[8]*$75,000 to < $95,000*
[9]*$155,000 to < $255,000*

6.54 The pre-PBAC response (p3) provided a revised base case with the following changes:

- the SLEDAI-2K effect coefficient in the utility regression was changed to zero;
- the coefficient for SLEDAI-2K on hospitalisation was changed to zero (which assumes that all hospitalisations are due to flares and organ damage).
- an effective DPMQ of $[redacted] was applied, corresponding to a [redacted]% price reduction compared to the price proposed in the submission.

With these changes, the pre-PBAC response calculated a revised ICER of $55,000 to <$75,000 per QALY over a 30 year time horizon.

Anifrolumab cost/patient/year

6.55 Table 11 presents the drug cost per patient for anifrolumab based on the price proposed in the submission. Note that the pre-PBAC response proposed a lower price.

Table 11: Drug cost per patient for anifrolumab

	Trial dose and duration	Model	Financial estimates
Mean dose anifrolumab	300 mg	300 mg	300 mg
Mean number of administrations per year	[redacted]		
Mean duration anifrolumab	NR[a]	4.21 years (30 year time horizon)	3.14 years (6 year time horizon)
Cost/patient/month ($)	NA	[redacted][b]	[redacted][b]
Cost/patient/year ($)	NA	[redacted]	

Source: compiled during the evaluation
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.
a The proportions 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.
b The pre-PBAC response reduced the effective DPMQ (S100 HSD public) for anifrolumab from $[redacted] to $[redacted].

The redacted values correspond to the following ranges:
[1]< 500

Estimated PBS usage & financial implications

6.56 This submission was considered by DUSC.

6.57 The submission used an epidemiological approach to estimate the financial impact of listing anifrolumab on the PBS.

6.58 Table 12 summarises the sources of data and assumptions used in the financial estimates. No offsets were included for reduced use of other PBS-listed medicines for SLE which was reasonable as anifrolumab is expected to be used in addition to SOC, rather than replace it.

Table 12: Data sources and parameter values applied in the utilisation and financial estimates

Data	Source	Comment
Eligible population		
Prevalent patients with SLE	Australian adult population estimates (2023-2028) multiplied by prevalence of 94.3 in 100,000 based on Australian estimates.	Prevalence was estimated from multiple literature sources with inverse weighted variance adjustment which inflated the estimated prevalence rate.
Eligible population: patients with SLEDAI-2K ≥10	Prevalent patients multiplied by 32.12% from ALRB data. This value could not be verified but appeared to correspond to 32.1% with at least one episode of SLEDAI-2K ≥10 in the ALRB. This was revised to 15.83% in the pre-PBAC response, which was stated to be adapted from the IQVIA report.	The submission's estimate of 32.12% was based on a population that did not match the restriction criteria which also requires patients to be receiving triple therapy (incl OCS ≥7.5mg/day). In the TULIP trials and ALRB data this subgroup was small (<16% in TULIP and 14.42% in ALRB). In its consideration of belimumab for SLE, the PBAC considered the estimate of 15.36% may be an overestimate, as two of the four experts' opinions presented in the submission were that 5% of all SLE patients may be considered for a biologic (para 6.63, belimumab PSD, November 2019). The pre-PBAC response argued the PBS population proposed for belimumab was more restrictive than anifrolumab due to inclusion of serological restrictions.
Treatment utilisation		
Uptake rate	Assumption. Submission: [redacted]% in Yr1 increasing to [redacted]% in Yr6, similar to those suggested in para 6.72, belimumab PSD, July 2020. Pre-PBAC response: [redacted]% in Yr1 increasing to [redacted]% in Yr6.	DUSC considered that the static uptake rate of [redacted]% applied beyond Year 3 was unlikely to occur in practice.
Continuing patients 6-12 months	Initiating patients x 55.4% (44.6% initiating patients receive only 6 months of treatment)	Continuation at 6 months was lower than in the economic model. 100% of patients who continued past 6 months of treatment received full year of treatment, which was higher than estimated in the model (92.4%)
Continuing patients beyond 12 months	Annual continuation rate 86.1% applied based on 3-year data from MUSE LTE.	Calculations matched the model calculations.
Scripts dispensed	[redacted][1] scripts per patient-year. 100% compliance assumed	[redacted][1] scripts per year used in the economic model
Costs		
MBS costs	$81.52 based on MBS item 14245 (infusion cost for immunotherapy) at 80% rebate ($101.90 full fee)	Reasonable

