CADTH

CADTH Reimbursement Recommendation

Anifrolumab (Saphnelo)

Indication: in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

Recommendation

Summary

What Is the CADTH Reimbursement Recommendation for Saphnelo?

CADTH recommends that Saphnelo be reimbursed by public drug plans in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE).

Which Patients Are Eligible for Coverage?

Saphnelo should only be covered to treat adult patients with moderate-severe SLE whose disease cannot be controlled with an oral corticosteroids (OCS) dose of at least 10 mg per day of prednisone or its equivalent in addition to standard of care. Saphnelo should not be covered to treat patients with active severe SLE nephritis or patients with severe or unstable neuropsychiatric SLE.

What Are the Conditions for Reimbursement?

Saphnelo should only be reimbursed if prescribed by a physician with expertise in diagnosing and managing SLE and if the cost of Saphnelo is reduced. Saphnelo should not be covered when used in combination with other biologic treatments. After 12 months of treatment, Saphnelo can be prescribed again for patients who show a reduction in disease activity and reduction in glucocorticoid intake compared to when they first started treatment.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Saphnelo reduced disease activity and use of OCS for patients with moderate-to-severe SLE.
- Saphnelo may address some of the needs that are important to patients as it reduce disease activity and the use of OCS.
- Based on CADTH's assessment of the health economic evidence, Saphnelo does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Saphnelo is estimated to cost the public drug plans approximately $12 million over the next 3 years.

Additional Information

What Is SLE?

Lupus is a disease affecting approximately 1 in 1,000 Canadians. The most serious form of lupus is SLE, in which the body's immune system attacks its cells and organs. Patients with SLE can experience fatigue and joint pain, which can be disabling, as well as neurological, renal and cardiovascular sequelae, rash and a variety of other symptoms. The disease has a variable course, and patients can cycle between a chronic state to flares (acute worsening of their condition) to remission. Long-term organ damage is the main risk factor for mortality.

Unmet Needs in SLE

Patients with SLE identified a need for new treatments that control the disease for patients who fail to respond to currently available therapies or who are unable to tolerate the adverse effects related to these therapies, and which reduce dependence on OCS.

How Much Does Saphnelo Cost?

Treatment with Saphnelo is expected to cost approximately $21,934 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that anifrolumab be reimbursed for use in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, SLE only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One double-blind, randomized controlled trial (RCT) TULIP-2 (N = 362) in adult patients with moderate-to-severe autoantibody positive SLE receiving standard of care demonstrated that treatment with anifrolumab reduced disease activity and use of OCS. In the TULIP-2 study, anifrolumab was associated with a statistically significant reduction in disease activity after 52 weeks compared to placebo, as measured by British Isles lupus assessment group-based composite lupus assessment (BICLA) response (47.8% in the anifrolumab 300 mg group versus 31.5% in the placebo group; treatment difference of 16.3%, 95% CI 6.3% to 26.3%, P value = 0.0013). In addition, statistically significant differences in favour of anifrolumab 300 mg group were reported for the key secondary end points of maintenance of reduction in the OCS dose to 7.5 mg or less per day in patients with baseline OCS of at least 10 mg per day, and a reduction of 50% or more in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in patients with baseline CLASI activity score of at least 10. The clinical expert stated that based on the results of TULIP-2 the clinical benefits of anifrolumab were clinically meaningful. CDEC recognizes that SLE is a complex and heterogeneous disease with significant needs for patients who are refractory to current therapies.

Patient-identified unmet needs include treatment options that control the disease for patients who fail to respond to currently available therapies or who are unable to tolerate the adverse effects related to these therapies, and which reduce dependence on OCS. CDEC noted that available evidence supports that anifrolumab addresses some of the unmet needs identified by patients by reducing disease activity and the use of OCS.

Using the sponsor submitted price for anifrolumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for anifrolumab plus best supportive care (BSC) was $181,708 per quality-adjusted life-year (QALY) compared with BSC alone based on a pooled analysis of the results of the TULIP-1 and TULIP-2 trials. At this ICER, anifrolumab is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients with moderate-to-severe SLE (based on systemic lupus erythematosus disease activity index 2000 [SLEDAI-2K] score ≥ 6), whose disease activity cannot be controlled despite therapy that included an OCS dose of at least 10 mg per day of prednisone or its equivalent. A price reduction is required for anifrolumab to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with anifrolumab	Patients enrolled in both trials were adult	Standard therapy currently includes

Reimbursement condition	Reason	Implementation guidance
should be reimbursed when initiated in adult patients with moderate-to-severe SLE (defined as SLEDAI-2K score of at least 6) and who are unable to control their disease while using OCS dose of at least 10 mg/day of prednisone or its equivalent in addition to standard of care.	with moderate-to-severe SLE, had a SLEDAI-2K score of 6 points or more, and receiving either one or any combination of OCS, antimalarials, and/or immunosuppressants at baseline.	using an antimalarial drug (e.g., hydroxychloroquine) or immunosuppressive drugs (e.g., cyclophosphamide, azathioprine, methotrexate, cyclosporine, and mycophenolate) with or without NSAIDs. CDEC noted that a validated instrument such as SLEDAI-2K or BILAG should be used to assess disease activity at baseline and follow-up visits. The same scale should be used both at baseline and all subsequent renewals.
2. Treatment with anifrolumab must not be reimbursed when initiated in patients with any of the following: 2.1. Severe or unstable neuropsychiatric SLE 2.2. Active severe SLE nephritis	There is no evidence to support the efficacy of anifrolumab in patients with severe or unstable neuropsychiatric SLE, or active severe SLE nephritis.	—
3. The maximum duration of initial reimbursement is for 12 months.	The treatment effects of anifrolumab were evaluated at 52-weeks in the TULIP-2 study.	—
Renewal		
4. Treatment with anifrolumab can be renewed as long as all of the following are met: 4.1. OCS dose decreased to ≤ 7.5 mg/day of prednisone or its equivalent 4.2. Reduction in disease activity measured by: 4.2.1. reducing the SLEDAI-2K score to 5 or less 4.2.2. BILAG improvement in organ systems and no new worsening.	TULIP-2 study demonstrated that treatment with anifrolumab was associated with statistically significant and clinically meaningful improvements in reduction OCS use, and reduction in disease activity. These outcomes were important to patients and there is a significant unmet need to provide therapies that address these outcomes.	CDEC noted that after the first 12 months of therapy with anifrolumab, patients whose OCS dose remains higher than 7.5 mg/day of prednisone or its equivalent but have their OCS dose decreased by at least 50% from baseline could be considered as if they achieved the OCS dose reduction condition. CDEC noted that improvement in involved BILAG organs (A [severe] and B [moderate]) at baseline (e.g., reduction of all baseline BILAG-2004 A to B,C, or D or baseline BILAG-2004 B to C, or D, and no BILAG) with no worsening (where worsening is defined as ≥ 1 new BILAG-2004 A or ≥ 2 new BILAG-2004 B item). A minor improvement is considered a change from grade A to B or grade B to C; minor deterioration is considered a change from grade C to B.
5. For subsequent renewal, the physician must provide proof that the initial response achieved after the first 12 months of therapy with anifrolumab has been	Annual assessments will help ensure that the treatment is used for those who are benefiting from the therapy.	Experts must document SLEDAI-2K or BILAG assessments at start of therapy and provide yearly assessments to renew therapy. The same scale should be used

