CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

ANIFROLUMAB (Saphnelo)
(AstraZeneca Canada Inc.)

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

July 28, 2022

The Toronto Lupus Program, University of Toronto

[redacted]

July 28, 2022

To whom it may concern

Re: CADTH Reimbursement Recommendation Anifrolumab (Saphnelo)

The Toronto Lupus Program, University of Toronto

Our comments regarding the discussion points raised by CADTH

1. **The duration of TULIP 1 and 2, and MUSE trials is not sufficient to assess the risk of damage in patients with SLE. In addition, these trials were not designed to demonstrate a lower risk of damage with Anifrolumab compared to placebo. The majority of damage in patients with SLE is the direct result of glucocorticoids use. Thus, it is obvious that with the use of appropriate drugs that allow glucocorticoids dose reduction and complete stopping of glucocorticoids, the risk of damage will be minimized. This was already demonstrated in the extension trials of Belimumab with data beyond 4 years [1, 2].**

   Unfortunately, Belimumab, is another medication that CADTH refused to approve for patients with lupus when trials demonstrated clear benefit over the use of standard of care alone. In addition, the data from patients followed for at least 4 years, showed reduced damaged in patients who took Belimumab compared to patients who received only standard of care treatment. Currently, only patients with a drug plan have access to Belimumab and can benefit from this drug. It is very unfortunate that the CADTH position regarding Anifrolumab is also preventing patients with lupus to benefit from this drug. This will further widen the gap to drug access between patients with and without drug plans. Lack of public access for Anifrolumab potentially leads to inequity in the healthcare system. In addition, since the majority of lupus patients are young women in reproductive and productive years of their lives, withholding medications leads to inequality of care.

2. **The recent data analyzed by Strand et al demonstrated clear benefit of health-related quality of life (HRQoL) favoring the use of Anifrolumab over placebo [3]. HRQoL was measured with the Short Form 36 Health Survey (SF-36; version 2) and the Lupus Quality of Life (a lupus specific tool). BICLA responders had a clinically meaningful improvements, from baseline at week 52, in Patient Global Assessment, fatigue, pain and HRQoL (across all SF-36 domains) and Lupus Quality of Life domains compared to patients who received placebo [3].**

3. **SLE is a very heterogenous disease, and SLE outcome measures are also very heterogenous and hence some inconsistencies in trial results at 52 weeks. It is important for CADTH to understand that treating SLE patients with limited therapeutic options is a huge challenge as different patients respond differently to available therapies. Given the heterogenous presentation of the disease and lack of targeted therapies for standard of care, some inconsistencies in clinical trial results are not unexpected as seen from clinical trials for other molecules for lupus. Nevertheless, BICLA response is a valid endpoint and a recent analysis of TULIP 1 and 2 data confirmed the clinical benefit in SLE assessments of BICLA response – BICLA response was associated with a clinical benefit in SLE assessments, PROs, and medical resource utilization [4].**

4. **Long term extension (LTE) data up to 4 years (data reviewed under confidentiality) shows sustained efficacy, glucocorticoids reduction (particularly in patients starting with glucocorticoids dose ≥ 10 mg/d) and reassuring safety. Moreover, the patients' characteristics, in the LTE data, did not differ between patients who received Anifrolumab compared to placebo.**

5. **CADTH is considering TULIP-1 results prior to the rules for amendments for restricted medication use were applied to the analysis which was not the case with TULIP-2 results. The prespecified analysis for TULIP-1 was prior to Amended Rules for restricted medications. TULIP-1 trial results after the restricted medications rules amendment (shown in TULIP-1 publication) and pooled analysis for TULIP-1 and TULIP-2 for BICLA show that the trial results are fairly consistent [4]. It is very important for CADTH to understand that the use of NSAIDs is very common among patients with SLE and NSAIDs use doesn't require a prescription. CADTH is focusing on the results of TULIP-1 before applying the amendment rules and we strongly believe that the data after amendment is valid and reliable.**

[redacted]