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 complied during the evaluation
ALRB = Australian Lupus Registry and Biobank; Yr = year; mth = month

The redacted values correspond to the following ranges:
[1]< 500

6.59 A summary of the financial impact of anifrolumab for SLE is presented in Table 13.

Table 13: Estimation of number of treated patients, prescriptions and financial impact of proposed medicine

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Patients							
SLE pop.	[1]	[4]	[4]	[4]	[4]	[4]	[redacted]
Eligible pop.	[2]	[2]	[2]	[2]	[2]	[2]	[5]
Uptake rate	[redacted]						-
Initiating pts	[3]	[3]	[3]	[3]	[3]	[3]	[1]
Continuing pts	[3]	[3]	[3]	[3]	[2]	[2]	[4]
Total pts	[3]	[3]	[3]	[2]	[2]	[2]	[5]
Total pt yrs	[3]	[3]	[3]	[2]	[2]	[2]	[4]
Number of anifrolumab scripts							
PBS/RPBS	[1]	[4]	[6]	[7]	[8]	[9]	[10]
Net cost to R/PBS ($)	[11]	[12]	[14]	[16]	[16]	[16]	[redacted]
MBS cost	$1,789,623	$2,181,099	$2,953,312	$3,747,448	$3,801,755	$3,856,266	$18,329,504
Cost to R/PBS and MBS	[11]	[12]	[14]	[16]	[16]	[16]	[19]
Pre-PBAC response							
Scripts	[4]	[4]	[5]	[5]	[5]	[5]	[18]
Cost to R/PBS [a] ($)	[11]	[13]	[13]	[15]	[15]	[15]	[17]
Cost to R/PBS and MBS ($)	[11]	[13]	[15]	[15]	[15]	[12]	[17]

Source: Tables 4.2-1,4.2-6, 4.5-1, 4.5-2, 4.5-4, 4.5-5 of the submission, Financial impacts worksheet submitted with the pre-PBAC response
pop = population, pt = patient; yr = year
[a] This differs to the values in Table 3 of the pre-PBAC response, which appeared to be based on the proposed published price (rather than the proposed effective price of $[redacted])

The redacted values correspond to the following ranges:
[1]10,000 to < 20,000
[2]5,000 to < 10,000
[3]500 to < 5,000
[4]20,000 to < 30,000
[5]30,000 to < 40,000
[6]40,000 to < 50,000
[7]60,000 to < 70,000
[8]80,000 to < 90,000
[9]90,000 to < 100,000
[10]300,000 to < 400,000
[11]$20 million to < $30 million
[12]$50 million to < $60 million
[13]$30 million to < $40 million
[14]$80 million to <90 million
[15]$40 million to < $50 million
[16]$100 million to < $200 million
[17]$200 million to < $300 million
[18]100,000 to < 200,000
[19]$600 million to <$700 million

6.60 The submission estimated that the total net cost to the R/PBS and MBS would be $600 million to < $700 million over the first six years of listing. This was reduced to $200 million to < $300 million in the pre-PBAC response (based on the effective price proposed; the pre-PBAC response stated the cost to the PBS/RPBS would be $300 million to < $400 million over six years but this appeared to be based on the proposed published price).

6.61 The submission estimated that there would be over 90,000 to <100,000 anifrolumab scripts dispensed in Year 6, which is significantly higher than the number estimated for belimumab in July 2020, with the PSD stating 'the redacted table shows that at Year 6, the estimated total number of belimumab scripts was 10,000 to <20,000 (page 39, belimumab PSD, July 2020 PBAC meeting). The pre-PBAC response continued to estimate a substantially higher number of scripts in Year 6 (30,000 to < 40,000) compared with the range reported in the belimumab PSD.