Reimbursement condition	Reason	Implementation guidance
maintained. Subsequent renewals should be assessed annually.		both at baseline and all subsequent renewals.
Prescribing		
6. Patient should be under the care of a physician with expertise in the diagnosis and management of SLE.	Accurate diagnosis and follow-up of patients with SLE are important to ensure that anifrolumab is prescribed to the most appropriate patients.	—
7. Anifrolumab should not be reimbursed when used in combination with other biologic treatments.	There is no evidence to demonstrate a beneficial effect of anifrolumab when used in combination with other biologics in patients with SLE.	—
Pricing		
8. A reduction in price	The ICER for anifrolumab plus BSC is $181,709 per QALY when compared with BSC alone based on a pooled analysis of the TULIP-1 and TULIP-2 trial data in patients with SLE who have a SLEDAI-2K score ≥ 6) and OCS dose of ≥ 10 mg/day. A price reduction of at least 74% for anifrolumab would be required for anifrolumab plus BSC to be able to achieve an ICER of $50,000 per QALY compared to BSC alone.	—

BILAG = British Isles Lupus Activity Group; BILAG-2004 = British Isles Lupus Activity Group 2004; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; OCS = oral corticosteroids; QALY = quality-adjusted life-year; SLE = systemic lupus erythematosus; SLEDAI-2K = systemic lupus erythematosus disease activity index 2000.

Discussion Points

- During the initial and reconsideration meetings, CDEC recognized that SLE is a heterogenous disease, and that there is a need to better identify patients who might respond to different treatments or combinations of treatment.
- CDEC noted that the SLE Responder Index of at least 4 (SRI[4]) used to define outcomes in the TULIP-1 trial is widely accepted as an assessment tool in research, but may not accurately identify all patients who have improved with time. The clinical expert noted to CDEC that there is a shift toward the BICLA given its ability to capture partial responses and discriminative nature to detect difference between placebo and active treatment better than the SRI[4]. The British Isles Lupus Activity Group 2004 (BILAG-2004), a main component and driver of the BICLA, is a valid and reliable instrument for patients with SLE and is more responsive to change than the SLEDAI-2K. Compared with BILAG, the SLEDAI is less responsive to change, does not capture improvement or worsening, and does not assess severity in an organ system.
- CDEC discussed the need for new treatments for SLE, to prevent organ damage and improve quality of life; however, currently available trials provided no evidence that

anifrolumab alters the risk of organ damage or improves quality of life which were needs identified by patients.

- CDEC discussed that the relapsing, remitting, and chronic disabling nature of SLE often results in patients requiring intermittent or continuous use of corticosteroids for flares. Patients expressed a desire for treatments that can mitigate the potential adverse effects of long-term corticosteroid use. While the short-term results of TULIP 1 and TULIP 2 indicated a reduction in OCS dose was possible in some patients, the trials were of insufficient duration to determine if anifrolumab would reduce corticosteroid use in the long-term and/or the adverse effects of cumulative exposure to corticosteroids.

- During the discussion of the request for reconsideration, CDEC discussed the results from TULIP-LTE, which indicated a reduction in disease activity measured by SLEDAI-2K score, and reduced use of OCS in patients who are treated with anifrolumab, was sustained out to 3 years. While the design of the TULIP-LTE with continued blinding of the investigational drug and re-randomizing placebo patients to anifrolumab or placebo does reduce both bias and the uncertainty in the results, the lack of statistical testing for efficacy end points does not allow conclusions to be drawn. In addition, CDEC noted that the TULIP-LTE was not included in the sponsor's economic evaluation.

- During the discussion of the request for reconsideration, CDEC discussed the post hoc results from TULIP 1, which used different restricted medication rules than the preplanned analysis. CDEC noted that post hoc results from the British Isles lupus assessment group-BICLA score in the TULIP 1 data were consistent with those reported in TULIP 2. However, the results in SRI-4, the primary outcome measure, the difference in comparison with placebo did not reach statistical significance.

- During the initial and reconsideration meetings, CDEC discussed the percentage of patients who discontinued in the TULIP-1 study was similar between treatment groups, there was an imbalance in the discontinuation rates between the treatment groups in TULIP-2, with the percentage of patients who discontinued anifrolumab was lower than those who discontinued placebo (13.3% versus 25.3%). This inconsistency between the studies in terms of discontinuation increased the uncertainty around the results of the trials. While CDEC acknowledged that the sensitivity analyses conducted reduce some of the concerns regarding attrition bias, the imbalance in discontinuation rates remains a concern.

- CDEC acknowledged that as CADTH was unable to consider the impact of the use of incremental response rate in the anifrolumab group, the incremental QALYs may be overestimated. As a result, a greater price reduction may be required to address the uncertainty identified in the economic evaluation.

Background

Lupus is an autoimmune disease that affects approximately 1 in 1,000 Canadians, and the most serious form of lupus is SLE. The age of onset is primarily between 16 and 55, although the disease can present at any age. Patients can experience fatigue and joint pain, which can be disabling, as well as neurological, renal and cardiovascular sequelae, rash and a variety of other symptoms. The disease has a variable course, and patients can cycle between a chronic state to flares (acute worsening of their condition) to remission. Long-term organ damage is the main risk factor for mortality and may occur from the disease pathology as well as during periods of low disease activity due to toxicity from treatment.

The first line of treatment among the chronically administered drugs is an antimalarial, that interferes with intracellular toll-like receptor signalling. Given that SLE is an autoimmune disorder, immunosuppressants also play an important role, and there are a variety that are used. The immunosuppressants have multiple harms associated with them, including risk of serious infection and malignancy, and present significant tolerability issues for patients. Corticosteroids are used to reduce inflammation and pain. This treatment is well known for toxicities, particularly when used chronically, and thus although they are relied upon for flares, chronic use is avoided as much as possible.

Anifrolumab has been approved by Health Canada in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, SLE. Anifrolumab is a type I interferon (IFN) receptor antagonist. Anifrolumab is available as an IV infusion and the dosage recommended in the product monograph is 300 mg administered as an IV infusion over a 30-minute period, every 4 weeks.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information or sources of information:

- a review of 2 RCTs in adult patients moderate-to-severe, autoantibody positive SLE
- patients perspectives gathered by 4 patient groups, (Arthritis Consumer Experts [ACE], Lupus Canada, Lupus Ontario, and a cooperative submission from CAPA, the Arthritis Society, and the Canadian Skin Patient Alliance [CSPA])
- input from public drug plans and cancer agencies that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with SLE
- input from 2 clinician groups, including the Canadian Network for Improved Outcomes for Systemic Lupus Erythematosus (CaNIOS) and the Toronto Lupus Program from the University of Toronto
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the request for reconsideration (described later in this document).

Stakeholder Perspectives

Patient Input

Four responses to CADTH's call for patient input for the anifrolumab submission were received. These consisted of submissions from ACE, Lupus Canada, Lupus Ontario, and a cooperative submission from CAPA, the Arthritis Society, and the CSPA. Patient input was gathered from surveys among lupus patients across Canada for a total of 148 survey response: 34 respondents (88% female) from ACE, 112 (96.4% female) from Lupus Canada, and 2 respondents with SLE from Lupus Ontario. The cooperative submission conducted a

focus group of 10 patients (90% female) with SLE. The submission from ACE also conducted an in-depth interview with 1 patient. None of the patients in the included submissions had experience with the treatment under review.

Patients reported managing SLE was difficult given the severity of the physical symptoms such as debilitating fatigue, pain, persistent headaches, and difficulty breathing. Respondents reported that current treatments are difficult to tolerate because of the many side effects, such as headaches, brain fog, additional fatigue, frequent infections, osteoporosis, gastric issues, insomnia, hair loss, weight gain or loss, mood swings, allergic reactions, nausea, anxiety, tremors, as well as concerns about organ damage.