References

1. Urowitz, M.B., et al., *Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis.* Ann Rheum Dis, 2019. **78**(3): p. 372-379.
2. Urowitz, M.B., et al., *Impact of belimumab on organ damage in systemic lupus erythematosus.* Arthritis Care Res (Hoboken), 2022.
3. Vibeke Strand, S.O.Q., Richard A Furie, Eric F Morand, Kenneth C Kalunian, Erik G Schwetje, Gabriel Abreu, Raj Tummala. Clinical meaningfulness of a British Isles Lupus Assessment Group-based Composite Lupus Assessment response in terms of patient-reported outcomes in moderate to severe systemic lupus erythematosus: a post-hoc analysis of the phase 3 TULIP-1 and TULIP-2 trials of anifrolumab. Lancet Rheumatol, 2022: **p. e198–207**.
4. Furie, R., et al., *What Does It Mean to Be a British Isles Lupus Assessment Group-Based Composite Lupus Assessment Responder? Post Hoc Analysis of Two Phase III Trials.* Arthritis Rheumatol, 2021. **73**(11): p. 2059-2068.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717
Brand name (generic)	Saphnelo (Anifrolumab)
Indication(s)	Systemic Lupus Erythematosus (adults)
Organization	Canadian Network for Improved Outcomes in SLE
Contact information	Name: Dr. Konstantinos Tselios

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

The Committee based their recommendation on the inconsistency of the results in the two separate randomized clinical trials (RCTs) of anifrolumab in SLE (TULIP-1 and TULIP-2). Although different primary end-points were used in the two trials, the totality of evidence demonstrates superiority of anifrolumab vs. placebo for both primary end-points (SRI-4 and BICLA).

The Committee considered only the pre-specified analysis and not the one after the amended rules for restricted medications. In the latter, the only amendment was that the analysis did not consider patients who briefly used non-steroidal anti-inflammatory drugs (NSAIDs) as non-responders (treatment failure). This approach reflects the routine clinical practice, where occasional use of NSAIDs is quite common for lupus patients even for reasons that are not necessarily related to disease activity. Therefore, the post-hoc analysis of TULIP-1 should have been considered by the Committee.

In such case, the outcomes of interest shift dramatically in favor of anifrolumab. More specifically, SRI-4 was achieved by 84/180 anifrolumab-treated patients in TULIP-1 and 100/180 in TULIP-2 for a total response rate of 51.1% (184/360). Placebo-treated patients achieved SRI-4 response in 38.1% of the cases (79/184 and 68/182 for TULIP-1 and TULIP-2 respectively). The cumulative treatment difference is 13% for a HR=1.27 (95%CI=1.08-1.49, fixed effects model assuming that the studies were identical in design).

Regarding the sustained BICLA response, in a pooled analysis of TULIP-1 and TULIP-2, the Hazard Ratio was 1.73 (95%CI=1.37-2.20) demonstrating superiority of anifrolumab.

Regarding the notion that the magnitude of treatment effect is uncertain (Rationale for Recommendation, 1st paragraph), the high response rate in the placebo group has been shown in all previous RCTs in SLE and is attributed to the fact that these patients are actually treated with the standard of care (combination of antimalarials, glucocorticoids and immunosuppressives) and not with placebo alone. Therefore, the adjusted treatment difference (16.4% and 16.3% for BICLA response in TULIP-1 and TULIP-2 respectively) reflects the additional benefit that anifrolumab offers when added to the standard of care.

Regarding the notion that the duration of the trials was too short to capture the relapsing-remitting nature of SLE (Rationale for Recommendation, 1st paragraph), all previous RCTs in SLE are of similar duration. With the standard of care, a significant proportion of lupus patients will flare during the next 12 months as has been demonstrated in observational cohort studies. Therefore, 52 weeks are adequate to capture a significant number of clinical flares and assess the effect of the drug in re-

achieving remission or demonstrate effectiveness in preventing flares. Based on the Long Term Extension data (confidential), anifrolumab sustains remission and reduced glucocorticoid doses up to 4 years from treatment initiation; hence, it does prevent flares.

Regarding the notion that the reduction of oral glucocorticoids was inconsistent (Rationale for Recommendation, 2nd paragraph), the totality of evidence demonstrates superiority of anifrolumab versus placebo (plus standard of care). Regarding patients who started with a daily prednisone dose equal or greater than 10mg, more anifrolumab-treated patients achieved reduction to less than 7.5mg/day (48.8% vs. 32.1% for TULIP-1 and 51.5% vs. 30.2% for TULIP-2, both differences statistically significant). Regarding the concomitant medications (penultimate sentence of the 2nd paragraph), the current paradigm for treatment withdrawal in SLE is the reduction and withdrawal of glucocorticoids first, then immunosuppressives and, finally, antimalarials. De-escalation and/or withdrawal of immunosuppressives occurs later in disease course and, mostly, in patients with prolonged remission (of several years duration) and not in patients who remitted briefly. Therefore, reduction in concomitant medications (other than glucocorticoids) should not be expected in the span of 52 weeks.