6.62 The DUSC considered that the estimates presented in the submission were significantly overestimated. The DUSC listed the main issues as:

- The proportion of eligible patients (32.12%) was overestimated. This estimate was based on the Australian Lupus Registry and Biobank (ALRB) data for patients with SLEDAI-2K≥10 irrespective of triple therapy, and so was broader than the proposed population. Further, DUSC noted the ALRB data contained information from specialist centres and considered it was not necessarily representative of the entire PBS population. The evaluation noted that in the TULIP trials and ALRB data this subgroup was small (<16% in TULIP and 14.42% in ALRB). Further, the evaluation and DUSC noted that, in its consideration of belimumab for SLE, the PBAC had previously considered the estimate of 15.36% may be an overestimate as two of the four experts' opinions presented in the submission were that 5% of all SLE patients may be considered for a biologic (para 6.63, belimumab PSD, November 2019). Overall, DUSC considered a value of <16% would be more appropriate. This was revised to 15.83% in the pre-PBAC response, which was stated to be adapted from a commissioned survey report.
- There was significant double counting. As noted in the evaluation, 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. DUSC presented revised estimates to address the double counting, and considered that a total six year cost of $300 million to < $400 million rather than $600 million to < $700 million would be closer to real world practice. The pre-PBAC response stated that its revised estimates had addressed concerns around double-counting.
- DUSC noted that the uptake rate was [redacted]% in Year 1 increasing to [redacted]% beyond Year 3. DUSC considered that the static uptake rate of [redacted]% applied beyond Year 3 was unlikely to occur in practice as clinicians are familiar with prescribing monoclonal antibody products especially when treating immune disorders. The pre-PBAC response increased the uptake rates to [redacted]% in Year 1 to [redacted]% in Year 6.

6.63 The evaluation noted the following additional issues with the financial estimates:

- The SLE population was estimated to be larger than previous estimates (94.33 per 100,000 compared to 65.26 per 100,000 presented in the belimumab submission, para 6.62, belimumab PSD, November 2019 PBAC meeting). However, DUSC considered that it was likely that the prevalence of SLE in Australia had grown over

time particularly due to the growth of sub-populations with predispositions towards SLE. DUSC considered that the estimated prevalence proposed in this submission was more appropriate than the belimumab submission given the paucity of current data.

- The estimates did not account for patient mortality, which may overestimate the length of time on treatment.
- The estimates assumed all patients who responded at 6 months would receive a further 6 months of treatment, but in the economic model this only applied to 92.4% of the patients.

6.64 The pre-PBAC response provided revised financial estimates, incorporating revised financial inputs and an effective DPMQ of $ (paragraph 6.54). The revised financial inputs assumed the proportion of eligible patients would be 15.83% (revised down from 32.12%) and the prevalent population was adjusted to avoid double counting. In addition, the uptake rates were increased from %–% (Years 1 to 6, respectively) to %–%. The pre-PBAC response also included grandfather patients. These patients were added onto the prevalent population, which would lead to double-counting as these patients would already be included in the prevalence approach used.

Quality Use of Medicines

6.65 The submission indicated that several post marketing surveillance studies were planned in EU and US, however results were not available at the time of evaluation. The sponsor stated that it plans to provide educational materials to patients and healthcare professionals including a website and text message reminders for infusions.

Risk-sharing arrangements

6.66 The submission did not propose a risk sharing arrangement (RSA) for anifrolumab. In its consideration of belimumab, the PBAC had previously considered there was a high risk of use outside the restriction and that a RSA with a rebate above the cap would be required given the uncertain size of the patient population, uncertain treatment duration and potential leakage (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 anifrolumab for the treatment of patients with severe systemic lupus erythematosus (SLE) with high disease activity despite standard of care (SOC). The PBAC acknowledged there is a clinical need in the requested patient population, but considered the magnitude of benefit was modest and uncertain, and the ICER was underestimated and highly uncertain. The PBAC considered that a revised economic model, along with a price reduction, would be required to achieve

acceptable incremental cost-effectiveness.

7.2 The PBAC accepted that there is a clinical need for effective treatments in the requested population. However, the Committee 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.