The key outcomes patients would like to see addressed by a new therapy are reduction of side effects and number of medications used; reduction in fatigue, flares, headaches, brain fog, joint and muscle pain, and rash and skin irritations; increased lifespan; overall improvement in quality of life (QoL); and improvement in sleep patterns. Patients would also like to see enhanced mobility, improved UV tolerance, productivity and ability to work and carry out activities of daily living (ADLs) and social roles. Overall, it is clear that SLE significantly impairs health-related quality of life (HRQoL), impairs function, and elicits a number of serious symptoms.

Clinician Input

Input From Clinical Experts Consulted by CADTH

SLE is currently treated chronically with immune modulators such as high dose corticosteroids, antimalarials, azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, and cyclosporine/tacrolimus. The clinical expert consulted by CADTH identified the major limitation as side effects of current treatment, namely prednisone and immunosuppressants. Other unmet needs include nonresponse, lack of adherence, side effects (e.g., prednisone), polypharmacy, chronic organ damage, and recurrent flares that cause progressive organ damage. Currently no treatments provide a long-term cure or long-term medication free survival. According to the clinical expert, the current place in therapy for anifrolumab would be after nonresponse or toxicity with antimalarials and OCS or prednisone dependency. In patients with major organ involvement, it could be used as a second-line therapy in combination with at least 1 immunosuppressive drug plus hydroxychloroquine after failure on standard of care. The clinical expert identified those patients most likely to benefit from anifrolumab are those with moderate-to-severe active disease (e.g., active skin manifestations and polyarthritis), those that are prednisone dependent or intolerant, and those for whom adherence to standard medication is an issue. In addition, the clinical expert noted that treatment effect with anifrolumab could be seen regardless of previous treatments, such as standard of care and/or failure to successfully taper prednisone. The clinical expert identified those least likely to benefit from anifrolumab as patients with severe nephritis or central nervous system (CNS) disease; clinicians are less likely to use anifrolumab in place of standard of care because of severity of illness in the aforementioned cases.

In the opinion of the clinical expert, a clinically meaningful response to anifrolumab would be meaningful reduction in disease activity as measured by clinical and laboratory outcomes such as autoantibodies; complement levels; hemoglobin level; improvement in ADLs; reduction of signs and symptoms; and tapering steroids. Treatment response should generally be assessed every 2 to 3 months for those with active disease; The rapidity of response depends on the treatment (e.g., corticosteroids are most rapid). In the opinion

of the clinical expert, treatment should be administered by a rheumatologist or physicians with extensive experience in the diagnosis and management of SLE. Treatment should be discontinued in the case of nonresponse, life threatening adverse events (AEs), or steroid dependency (e.g., unable to taper prednisone after 4 to 6 months of treatment, or increased dose of prednisone for more than 3 months).

Clinician Group Input

Twenty clinicians representing the following 2 clinician groups provided input for this review: The Canadian Network for Improved Outcomes for Systemic Lupus Erythematosus (CaNIOS) and the Toronto Lupus Program from the University of Toronto.

The views of the clinician groups were overall consistent with those of the clinical experts consulted by CADTH. The clinician groups indicated that the ideal treatment would have a meaningful impact on overall survival by reducing disease activity, risk of subsequent flares, use of OCS, risk of AEs, and long-term complications, while inducing remission, and improving HRQoL. The goal of treatment with anifrolumab should be the reduction of the daily prednisone dose below 7.5mg per day in the first 12 months of treatment or a reduction by 50% of the initial baseline dose. Both clinician groups indicated that all patients with SLE would benefit from anifrolumab regardless of previous treatment history. According to the clinician groups, anifrolumab is expected to cause a shift in the current treatment paradigm as it's novel interferon-blocking mechanism of action renders it most suitable for patients with serologically active disease, frequent flares, and steroid dependence, which represents the population with the greatest unmet need.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for anifrolumab:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Belimumab and rituximab could be considered comparators. However, belimumab was reviewed by	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
CDEC and the recommendation was to not reimburse for SLE, and this indication is off label for rituximab, and access to rituximab is limited for patients with SLE and reimbursed on case-by-case basis in some jurisdictions.	
Considerations for initiation of therapy	
Is the subgroup from the sponsors reimbursement request (patients with moderate-to-severe SLE (based on SLEDAI-2K score ≥ 6), whose disease activity cannot be controlled despite an OCS dose of ≥ 10 mg/day of prednisone or its equivalent) considered the subgroup of patients with the highest unmet need?	CDEC agreed with the clinical expert consulted by CADTH that the subgroup of patients with moderate-to-severe SLE (based on SLEDAI-2K score ≥ 6), whose disease activity cannot be controlled despite an OCS dose of ≥ 10 mg/day of prednisone or its equivalent is considered the subgroup of patients with the highest unmet need.
How do you define standard therapy?	CDEC agreed with the clinical expert consulted by CADTH that standard therapy includes the use of antimalarials (discontinuation after toxicity), OCS (namely, prednisone), and immunosuppressants (at least until failure of at least 1).
Could patients with lupus nephritis and neuropsychiatric lupus benefit and be considered for therapy although they were excluded from the trials?	CDEC agreed with the clinical expert consulted by CADTH that this population should be studied as further research is needed and anifrolumab should not be reimbursed in patients with lupus nephritis.
Considerations for continuation or renewal of therapy	
How would a continued response to the therapy be assessed and how often?	The clinical expert commented that if a response is seen after 1 year, they would like to see a 2-year renewal with assessment every 3 to 4 months. CDEC recommended that the maximum duration of initial reimbursement is for 12 months with subsequent renewals should be assessed annually.
Considerations for discontinuation of therapy	
How do you define refractory disease? What parameters you take into consideration?	The clinical expert noted to CDEC that the following would be considered treatment failure or refractory disease: • doubling prednisone dose after 3 months of treatment • failing to meet response criteria in SLEDAI-2K clinical response tool, failure in physician global score or lack of improvement in laboratory outcomes (e.g., decreasing anti-DNA antibody levels, lack of improvement in complement levels).
Considerations for prescribing of therapy	
Anifrolumab must be infused over 30-minutes, every 4 weeks in an appropriate setting. Patients will need access and the ability to travel.	Comment from the drug programs to inform CDEC deliberations. CDEC noted that the sponsor has indicated there will be a Patient Support Program to support infusions.
Should anifrolumab be prescribed by a rheumatologist or other specialist? Is there limited access to these specialists in some regions?	CDEC agreed with the clinical expert consulted by CADTH that only rheumatologists should be prescribing, even in areas that may be remote. Virtual appointments are acceptable for areas where geographic location is an issue. The clinical expert commented that an internist should not prescribe without consultation with a rheumatologist. The only alternative in the absence of a rheumatologist would be physicians with extensive experience with SLE.

Implementation issues	Response
Could anifrolumab be prescribed alongside belimumab and rituximab? Should that be restricted in the criteria?	CDEC agreed with the clinical expert consulted by CADTH that biologics should not be used in combination with anifrolumab.
Generalizability	
Pediatrics, and patients with lupus nephritis and neuropsychiatric lupus were excluded from the trial. Could pediatrics, and patients with lupus nephritis and neuropsychiatric lupus considered eligible for treatment?	For pediatric patients, anifrolumab could be used under the same circumstances as patients with adult-onset SLE. For severe, active, cases of lupus nephritis or lupus with CNS complications, if anifrolumab is administered, it must be done in addition to standard of care and only in patients who have not responded or who are prednisone dependent.
	CDEC noted that there is no evidence for use of anifrolumab in these patient populations, and that anifrolumab should not be prescribed to these patients.
Care provision issues	
There is an increased chance of infections which will need treatment.	Comment from the drug programs to inform CDEC deliberations.
Vaccinations required before initiating therapy due to immune suppressive action.	Comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Anifrolumab requires infusion in a health care setting. Locations and travel may not be the same in each province.	Comment from the drug programs to inform CDEC deliberations.