Regarding the notion that anifrolumab may not improve outcomes or mitigate the potential adverse effects of prolonged glucocorticoid use (Rationale for Recommendation, 3rd paragraph), Long-Term Extension data (confidential) demonstrate superiority of anifrolumab versus placebo in sustained reduction of glucocorticoids. The main outcome of interest in SLE is damage accrual that greatly depends on the cumulative glucocorticoid dose and disease activity over time. Both variables were improved in the anifrolumab-treated patients over 4 years of follow-up. Direct evidence of decrease in damage accrual should not be expected in 52 weeks; however, control of disease activity and the reduction of glucocorticoids will certainly impact damage accrual in the long term.

Regarding the notion that Quality of Life (QoL) measures were not statistically tested (Rationale for Recommendation, 3rd paragraph), all such measures depend mainly on disease activity and damage accrual. Since disease activity was controlled in more anifrolumab-treated patients and the rate of damage accrual is expected to decrease, the relevant QoL measures are also expected to improve in anifrolumab-treated patients. Indeed, in a post hoc analysis that was presented in EULAR 2022, patients from TULIP-1 and TULIP-2 who achieved a BICLA or an SRI-4 response demonstrated improved patient-reported outcomes (including FACIT-F for fatigue and SF-36 for both the physical and mental components) compared to non-responders. Since anifrolumab achieved higher response rates for both outcomes, it is expected that QoL measures will improve as well.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

The Committee Recommendation mentioned the stakeholder input only once (Rationale for Recommendation, 3rd paragraph) and only cited the prevention of target organ damage as the main outcome. However, damage accrual is a “late” outcome in SLE. Uncontrolled disease activity and frequent flares will lead to increased use of glucocorticoids that will be used for prolonged periods before the patient’s condition allows dose reduction and, eventually, withdrawal. Damage accrual is the result of all these parameters and will only appear years after the acute event. This sequence of events has been shown by long-term longitudinal studies from different cohorts.

The main focus of our input was the unmet needs in certain subgroups of patients (i.e. those who do not achieve remission after 3-6 months of standard-of-care therapy, those who experience frequent flares despite treatment and those who are “glucocorticoid-dependent”) and not to all lupus patients.

There is no mention of these subgroups of patients in the CDEC Recommendation and we request that the Committee reconsider their decision for these patients.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
The CDEC bases the recommendation on the inconsistency of the results of TULIP-1 and TULIP-2. However, it seems that the totality of evidence (hence analysing the results in a larger number of patients that greatly improved statistical power) was not taken into consideration. Please see our response in Section 1 (2nd and 3rd paragraph).		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
Not applicable.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
Not applicable.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717-000
Brand name (generic)	Saphnelo
Indication(s)	Systemic Lupus Erythematosus
Organization	Toronto Lupus Program, University of Toronto
Contact information[a]	Name: Zahi Touma

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale. We have justified this in the attached letter.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
If not, what aspects are missing from the draft recommendation? We have justified this in the attached letter.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

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- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Zahi Touma
Position	Associate Professor of medicine
Date	28-07-2022
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☐	☒	☐	☐
GlaxoSmithKline	☐	☒	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	Dafna Gladman
Position	Professor of Medicine
Date	28-07-2022
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
GlaxoSmithKline	☒	☐	☐	☐
	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717
Name of the drug and Indication(s)	Anifrolumab (Saphnelo) in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE)
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717 Stakeholder Feedback on Draft Recommendation
Brand name (generic)	Saphnelo
Indication(s)	Systemic lupus erythematosus
Organization	Lupus Canada
Contact information[a]	Name: Leanne Mielczarek

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Given the complexity and diversity of lupus, no one expects a one size fits all treatment. Which is why it is imperative that CADTH revisit their recommendation. A diverse illness requires a diversity of treatments. Though lupus has not been defined as a rare disease, lupus does present shared commonalities with other rare diseases. Given this, with fewer cases, the evidence will not present as consistent as the committee indicates in their recommendations.
With the severity of lupus, the economic, societal, and mental health impact, without a diversity of treatment options, will no doubt pose a much higher burden to patients and ultimately the health care system. Without a diversity of treatments, we will continue to see high level of costs for treatments, which is directly attributed to a lack of generic competition in this market. There is a direct relationship between income and accessibility to medical treatment. Will there ever be new and publicly funded drug for lupus, if these standards are being used to evaluate the impact of new treatments? What hope are we giving those impacted by this debilitating and life-threatening disease?