7.3 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 agreed with the ESC that patients should be able to discontinue anifrolumab without excluding them from future treatment for flares; therefore, the statement "Patient must not have previously received PBS-subsidised treatment with this drug for this condition" is not required in the initial treatment restriction.

7.4 The PBAC considered the nominated comparator of SOC alone, 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, was appropriate.

7.5 The PBAC considered that anifrolumab likely confers 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 52.5% in the anifrolumab arm versus 40.2% in the placebo arm, pooled results). However, the PBAC considered that the magnitude of benefit was uncertain due to the:

- differing results between TULIP-1 and TULIP-2 with respect to SRI(4), despite similar trial designs and patient characteristics. While the submission and PSCR argued this heterogeneity was primarily driven by the sensitivity of SRI(4) to single organ (arthritis) improvement, the PBAC considered this explanation was unlikely to fully account for the differences, as outlined in Paragraph 6.15.
- the 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, which were: (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, in which no difference between anifrolumab and placebo was observed in terms of SRI(4) response.

7.6 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 Rhematology (ACR) response criteria are used, or psoriasis where the Psoriasis Area and Severity Index (PASI) score is used). Overall, 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.

7.7 The PBAC considered that a claim of inferior but manageable safety was reasonable.

7.8 The PBAC noted that the economic model used data from the subgroup of patients in the TULIP trials with a SLEDAI-2K ≥10, and considered this was appropriate. The PBAC considered that the subgroup analyses presented, while exploratory, did not raise concerns of potentially lower efficacy in the proposed PBS population.

7.9 The PBAC noted that the ESC had raised a number of concerns with the economic model presented with the submission including:

- 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 relationship between SLEDAI-2K and the long-term outcomes to which it contributed.
- the multicollinearity of regressors, the appropriateness of model fit and the extrapolation of the regression coefficients across the time horizon (as outlined in paragraph 6.42). Further, ESC considered there was a high chance of double counting the SLEDAI-2K effect (as outlined in paragraph 6.39).

7.10 Further, the PBAC considered that some outputs of the economic model did not appear to be clinically plausible:

- the PBAC noted Figure 3, which shows the modelled changes in SLEDAI-2K for a particular simulated patient. The PBAC considered the changes in SLEDAI-2K were implausible as the patient discontinued anifrolumab at Year 1, however the greatest difference between the arms in SLEDAI-2K occurred after Year 10. The PBAC considered that it was unreasonable that differences would commence so long after the patient had discontinued anifrolumab therapy.
- the PBAC noted there was a 10% difference in survival between the arms at Year 30 (as shown in Figure 4) despite fewer than 10% of patients still being on treatment at Year 15.
- compared with data from the Australian Lupus Registry and Biobank, the model appeared to overestimate the average mean SLEDAI-2K for patients receiving only SOC (as shown in Figure 6).
- 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.

7.11 Overall, the PBAC considered that the ICER was highly uncertain and favourable to

anifrolumab. The PBAC considered that a revised economic model addressing the ESC's concerns, along with a price reduction, would be required to achieve acceptable cost-effectiveness.

7.12 The PBAC noted that the net cost to the PBS/RPBS and MBS was revised from $600 million to < $700 million over six years in the submission to $200 million to < $300 million in the pre-PBAC response (the pre-PBAC response stated the cost to the PBS/RPBS would be $300 million to < $400 million but this appeared to be based on the published price). 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 (refer to Paragraph 6.61). 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 (% in Year 1 increasing to % in Year 6) may have been overestimated in the later years. Further, the PBAC noted that the financial estimates had assumed 100% compliance, which it considered was unreasonable in the context of an IV infusion.

7.13 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.

7.14 The PBAC considered a resubmission for anifrolumab should address the following issues:

- Present a revised economic evaluation addressing the concerns raised in paragraphs 7.9, 7.10, 7.11 and the 'economic analysis' section, including a reduction in the anifrolumab price to achieve acceptable incremental cost-effectiveness;
- Address the issues with the financial estimates raised in paragraph 7.12; and
- Include a RSA with a rebate above the cap to account for the uncertain size of the patient population.

7.15 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.16 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.