CDEC = CADTH Canadian Drug Expert Committee; CNS = central nervous system; OCS = oral corticosteroids; SLE = systemic lupus erythematosus; SLEDAI-2K = systemic lupus erythematosus disease activity index 2000.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two sponsor submitted trials, TULIP-1 and TULIP-2 were included in this review. TULIP-1 (123 sites in 18 countries, N = 457) and TULIP-2 (119 sites in 16 countries, N = 362) are phase III multicenter, randomized, double-blind, placebo-controlled, studies evaluating the efficacy and safety of IV treatment regimen of anifrolumab 300 mg in adult patients (18 to 70 years of age) with moderate to severe, autoantibody positive SLE while receiving standard of care treatment. The primary objective was to evaluate the effect of anifrolumab 300 mg compared to placebo on disease activity as measured by the difference in the proportion of patients who achieve an SLE Responder Index of at least 4 (SRI[4]) at week 52 for TULIP-1 or BICLA response at week 52 in TULIP-2. In TULIP-1, the key secondary objectives were to evaluate the effect of anifrolumab 300 mg compared to placebo on the following:

- the proportion of patients with SRI[4] at week 52 in the type I IFN gene signature test high subgroup

- the proportion of patients who achieved an OCS dose of 7.5 mg per day or less at week 40, which was maintained through week 52 in the subgroup of patients with baseline OCS at least 10 mg per day;
- the proportion of patients with a at least 50% reduction in cutaneous lupus erythematosus disease area and severity index (CLASI) activity score at week 12 in the subgroup of patients with baseline CLASI activity score of at least 10
- the number of patients who achieved a SRI[4] at week 24
- the annualized flare rate through 52 weeks.

The key secondary objectives in the TULIP-2 trial were the same as TULIP-1 with the addition of following objectives:

- the proportion of patients with a BICLA response at week 52 (replaces SRI[4] response at week 52)
- the proportion of patients with a BICLA response at week 52 in the type I IFN gene signature test high subgroup and
- the proportion of patients with at least 50% reduction in joint counts at week 52 in the subgroup of patients with at least 6 swollen and at least 6 tender joints at baseline (the number of patients who achieved a SRI[4] at week 24 was removed).

BICLA was achieved when all 5 of the following components were met:

- improvement in involved BILAG organs (A [severe] and B [moderate]) at baseline (e.g., reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG) with no worsening (where worsening is defined as at least 1 new BILAG-2004 A or at least 2 new BILAG-2004 B item)
- no worsening from baseline in disease activity, as determined by the SLEDAI-2K score, where worsening is defined as an increase from baseline of > 0 points in SLEDAI-2K
- no worsening from baseline in the patients' lupus disease activity, where worsening is defined by an increase of at least 0.30 points on physician global assessment (PGA) VAS (scale 0 to 3)
- no discontinuation of trial intervention
- no use of restricted medications beyond the protocol-allowed threshold before assessment.

CLASI is a measure of skin-disease severity with scores ranging from 0 [least severe] to 70 [most severe]

Patients that were automatically considered nonresponders included: patients who withdrew or discontinued the investigational product, received concomitant medications beyond the protocol-allowed threshold, required OCS dose beyond their baseline max dose, and those who had missing data for a component for more than 2 consecutive visits. While there was some variance between trials in terms of the participating countries, most sites in both trials were based in the US (40.7% in TULIP-1 and 36.5% in TULIP-2) and Europe (37.9% in TULIP-1 and 26.8% in TULIP-2), with no sites in Canada for TULIP-1 and 2 sites in Canada for TULIP-2. Except for different primary outcomes and some variance in key secondary outcomes, the trials were similar, in terms of blinding, randomization, inclusion/exclusion criteria, and drug administration procedures. Baseline patient characteristics, including age, race, sex, height, weight, and body mass index (BMI) were balanced between groups in both trials. The median age of enrolled patients 41 and 43 years in the TULIP-1 and TULIP-2 trials, respectively, and

were predominantly female (92.3% in TULIP-1 and 93.4% in TULIP-2) and White (71.3% in TULIP-1 and 59.9% in TULIP-2). TULIP-2 had a greater missing data on race (4.4% versus 0) compared to TULIP-1. Majority of patients were type 1 IFN gene high (approximately 82% across groups and studies). SLE characteristics (systemic lupus erythematosus disease activity index 2000 [SLEDAI-2K], British Isles Lupus Activity Group 2004 [BILAG-2004], PGA scores, CLASI, joints etc.) were balanced between treatment groups and were similar between studies. Median time from initial SLE diagnosis to randomization was highest in patients in the treatment arm of TULIP-2 (mean 130.2 months SD 109.28). Cushingoid features were higher in TULIP-1 compared to TULIP-2 (39% versus 26%) and there was slightly higher number of patients with a greater than 10 mg dose of OCS at baseline in TULIP-1 (56.3%) than TULIP-2 (47%). Overall previous medication use at baseline was balanced between groups and between studies.

Efficacy Results

In TULIP-1, the primary end point, SRI[4] response at week 52, was not statistically significant (36.2% in the anifrolumab 300 mg group versus 40.4% in the placebo group; treatment difference of 4.2%, 95% CI −14.2% to 5.8%, P value = 0.412) and the key secondary end points did not demonstrate statistical significance either: SRI[4] IFN-test high subgroup (P value for the between group difference was 0.549); maintained OCS dose (P value for the between group difference was 0.180); CLASI activity (P value for the between group difference was 0.054); and annualized flare rate (P value for the between group difference was 0.258).

Revised restricted medication rules were used in a post-hoc analysis of TULIP-1 to correct for inappropriately classified NSAID use; These same rules were applied to TULIP-2 pre-unblinding of the data. Using the revised restricted medication rules in the post-hoc analyses for TULIP-1, higher SRI[4] response rates at week 52 were observed in the anifrolumab 300 mg treatment group as compared to the original prespecified analysis; however, there was no statistically significant difference between patients in the anifrolumab versus the placebo group (46.9% in the anifrolumab 300 mg group versus 43.0% in the placebo group; with between groups treatment difference of 3.9%, 95% CI, −6.3% to 14.1%, P value = 0.455). When BICLA was used to measure overall disease activity, numerically higher rates of improvements were observed for anifrolumab 300 mg compared with placebo in the post-hoc analysis using revised restricted medication rules (with between groups treatment difference of 16.4%, 95% CI, 6.7% to 26.2%). In terms of maintained OCS dose, a numerically greater number of patients were able to taper their OCS dose to less than 7.5 mg at week 40 to 52 in the anifrolumab 300 mg group versus the placebo group (48.5% versus 32.1%, with between groups treatment difference of 16.7%, 95% CI, 3.5% to 29.8%). In terms of CLASI score, a numerically greater number of patients were able to achieve a reduction of at least 50% from baseline in CLASI activity score in the anifrolumab 300 mg group compared with the placebo group at 12 weeks (43.6% versus 24.9%, with between groups treatment difference of 18.7%, 95% CI, 1.4% to 36.0%). Formal statistical testing was not performed for any of the secondary objectives in the post-hoc analyses, and all results from the post-hoc analyses should be considered as hypothesis generating.