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

From our research, which included responses from 112 lupus patients, we feel that the committee has not considered all aspects that factor into determining a patient's quality of life. Many respondents indicated quality of life as one of many preferred outcomes from a diversity of treatments. Currently limited treatments include a variety of side effects, which can be challenging to manage, which can then require additional medications to treat those side effects. Not all patients respond well to the medications currently available. Options remain limited and can be poorly tolerated or ineffective. The potential to reduce corticosteroid use is significant, as long-term steroid use has enormous adverse impact on one's organs. Other health complications stemming from lupus are very common, therefore, treating lupus with drugs that have been specifically designed for lupus is paramount to potentially staving off other potential health issues.

Lupus has proven to affect a wide population of people who experience a diverse range of symptoms. Lupus is unpredictable and it deeply affects all aspects of one's life. Due to the unpredictable nature of lupus and the silent nature of the disease, it is often misdiagnosed. Once diagnosed patients require different medications which often has negative side effects and can worsen symptoms (i.e., weight gain, nausea, heart arrythmias, increased infections, disturbances in blood health etc.) which is why Lupus Canada firmly believes Canadians living with lupus need more treatment options. Specifically in a recent Lupus Canada survey, patients stated that they, "always

have to advocate for their own health [and cannot] blindly trust the medical system" due to the lack of resources, visibility and treatment options for lupus.

It is imperative that given the severity of this disease that the committee reconsider their recommendations as patients deserve an alternate treatment option. The current treatments were not specifically developed for managing lupus. Data alone cannot determine quality of life.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
For future, it would be helpful if CADTH submissions were written in plain language.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
For future, it would be helpful if CADTH submissions were written in plain language.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Leanne Mielczarek, Lupus Canada*
Position	*Executive Director*
Date	*July 28, 2022*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

August 4, 2022

To whom it may concern,

We are writing on behalf of the Canadian Arthritis Patient Alliance, Arthritis Society, and Canadian Skin Patient Alliance as these organizations represent the rheumatic disease and skin patient communities in Canada. Our organizations jointly developed a patient input submission for anifrolumab (Saphnelo) in response to the review of this medication by CADTH. Our organizations are disappointed with the recommendation that anifrolumab (Saphnelo) not be reimbursed for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE) and we wish to convey our concerns about the recommendation.

Unlike other rheumatic diseases like inflammatory arthritis, SLE patients have not had the benefit of any significant treatment advances in over thirty years. Some medications have come onto the market in Canada, like belimumab (Benlysta), however these medications are not widely reimbursed by public drug plans across Canada and were also not recommended for reimbursement by CADTH. While patients living with SLE wait for better scientific evidence, SLE patients face continued barriers to diagnosis and the limitations of current treatment options. For example, current treatment protocols rely heavily on traditional disease modifying anti-rheumatic drugs and corticosteroids which significantly impact patient quality of life and cause other often irreversible side effects like bone deterioration, vision loss, and weight gain. The disease or treatment side effects impacts the ability of patients to participate in various aspects of life, such as work, parenting, romantic and social relationships, and activities of daily living. Our recent interview with Nadine Lalonde, a person who has lived with SLE for close to 15 years, expresses the impact of SLE on her life including significant work disability and financial insecurity.

Patients' responses to currently available treatments vary significantly. Some medications are effective for some people while not effective for others. People can often go through a process of trial and error with SLE medications to develop a treatment plan that meets their needs. This highlights why a variety of treatment options are needed to help manage a patient's disease including newer medications like anifrolumab (Saphnelo). We anticipate that anifrolumab (Saphnelo) would only be available to patients who have previously tried traditional DMARD's and be available to sub-set of the patient population reducing overall payer costs. If patients could benefit from anifrolumab, it would be stressful for patients to find out that the medication would not be reimbursed. It is important to remember that many public drug plans require that

the patient benefit from the medication in order to continue treatment. Current economic analysis often does not consider other relevant costs for patients such as early work disability and health care costs like Emergency Department usage and hospitalization.