In TULIP-2, the primary end point BICLA response at week 52 was statistically significant in favour of anifrolumab 300 mg group (47.8% in the anifrolumab 300 mg group versus 31.5% in the placebo group; treatment difference of 16.3%, 95% CI, 6.3% to 26.3%, P value = 0.0013), in addition, statistically significant differences in favour of anifrolumab 300 mg group were reported for the key secondary end points of BICLA in IFN-test High patients, maintained OCS reduction in patients with baseline OCS at least 10 mg per day, and CLASI response in

patients with baseline CLASI activity score at least 10. However, no statistically significant differences were seen in the at least 50% reduction in joint count (42.2% in the anifrolumab 300 mg group versus 37.5% in the placebo group; between group difference of 4.7%, 95% CI, −13.5 to 17.6, P value = 0.5469) and annual flare rate (0.43 in the anifrolumab 300 mg group versus 0.64 in the placebo group; ratio difference of 0.67, 95% CI, 0.48 to 0.94, P value = 0.0809) in TULIP-2.

The primary and key secondary end points were also measured in the subgroup of patients with an OCS dose of at least 10 mg per day at baseline. However, statistical analyses were not conducted for this subgroup, except for the key secondary end point, maintenance of OCS reduction. Overall, a numerically higher proportion of patients in the anifrolumab group than the placebo group for this subgroup of patients achieved the primary and key secondary end points in TULIP-2 (except joint count reduction). In TULIP-1, the results were mixed, with only the outcomes of CLASI activity and annualized flare rate having an improved response in the anifrolumab group compared to placebo.

In both studies, the difference in response between the treatment groups was minimal for HRQoL (measured by SF-36, Lupus-QoL, EQ-5D-5L) and symptom scores (measured by pain NRS, FACIT-F). The proportion of patients who exceeded the estimated minimal important difference (MID) were only provided for the SF-36 and FACIT-F. In TULIP-1, at week 52, the proportion of mental component summary (MCS) responders (defined as change from baseline of at least 4.6 points, the MID for MCS), in the anifrolumab 300 mg group was 20.9% and in the placebo group it was 16.7%, with a between group difference of 4.2%, 95% CI (−4.1 to 12.6); the proportion of physical component summary (PCS) responders (defined as change from baseline of at least 3.4 points, the MID for PCS) in the anifrolumab 300 mg group was lower compared with the placebo group by 25% versus 26.7%, with a between group difference of −1.7%, (95% CI, −10.9 to 7.5). In TULIP-2, at week 52, the proportion of MCS responders in the anifrolumab 300 mg group compared with the placebo group was 27.4% versus 21.2%, with a between group difference of 6.2%, (95% CI, −2.71 to 15.2) and the proportion of PCS responders in the anifrolumab 300 mg group compared with the placebo group was 32.8% versus 24.4%, with a between group difference of 8.4%, (95% CI −1.1 to 17.8). In TULIP-1, a slightly higher proportion of patients in the anifrolumab 300 mg group had reduced fatigue at week 52, as measured by FACIT-F responder rate (defined as improvement from baseline to week 52 of > 3 points), compared with the placebo group (29.3% versus 26.8%; between group difference of 2.4%, (95% CI, −0.9 to 17.9). TULIP-2 also had a numerically higher proportion of patients in the anifrolumab 300 mg group who had reduced fatigue at week 52, as measured by FACIT-F responder rate compared with the placebo group (33.2% versus 24.7%; between group difference of 8.5%, (95% CI, 6.9 to 11.8).

Harms Results

Rates of AEs were similar across treatment groups and across trials (approximately 85% to 90% prevalence). In TULIP-1 and TULIP-2, the most common AEs were nasopharyngitis (20.0% and 15.6% in the anifrolumab 300 mg group versus 12.0% and 11% in the placebo group, respectively), upper respiratory tract infection (12.2% and 21.7% versus 9.8% and 9.9%), and urinary tract infection (12.2% and 11.1% versus 14.7% and 13.7%). Serious adverse events (SAEs) were more common in the placebo group versus the anifrolumab group across TULIP-1 and TULIP-2 trials (13.9% versus 16.3% and 8.3% versus 17%, respectively). In TULIP-1, the most common SAEs were SLE (1.7% and 1.6%) and pneumonia (1.7% and 0.5%). In TULIP-2, the most common SAEs were pneumonia (1.7% and 3.8%), followed by SLE (0.6% and 3.3%).

Withdrawals were greater in the anifrolumab group versus the placebo group in TULIP-1 (6.7% versus 3.8%). Whereas withdrawals were lower in the anifrolumab group compared to the placebo group in TULIP-2 (2.8% versus 7.7%). In TULIP-1, the most common reason for withdrawal in the anifrolumab group was herpes zoster (1.1%). In TULIP-2, the most common reason for withdrawal in the placebo group was SLE (1.6%) followed by pneumonia (1.1%).

There was a total of 2 deaths during the TULIP-1 study and 1 death in the TULIP-2 study. One patient in the anifrolumab 300 mg group of each trial had a fatal SAE of pneumonia during the treatment period. In TULIP-1, 1 patient in the placebo group had a fatal SAE of encephalitis during the follow-up period. The study investigators deemed these deaths to be unrelated to the investigational product.

In TULIP-1 notable harms included hypersensitivity reactions (6.1% anifrolumab 300 mg versus 1.1% placebo), infusion-related reaction (8.9% versus 7.1%), herpes zoster (5.6% versus 1.6%), serious, nonopportunistic infection (5.0% versus 4.3%), malignancy (1.7% versus 0.5%), depression (2.8% versus 2.7%), and suicidal ideation or behaviour (1.1% versus 1.6%). In TULIP-2, notable harms included infusion-related reactions (13.9% versus 7.7%), herpes zoster (7.2% anifrolumab 300 mg versus 1.1%, placebo), serious, nonopportunistic infection (2.8% versus 5.5%), hypersensitivity (1.1% versus 0.5%), malignancy (0% versus 0.5%), depression (2.8% versus 1.6%) and suicidal ideation or behaviour (1.7% versus 4.4%). Herpes zoster was more common among the anifrolumab group across both trials, but none were considered SAEs. Depression was measured by PHQ-8, but no clinically meaningful changes were observed for any group across both trials. Suicidal ideation and behaviour were measured by the Columbia suicide severity rating scale (C-SSRS). Overall, few patients reported suicidal ideation or suicidal behaviour at any time during the studies, with no imbalance observed between treatment groups.

Critical Appraisal

A number of factors between the 2 pivotal trials contributed to bias or general uncertainty of the outcomes. The primary outcome for TULIP-1 and TULIP-2 was the composite score of SRI[4] and BICLA, respectively. The decision to switch the primary end point in TULIP-2 was based on the results of the TULIP-1 and MUSE trials and this decision was made before the unblinding of the data in TULIP-2 at week 52. Hence the risk of operational bias is low. Both trials followed the same procedures for blinding, database lock, unblinding, and data analysis, hence concerns for potential investigator bias are low. The risk of confounding variables were accounted for through stratification (e.g., SLEDAI-2K score at screening, baseline OCS dose, and type I IFN gene signature test results). Baseline imbalances of these factors could impact efficacy and/or safety assessments of anifrolumab versus placebo. Overall baseline characteristics and disease activity scores (e.g., CLASI activity, SLEDAI-2K scores) were generally similar and balanced between groups across both trials; There was, however, a greater percentage of patients with a CLASI damage score at least 10 in the treatment arm compared to placebo TULIP-2 (8.9% versus 4.4%), versus TULIP-1 (6.1% versus 4.3%), which could potentially allow for greater leaps in improvement in patients with more severe disease for this outcome; other concerns include potential ceiling effects for patients with lower disease activity scores (e.g., if a patient has a baseline SLEDAI-2K score of 6, would be less likely to achieve a 4-point drop as someone who starts with a 12).

In TULIP-1, there was similar rates of withdrawal in both study arms (18.9% anifrolumab versus 19% placebo) while discontinuation was much lower in the treatment arm of TULIP-2 versus placebo (13.3% versus 25.3%). Discontinuations were primarily due to patient request,

AE, lack of efficacy and condition under investigation worsened. In TULIP-2, there was a slightly higher proportion of patients who discontinued due to patient request in the placebo group (10.4%) than in the anifrolumab group (6.1%) and there were also more patients in the placebo group who withdrew due to AEs (3.8% versus. 1.7%) and lack of efficacy (4.4% versus 1.1%) before the end of the study.

In TULIP-1, formal statistical testing was not performed for any of the secondary objectives in the post-hoc analyses, and all results from the post-hoc analyses should be considered as hypothesis generating.

The sponsor adhered to their statistical testing hierarchy for the multiplicity adjustment, testing outcomes in sequence. Sensitivity analyses and multiplicity adjustments were only conducted in TULIP-2 since TULIP-1 did not meet its primary end point. The sponsor used a nonresponder imputation approach where if a patient who withdrew from the study or received restricted medications beyond the protocol-allowed threshold, such patient would be considered nonresponder. With this approach, when more patients withdraw in the placebo group, this may have biased the results in favour of anifrolumab as these patients would be considered nonresponders whether they were responding at the time of withdrawal or not. The sensitivity analyses performed by the sponsor support the findings of their primary analysis of TULIP-2, using approaches such as last observation carried forward (LOCF) as well as tipping point analyses. LOCF was also used to impute missing data in cases where individual components of the primary composite outcome were missing. The situation of missing data was common among the BILAG-2004 component for both studies.

The clinical expert consulted by CADTH, agreed that the baseline patient characteristics of TULIP-1 and TULIP-2 trials were reflective of patients they see in clinical practice in Canada for the present indication. Although the majority of patients in each study were enrolled in trial sites from the US and Europe, the population enrolled in the trial was consistent with the population expected to be treated in clinical practice in Canada. The clinical expert noted that prescribing patterns may differ between countries (e.g., higher use of nervous system medication; or use of mizoribine, which is not prescribed in Canada), however no different treatment effect would be expected based on different disease management practices. Additionally, ACR criteria were used to identify patients with SLE in both trials, and these are rigorous criteria that are designed for use in clinical trials, rather than clinical practice. Thus, there is a higher risk of misdiagnosis of SLE occurring in clinical practice, although the clinical expert consulted by CADTH on this review noted that diagnosis of SLE should be straightforward for clinicians with specialty training. Furthermore, the subgroup analyses (e.g., IFN-test high versus low) had no statistical comparisons and even smaller sample sizes, which limits the generalizability to a broader population.

According to the clinical expert, improvements in organ damage or other longer-term outcomes (e.g., mortality) while on anifrolumab are unlikely to be detected during a 52-week double-blind treatment phase because of insufficient duration. The composite primary outcome, patients with an SRI[4] response or BICLA response, is not something that would be routinely used to assess patient status in clinical practice, however the components of the composite would be an important part of the assessment of patients with SLE (e.g., clinical SLEDAI score). Anifrolumab has not been studied versus an active comparator, therefore the efficacy and harms of this drug compared to the addition of other drugs used in the treatment of SLE is unknown. There are a variety of drugs used chronically to manage SLE, none of which were specifically developed for managing this disease.

Other Relevant Evidence

Description of Studies (MUSE and Study-1145)

Two submitted studies provided in the sponsor's submission to CADTH were considered to address long-term efficacy of the treatment under review. These include a phase-2, multinational, multicenter, randomized, double-blind, placebo-controlled study (MUSE) and a phase II, single-arm, open-label, long-term extension study to evaluate the long-term safety of anifrolumab (Study-1145). Inclusion and exclusion criteria and baseline demographics were consistent with TULIP-1 and TULIP-2 clinical trials. The primary efficacy end point for MUSE was the proportion of patients who at day 169 (week 24) achieved an SRI(4) response as defined in TULIP-1. Patients who were not able to taper their OCS dose to less than 10 mg per day (prednisone or equivalent) to equal to or less than their day 1 dose by day 85 (week 12) and maintain this decrease until day 169 (week 24) were declared nonresponders for the primary end point. Subgroup analyses included proportion of type I IFN signature diagnostic test-positive patients achieving an SRI(4) response with OCS tapering. Secondary efficacy end points included the proportion of patients achieving an SRI[4] response at day 365 and the proportion of patients on at least 10 mg per day of oral prednisone (or equivalent) at baseline who were able to taper to 7.5 mg per day or less at day 365 (week 52).

Study-1145 (N = 218) was a single-arm, open-label, long-term safety (up to 3 years; 70.6% of patients were treated for at least 30 months) and tolerability study of anifrolumab with a 300 mg every 4 weeks IV infusion adult patients with chronic, moderate to severe SLE who were previously treated with any dose of anifrolumab or placebo in the MUSE trial. Safety assessments consisted of reporting all adverse events including treatment-emergent adverse events (TEAEs), SAEs, as well as AEs of special interest results. The primary end points of the study were the safety and tolerability of IV anifrolumab in adult patients with moderately-to-severely active SLE and were assessed primarily by summarizing TEAEs, SAEs, DAEs, and AESIs. The secondary safety outcome included evaluating the immunogenicity results of anifrolumab by summarizing the proportion of patients who developed detectable antidrug antibodies (ADA). Other outcomes were also assessed in the trial however, they are not further reported in this review given that they were assessed as exploratory efficacy outcomes. These included outcomes to evaluate the efficacy, pharmacokinetic, pharmacodynamic, and HRQoL impact of anifrolumab.

Efficacy Results

In the MUSE study, A total of 34.3% of patients who had an SRI[4] response with OCS tapering at week 24 in the anifrolumab group compared to 17.6% in the placebo group with a statistically significant OR (90% CI) of 2.38 (1.33 to 4.26, P value = 0.014). The proportion of type I IFN-test high patients who had an SRI[4] response with OCS tapering at week 24 was 36.0% for the anifrolumab group and 13.2% for placebo group with an OR (90% CI) of 3.55 (1.72 to 7.32). The difference was statistically significant with a P value of 0.004. For this secondary end point at week 52, a total of 51.5% of patients had an SRI[4] response with OCS tapering in the anifrolumab group compared to 25.5% in the placebo group with an OR (90% CI) of 3.08 (1.86 to 5.09) with a P value of < 0.001. For this secondary end point, a total of 56.4% of patients in the anifrolumab group on at least 10 mg per day of oral prednisone (or equivalent) at baseline who were able to taper to 7.5 mg per day or less by week 52 compared to 26.6% in the placebo group with an OR (90% CI) of 3.59 (1.87 to 6.89) with a P value of less than 0.001.

Harms Results

In the MUSE trial, 84.8% of patients in the anifrolumab group and 77.2% of patients in the placebo group reported at least 1 TEAE, the most common being headache, upper respiratory tract infection, nasopharyngitis, and urinary tract infection. Nasopharyngitis occurred at a higher frequency in the anifrolumab group (12.1%) than in the placebo group (4.0%).