In 2021, we discussed reimbursement recommendations for SLE with the Vice-President of Pharmaceutical Reviews (Brent Fraser) to better understand the rationale for the decisions. As CADTH evolves into an organization focused on "*health technology management*", there is an opportunity to shift the focus of reviews to create real-world evidence. Focusing specifically on creating real world evidence for SLE patients can address the lack of efficacy data noted in the listing recommendations and track the long-term outcomes of importance to patients like reduction in organ damage and corticosteroid use. Using real world evidence in economic evaluations is critical to ensure we know the the proportion of patients that benefit from treatment and that other relevant costs, like work disability and health care utilization, are adequately considered.

We appreciate the opportunity to provide feedback on the draft recommendation and welcome the opportunity to meet to openly discuss our concerns and further understand the decision-making process.

Sincerely,

[redacted]

Laurie Proulx
Vice-President
Canadian Arthritis Patient Alliance

Sian Bevan
Vice-President
Arthritis Society

Rachael Manion
Executive Director
Canadian Skin Patient Alliance

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717
Brand name (generic)	Saphnelo (anifrolumab)
Indication(s)	SLE (Lupus)
Organization	Lupus Ontario
Contact information[a]	Name: Linda Keill, President/June Alikhan, Vice President

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.
Lupus Ontario does not agree with the committee's recommendation:

- Patients would like to see a reduction in corticosteroid use in their treatment and TULIP-2 demonstrates that it is possible to reduce the dose to 7.5mg/day or less. There is consensus on the damage done to patients by long-term corticosteroid usage so any medication that allows reduction is beneficial and improves the patients quality of life.
- Every lupus patient is different and needs a different mix of medications and treatments to force them into remission. This means the more options available for treatment the greater the probability of patients having a drug induced remission.
- Additionally, because no two lupus patients are the same the disease could be redefined as being rare to each patient making it almost impossible for 2 studies to have the similar outcomes.
- 30% of the Lupus Ontario provincial focus group (consisting of 10 SLE patients) participants still have no medications/treatments for their disease. They are in chronic pain and continue to flare periodically and require frequent emergency department and specialist visits. This medication might be an option with this group of patients who currently have no way to control the disease.
- Failing to reimburse the medication is creating a 2 tier system for patients living in Ontario, those who have private coverage or the means to pay directly will be able to access this medication and those that don't will have to live with the chronic pain, fatigue and other challenges of lupus.
- The lupus population is usually considered to consist of 1.5 per thousand however this number is thought to be much higher in the BIPOC community. Medical professionals think that the BIPOC population number is closer to 3 per thousand people. Therefore by not recommending reimbursement this marginalized population is being further penalized.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

- Patients primary unmet need to reduce/eliminate corticosteroids was not addressed in the Discussion points section.
- Note that the Committee confused our submission with another group. Lupus Ontario

provided a submission from a focus group consisting of 10 SLE patients and **not** 2 patients. All other points provided were noted.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
• Although they fail to take into consideration patient's unmet needs.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification. N/A		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification. N/A		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Linda Keill / June Alikhan*
Position	*President / Vice President*
Date	*26-07-2022*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☐	☐	☒	☐
GSK	☐	☐	☐	☒
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

ANIFROLUMAB (Saphnelo)
(AstraZeneca Canada Inc.)

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

January 6, 2023

ANIFROLUMAB

I am a clinician that looks after very ill patients with Lupus.

The challenge with this disease is the lack of approved medications to treat patients with major symptoms and prevent end organ damage and death.

It is only recently that options are available to treat these patients. It is promising that the unmet need to improve quality of life in often young females who have suffered in silence and been exposed to high doses of steroids with the attendant steroid side effects can be addressed.

The challenge for the physician is helping the payors make hard choices in cost effectiveness of newer medications. This medication needs to be available for our patients and it is hoped that industry and payors can make it happen.

I would be pleased to address the group and answer questions if that is helpful.

John P Wade MD FRCP (C) (Rheum)

UNIVERSITY OF TORONTO
FACULTY OF MEDICINE

The Toronto Lupus Program, University of Toronto

[redacted]

January 5, 2023

The Toronto Lupus Program, University of Toronto

Dear CDEC,

Re: CADTH Reimbursement Recommendation (Draft) Anifrolumab (Saphnelo)

We have the following comments regarding the Reimbursement Conditions and Reasons listed in table 1 of the CADTH Reimbursement Recommendation draft.