The proportion of patients with at least 1 SAE was similar between the anifrolumab and placebo groups, the most common being increased SLE activity and pneumonia. The most common AESI was infusion, hypersensitivity, and anaphylactic reactions which had a higher proportion in the placebo group (5.9%) than in the anifrolumab group (2.0%). No deaths were reported in the anifrolumab 300 mg per day or placebo groups.

In the long-term extension study (Study-1145) through to week 52, the total patient-years of exposure was 93.4 for the anifrolumab arm and 84.3 for the placebo arm. A higher proportion of patients in the anifrolumab group (65.7%) received the full course of treatment (13 doses) than those in the placebo group (53.5%). A total of 78% of patients (n = 170) experienced an adverse event; with the most common including nasopharyngitis (14.7%), bronchitis (13.8%), and upper respiratory tract infections (9.2%). A total of 22% (n = 48) of patients had a drug-related TEAE and 22.9% (n = 50) had at least 1 SAE event, with an exposure-adjusted SAE rate of 8.56 per 100 patient-years. The most common SAEs were increased SLE activity and pneumonia, each of which occurred in 2.3% of patients. One patient died from community-acquired pneumonia and this death was assessed by the investigator as related to treatment. In terms of AESIs, 7 patients (3.2%) had infusion, hypersensitivity, or anaphylactic reactions and 5 patients (2.3%) had latent TB. A total of 5 patients had ADA-positive measurements at any time during Study-1145, 3 of which were at baseline only and 2 of which were considered persistent.

Critical Appraisal

In the MUSE study, a number of factors contributed to bias in favour of anifrolumab or general uncertainty. A higher proportion of patients in the placebo group used at least 10 mg per day of OCS at baseline than those in the anifrolumab group (62.7% versus 55.6%). Risk of attrition bias may be present due to the greater number of withdrawals in the placebo group. Discontinued patients were classified as nonresponders in the primary analyses which can bias the results in the direction of treatment. Furthermore, it was unclear whether the patients who discontinued were different from those who did not. The primary outcome, SRI[4], is a reliable and valid composite measure for disease activity and response in SLE. The primary outcome was measured at 24 and 56 weeks in the MUSE study, which provided data on long-term treatment effects. The clinical expert for this review agreed that a treatment response is expected within 24 weeks. In terms of statistical analyses, multiplicity was not controlled across populations and there was no control for multiplicity in the secondary efficacy outcomes which increases the likelihood of a type I error.

While baseline demographics of the patients in the MUSE trial were representative of moderate to severe active SLE in Canada, the high dropout rate in the placebo group may have led to patients that are less representative of the recruited population, decreasing the generalizability of the results of the study.

The extension study allowed for the investigation of long-term efficacy and harms of anifrolumab. Limitations of the extension study include the absence of an active comparator which limits causal conclusions. Furthermore, the analysis does not take account of

frequency or recurrence of AEs. As a greater proportion of patients in STUDY-1145 had previously been treated with anifrolumab in the MUSE study, observations based on frequencies of overall AEs in STUDY-1145 should be interpreted with caution. This could have resulted in a population of patients that were more tolerant of anifrolumab and therefore potentially less likely to experience harms. A high proportion of patients discontinued the study (36.2%) which can increase the risk of attrition bias in favour of the intervention as patients who do not do well on the intervention tend to withdraw from the study. Though these patients were included in the safety analyses, their characteristics were not reported. Thus, it was unclear whether the patients who discontinued were different from those who did not.

Description of Study (TULIP-LTE)

The TULIP-LTE was a 3 year, double-blind, placebo-controlled LTE study in adult patients who had moderately-to-severely active SLE at the start of TULIP-1 and TULIP-2 studies. TULIP-LTE study enrolled patients who had completed the 52-week double-blind treatment period in 1 of the phase III studies (TULIP-1 or TULIP-2), met all TULIP LTE eligibility criteria and were willing to continue into the extension study. Patients who received anifrolumab in TULIP-1 or TULIP-2 and entered the LTE remained on anifrolumab. Patients who received placebo and entered the LTE were re-randomized 1:1 to receive either anifrolumab or placebo in the LTE. This resulted in an approximate ratio of 4:1 anifrolumab 300 mg (n = 435; of these, 257 patients treated with anifrolumab 300 mg continued on anifrolumab 300 mg) versus placebo (n = 112) in the LTE study. The primary objective was to characterize long-term safety and tolerability of IV anifrolumab in patients who completed TULIP-1 or TULIP-2 (e.g., adverse events of special interest [AESIs], SAEs). The exploratory objectives were efficacy assessments (i.e., overall disease activity [SLEDAI-2K], OCS use, damage accrual [SDI]) and HRQoL. The LTE study consisted of a 156-week treatment period, after which patients continued in the study for another 8 weeks to complete a 12-week safety follow-up after last dose of investigational product.

Efficacy Results

The proportion of patients who achieved at least a 4-point reduction in SLEDAI-2K from baseline was consistently higher in the anifrolumab 300 mg group than in the placebo group. In the anifrolumab 300 mg group, 76.1% of patients who reached the week 52 visit had a at least 4-point reduction and 90.0% of those who reached week 208, compared with 69.5% and 81.8%, respectively, in the placebo group. In addition, larger improvements were seen from baseline to week 208 across all domains in the anifrolumab group compared to placebo.

In terms of OCS use, for each year of study, the mean OCS standardized area under the curve (AUC) was lower for the anifrolumab 300 mg group compared to placebo.

In terms of organ damage, overall, 30% to 40% of patients had organ damage (i.e., SDI score ≥ 1), at baseline of TULIP-1 and TULIP-2. Organ damage remained stable in both groups throughout the LTE; at week 208 the mean SDI score in patients with a baseline SDI score at least 1 was 2.1 in the anifrolumab 300 mg and 2.0 in the placebo group.

HRQoL was measured by the SF-36 v2 and EQ-5D-5L. Larger improvements in HRQoL, as measured by SF-36v2 PCS and MCS response rates, were observed for the anifrolumab 300 mg group compared with patients in the placebo group. In terms of EQ-5D-5l, the improvements in QoL as measured by change from baseline in were small but consistently higher for the anifrolumab 300 mg compared to the placebo group throughout the 4 years.

Harms Results

The safety profile up to 4 years of exposure, including assessment of rare events, remains unchanged. In addition, there was no increase in malignancy, MACE, no anaphylaxis or active tuberculosis. During the 52-week period, 87.5% of patients in the anifrolumab group and 81.3% of patients in the placebo group reported of at least 1 TEAE, the most common being nasopharyngitis, urinary tract infection, upper respiratory tract infection, bronchitis, and headache.

The proportion of patients with at least 1 SAE was similar between the anifrolumab and placebo groups, the most common being infections and infestations. The most common AESI was nonopportunistic infections. Three deaths were reported in the anifrolumab group (1.2%) and 1 death was reported in the placebo group (0.9%). Overall, no new safety signals were identified.

Critical Appraisal

Demographics and baseline characteristics were generally well balanced between groups. At the start of LTE, fewer anifrolumab patients were on steroids compared to placebo. This may contribute to bias in terms of reducing OCS use if greater number of patients in the anifrolumab group were already not using OCS. Approximately 72% anifrolumab and 62% placebo of eligible patients completing treatment in predecessor studies (TULIP-1 and TULIP-2) enrolled into TULIP LTE. More patients on anifrolumab completed the 3-year extension (66% across all anifrolumab groups versus 48%) in placebo. The differential dropout rate may increase the risk of attrition bias in favour of anifrolumab.