Initiation:
CDEC noted that treatment with anifrolumab should be reimbursed when initiated in adult patients with moderate-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.

Our Comment:
As rheumatologists who treat mainly patients with systemic lupus we want to further elaborate on the definition of standard of care therapy to facilitate the implementation guidance.

Standard of care therapy should include the use of a combination of antimalarial drug (e.g. hydroxychloroquine) AND immunosuppressive agents (e.g., cyclophosphamide, azathioprine, methotrexate, cyclosporine, and mycophenolate) with or without NSAIDs, and with no signs of adverse events/toxicity related to any of the used drugs (.e.g., cyclophosphamide, azathioprine, methotrexate, cyclosporine, and mycophenolate).

Renewal
CDEC noted that 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:
- ***Reducing the SLEDAI2K score to less than 6***

or
- ***BILAG improvement in organ systems and no new worsening***

Our Comment:

Achieving a dose of prednisone ≤ 7.5 mg/day at 1year can be very challenging in patients with very severe disease manifestations particularly in those who start on a moderate (20-30 mg/d) and particularly large (≥30 mg/d) dose of prednisone at baseline. In real practice, often we can't lower the prednisone ≤ 7.5 mg/day in this group of patients at 1 year. Thus we recommend that in patients with ≥ prednisone 20 mg/d at baseline to allow a different approach – relative change in the dose of prednisone at 1 year compared to baseline – a decrease by ≥ 50% of the baseline dose of prednisone at 1 year should be accepted as a good target.

For subsequent renewal, the physician must provide proof that the initial response achieved after the first 12 months of therapy with anifrolumab has been maintained. Subsequent renewals should be assessed annually.

Our Comment:
We strongly recommend the use of validated instruments for the assessment of disease activity such as SLEDAI-2K, BILAG or PGA (Physician Global Assessment) at baseline and follow up visits.

Kind regards,

[redacted]

Zahi Touma, MD, PhD
Associate Professor of Medicine
Director, UHN Lupus Clinic
University of Toronto
Scientist Krembil Research Institute

[redacted]

Joan Wither, MD, PhD
Professor of Medicine and Immunology,
University of Toronto, Senior Scientist,
Krembil Research Institute

[redacted]

Dafna D. Gladman, MD
Professor of Medicine
Director, Centre for Prognosis Studies in the Rheumatic Diseases

University of Toronto
Senior Scientist, Krembil Research Institute

[redacted]

Jorge Sanchez-Guerrero, MD MSc
Professor of Medicine
University of Toronto
Clinician Investigator, Krembil Research Institute

[redacted]

Murray Urowitz, MD
M.B. Urowitz MD FRCP(C)
Professor Emeritus, Temerty Faculty of Medicine
University of Toronto

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Saphnelo (anifrolumab)
Indication(s)	For the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy
Organization	**The Toronto Lupus Program, University of Toronto**
Contact information[a]	Zahi Touma

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale. Please see attached recommendation letter. While we agree with the most of it, we have suggested the following issues for your consideration (see attached letter).		
Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation? Please refer to the attached letter to review our suggestions.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. We think that this can be improved - We have elaborated on this in the attached letter.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Zahi Touma*
Position	*Director, Toronto Lupus Program at UHN* *Associate Professor of Medicine, University of Toronto Institute of Health Policy, Management and Evaluation Institute of Medical Sciences,* *Adjunct Scientist, Institute for Work and Health* *Clinician-Scientist, Rheumatology, University Health Network* *Scientist, Schroeder Arthritis Institute, Krembil Research Institute*
Date	*05-01-2023*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☒	☐	☐	☐
AstraZeneca	☐	☒	☐	☐
UCB	☒	☐	☐	☐
BioPharma	☒	☒	☐	☐
GlaxoSmithKline	☐	☒	☐	☐
Merck	☐	☒	☐	☐
KgaA	☒	☐	☐	☐
AMPEL BioSolutions	☒	☐	☐	☐
Sarkana Pharma	☐	☒	☐	☐

Sarkana Pharma	☐	☒	☐	☐

New or Updated Declaration for Clinician 2

Name	*Dafna D. Gladman*
Position	*Professor of Medicine, University of Toronto Senior Scientist, Schroeder Arthritis Institute, Krembil Research Institute Deputy Director, Centre for Prognosis Studies in The Rheumatic Diseases Toronto Western Hospital*
Date	*01-05-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☐	☒	☐	☐
Eli Lilly	☐	☒	☐	☐
Janssen	☐	☒	☐	☐
Gilead	☐	☒	☐	☐

Novartis	☐	☒	☐	☐
Pfizer	☐	☒	☐	☐
Bristol-Myers Squibb	☐	☒	☐	☐
Galapagos	☐	☒	☐	☐
UCB Pharma	☐	☒	☐	☐
Celgene	☐	☒	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Joan Elizabeth Wither*
Position	*Professor Medicine and Immunology U of T, Staff Physician, University Health Network*
Date	*05-01-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☒	☐	☐	☐
Pfizer	☐	☐	☐	☒

New or Updated Declaration for Clinician 4	
Name	*Dr. Jorge Sanchez-Guerrero*
Position	*Professor of Medicine, University of Toronto* *Clinician Investigator, Krembil Research Institute*
Date	*2023-01-06*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
n/a	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Murray B Urowitz*
Position	*Professor Emeritus, Temerty Faculty of Medicine University of Toronto*
Date	*2023-01-09*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
GlaxoSmithKline	☒	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717-000
Brand name (generic)	Saphnelo (Anifrolumab)
Indication(s)	Systemic lupus erythematosus
Organization	Canadian Network for Improved Outcomes in SLE
Contact information[a]	Name: Dr. Konstantinos Tselios

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		
Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. Given that reimbursement is pertinent on the conditions listed in Table 1, we request that for Renewal (paragraph 4), a 50% reduction of the baseline dose of oral corticosteroids (OCS) after 12 months will be considered as the patients achieved the OCS dose reduction condition (of ≤7.5mg/day of prednisone or equivalent). The phrase "or 50% reduction of the baseline dose of OCS" should be added in paragraph 4.1 (in the Reimbursement Condition column). This will clarify the reimbursement criteria and resolve any misunderstandings from the treating physicians.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
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  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: **1.** Dr. Konstantinos Tselios, MD, PhD, Assistant Professor **2.** Dr. Christine Peschken MD, Professor of Medicine, Chair, CaNIOS **3.** Dr. John Hanly, MD, Professor of Medicine **4.** Dr. Judah Denburg, MD, FRCP(C), William J. Walsh Chair in Medicine, Professor **5.** Dr. Mark Matsos, MD, FRCPC, Associate Professor **6.** Dr. Kimberly Legault, MD, FRCPC, Associate Professor **7.** Dr. Derek Haaland, MD, MSc, FRCPC, Associate Clinical Professor **8.** Dr. Janet Pope, MD, FRCPC, Professor **9.** Dr. Lily Lim, MBBS, MRCPCH, FRCPC, PhD, Assistant Professor **10.** Dr. Ann Clarke, MD, MSc, Professor **11.** Dr Carol Hitchon MD FRCPC Associate Professor **12.** Dr. Annaliese Tisseverasinghe, MD, MSc, FRCPC, Assistant Professor **13.** Dr. Megan Barber, MD, PhD, FRCPC, Clinical Assistant Professor **14.** Dr. Stephanie Keeling, MD, FRCPC Professor of Medicine		

McMaster University

RE: CADTH Reimbursement Recommendation for Anifrolumab (Saphnelo®)

Hamilton, 5 January 2023

Dear Members of the CADTH Canadian Drug Expert Committee (CDEC),

We greatly appreciate your recent positive recommendation for the public reimbursement of Anifrolumab for use in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE). This will certainly help a significant number of lupus patients to manage their disease more efficiently and with less long-term side effects.

Given that reimbursement is pertinent on the conditions listed in Table 1, we request that for Renewal (paragraph 4), a 50% reduction of the baseline dose of oral corticosteroids (OCS) after 12 months will be considered as the patients achieved the OCS dose reduction condition (of ≤7.5mg/day of prednisone or equivalent). The phrase "or 50% reduction of the baseline dose of OCS" should be added in paragraph 4.1 (in the Reimbursement Condition column). This will clarify the reimbursement criteria and resolve any misunderstandings from the treating physicians.