Limitations regarding efficacy and HRQoL outcomes included the lack of formal statistical testing and were exploratory. Hence, although a higher proportion of patients in the anifrolumab group had lower OCS use and improved SLEDAI-2K scored compared to placebo, no firm conclusions can be drawn based on the efficacy of anifrolumab and its steroid sparing effect based on the presented data. Also, the ability to draw conclusions on the effectiveness of anifrolumab in preventing organ damage was limited due to the lack of statistical testing.

While the patient population was considered to be representative of patients with moderate-to-severe SLE in Canada, patients enrolled in TULIP LTE had to have the 52-week double-blind treatment period in 1 of the phase III studies (TULIP-1 or TULIP-2) hence this is a selective patient population, as it only included those who were able to complete the TULIPs studies and while the baseline characteristics of the patients enrolled in TULIP LTE might not differ from those enrolled in TULIP-1 or TULIP-2 studies results from the TULIP LTE can't be generalized to all patients enrolled in the TULIPs trials.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Patient-level simulation
Target population	Treatment of adult patients with active, autoantibody positive, SLE
Treatment	Anifrolumab (300 mg every 4 weeks) + Best supportive care (BSC)
Submitted price	Anifrolumab: $1,687.21 per 300 mg single-dose vial
Treatment cost	The annual cost of anifrolumab is $21,934 at the recommended dose of 300 mg every 4 weeks
Comparator	BSC (antimalarials, oral corticosteroids, and immunosuppressants)
Perspective	Publicly funded health care payer in Canada
Outcomes	QALYs, LYs
Time horizon	Lifetime (80 years)
Key data source	A pooled analysis from TULIP I and II trials was used to compare anifrolumab + BSC with BSC alone. The MUSE trial and Toronto Lupus cohort data were used to inform efficacy parameters regarding year 2 and beyond.
Key limitations	• Inconsistency and uncertainty were observed across the results from TULIP 1 and TULIP 2 trials, as differences between treatment groups were not observed in the TULIP 1 trial for the primary and some secondary outcomes including SLEDAI-2K. The sponsor used a pooled analysis from TULIP 1 and 2 trials for their base-case analysis. A difference among groups in baseline CLASI damage score was observed in the treatment arm compared to BSC in TULIP 2 vs. TULIP 1 trial, which could potentially allow for greater leaps in improvement in patients with more severe disease. • The sponsor's model structure was not representative of relapsing-remitting nature of SLE and the order of key clinical events did not reflect the clinical natural path of the disease. • The sponsor assumed that only patients receiving anifrolumab could achieve response, which does not align with the clinical evidence and expected disease pathway. Furthermore, the sponsor assumed anifrolumab response was the absolute response rate from the clinical trials as opposed to the relative benefit. The sponsor's approach was methodologically inappropriate and overestimated the benefit of anifrolumab. • Health utility scores were calculated for each patient using a regression model which appears to overestimate utility values for anifrolumab relative to BSC treatment group. • Much of the clinical benefit for patients receiving anifrolumab (measured using SLEDAI-2K scores) is predicted to accrue between three and 10 years after the treatment initiation with anifrolumab. Due to the lack of long-term data, these benefits are associated with significant uncertainty. • The sponsor overestimated survival gains for anifrolumab, as there is no high-quality evidence that anifrolumab reduces mortality for patients with SLE. • The sponsor assumed that patients receiving anifrolumab + BSC could stay on treatment without any waning of treatment effect. Clinical expert feedback suggested that waning of treatment effect would occur after 5 years. • Several inputs were only coded in the VBA script that runs the sponsor's model, limiting the flexibility and transparency of the model. The sponsor's model also did not allow for changes in the time horizon without errors. As a result, CADTH could not validate many aspects of the model.

Component	Description
CADTH reanalysis results	• Due to the limitations with the sponsor's submitted model structure and assumptions, CADTH could not derive a base-case estimate of the cost-effectiveness of anifrolumab + BSC compared with BSC alone. • CADTH accounted for some of the identified issues through scenario analyses (i.e., assessing an alternate survival distribution, an alternate discontinuation rate, and assuming treatment efficacy waning). Given the different findings from the TULIP trials, the model was run using the pooled analysis (TULIP 1 + TULIP 2) and the TULIP 1 data, in combination with the above scenario analyses. Based on the pooled data from TULIP trials, the ICER for anifrolumab + BSC compared with BSC is $224,736 per QALY gained. A price reduction of 78% would be required to achieve a $50,000 per QALY threshold, respectively. When considering the reimbursement request population, based on the pooled data from TULIP trials, the ICER for anifrolumab + BSC compared with BSC is $181,708 per QALY gained. A price reduction of 74% would be required to achieve a $50,000 per QALY threshold, respectively. • CADTH was unable to consider the impact of the use of incremental response rate in the anifrolumab group, and as such, incremental QALYs may still be overestimated.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SLE = systemic lupus erythematosus; VBA = Visual Basic for Applications.

Budget Impact

CADTH identified the following key limitations: the market uptake for anifrolumab may be underestimated, and the proportion of patients receiving an OCS dosage equal or higher than 10 mg per day is uncertain.

CADTH's base-case revised the market uptake, which was increase to 5%, 7.5%, and 10%. CADTH also explored uncertainty in the proportion of patients receiving a dosage of OCS equal or higher than 10 mg per day in the reimbursement group and the impact of price reduction in scenario analyses.

Based on the CADTH's base-case, the expected budget impact for funding anifrolumab for the treatment of active, autoantibody positive, SLE in the drug plan perspective is expected to be $8,958,286 in year 1, $9,410,166 in year 2, and $11,362,161 in year 3, with a 3-year budget impact of $29,730,614. For the reimbursement population, the budged impact is expected to be $3,633,661 in year 1, $3,849,657 in year 2, and $4,636,881 in year 3, with a 3-year budget impact of $12,120,200.

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for anifrolumab for the treatment of adult patients with active, autoantibody positive, SLE. In their request, the sponsor identified the following issues:

- the meaningful clinical benefit of anifrolumab based on the results from the pivotal trials, TULIP 1 and TULIP 2, in addition to the newly available long-term extension data
- CDEC did not recognize the consistent reduction in OCS dose provided by treatment with anifrolumab
- disagreement with CDEC statement that there is no evidence that the use of anifrolumab would result in a reduction in the use of other treatments, and that the trials were

not designed to study the reduction in the use of other standard of care medications (hydroxychloroquine and immunosuppressants)

- the imbalance in discontinuation rates
- CDEC's assessment of unmet need and heterogeneity of SLE
- challenges in treating SLE.
- In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:
- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 1 clinical specialist with expertise in the diagnosis and management of SLE
- feedback from the public drug plans
- feedback from 2 clinician groups: The Canadian Network for Improved Outcomes in SLE and the Toronto Lupus Program, University of Toronto
- feedback from 3 patient groups: Lupus Ontario, Lupus Canada, and joint feedback submission by Canadian Arthritis Patient Alliance, Arthritis Society, and Canadian Skin Patient Alliance.

All stakeholder feedback received in response to the draft recommendation from patient and clinician groups and the public drug programs is available on the CADTH website.

CDEC Information

Initial Meeting Date: June 22, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Regrets: One of expert committee member did not attend

Conflicts of interest: None

Reconsideration Meeting Date: November 24, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Regrets: Two expert committee members did not attend

Conflicts of interest: None