Should you need further information, please do not hesitate to contact us.

Sincerely yours,

1. Dr. Konstantinos Tselios, MD, PhD, Assistant Professor
2. Dr. Christine Peschken MD, Professor of Medicine, Chair, CaNIOS
3. Dr. John Hanly, MD, Professor of Medicine
4. Dr. Judah Denburg, MD, FRCP(C), William J. Walsh Chair in Medicine, Professor
5. Dr. Mark Matsos, MD, FRCPC, Associate Professor
6. Dr. Kimberly Legault, MD, FRCPC, Associate Professor
7. Dr. Derek Haaland, MD, MSc, FRCPC, Associate Clinical Professor
8. Dr. Janet Pope, MD, FRCPC, Professor
9. Dr. Lily Lim, MBBS, MRCPCH, FRCPC, PhD, Assistant Professor
10. Dr. Ann Clarke, MD, MSc, Professor
11. Dr Carol Hitchon MD FRCPC Associate Professor
12. Dr. Annaliese Tisseverasinghe, MD, MSc, FRCPC, Assistant Professor
13. Dr. Megan Barber, MD, PhD, FRCPC, Clinical Assistant Professor
14. Dr. Stephanie Keeling, MD, FRCPC Professor of Medicine

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717
Name of the drug and Indication(s)	Anifrolumab (Saphnelo) in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE)
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X☐
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification. • In the renewal point, 4.2, first bullet. Consider revising to 'Reducing the SLEDAI-2K to a score of 5 or less' in order to separate it more clearly from the initiation criteria that requires a SLEDAI-2K score of at least 6.

c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. • If BILAG is included in renewal criteria assessment, consider capturing a baseline BILAG measure in the initiation criteria or in the implementation guidance for the initiation criteria. • Regarding prescribing condition #7, it states that Saphnelo should not be reimbursed when used in combination with other biologic treatments. Consider clarifying if this is intended to be other biologic treatments for SLE.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717-000
Brand name (generic)	ANIFROLUMAB (SAPHNELO)
Indication(s)	In addition to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE)
Organization	Lupus Canada
Contact information[a]	Name: Leanne Mielczarek

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

PAGE 4
PT 4 – *Treatment with anifrolumab can be renewed as long as long as all of the following are met:*
PT 4.1 *OCS dose decreased to ≤ 7.5 mg/ day prednisone or equivalent*
PT 4.2 *Reduction in disease activity measured by: Reducing the SLEDAI-2K score to less than 6 or BILAG improvement in organ systems and no new worsening*

The following language is used in the **Implementation Guidance**:
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

FEEDBACK

- Add percentage variable to the Reimbursement Guideline along with the PT 4.1 seen above to read: ***≤7.5 mg/ day prednisone and/or OCS dose decreased by at least 50% from baseline***

PAGE 4
PT 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 maintained. Subsequent renewals should be assessed annually. 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 in order to renew therapy. The same scale should be used both at baseline and all subsequent renewals.*

FEEDBACK

- Concerns about a one-time assessment result vs. macro-observation over a one-year period
- Could patients' renewal be determined by an average positive response to treatment

PAGE 5

PT. 6 - *Patient should be under the care of a rheumatologist who has experience in the diagnosis and management of SLE.*

FEEDBACK

- Expand the medical practitioner support guidelines to include various specialists outside of the field of Rheumatology
- To support patients who may not have access to one specific type of specialized care to manage their SLE (IE: patients outside of major urban settings)

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Leanne Mielczarek*
Position	*Executive Director*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☒
	Yes	☐

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca Canada	☐	☐	☒	☐
GSK Pharmaceuticals	☐	☐	☒	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717-000
Brand name (generic)	anifrolumab (Saphnelo)
Indication(s)	Systemic Lupus Erythematosus
Organization	Canadian Arthritis Patient Alliance, Canadian Skin Patient Alliance, Arthritis Society Canada, CreakyJoints Canada
Contact information[a]	Name: Laurie Proulx

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

(Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.)

We are pleased with the recommendation to reimburse anifrolumab (Saphnelo) for people with systemic lupus erythematosus (SLE). People with SLE have not benefited from significant changes in treatments for over thirty years. They have limited treatment options, and some will benefit tremendously from the committee's recommendation. We ask that information be added about simplifying medication renewals in order to reduce the impact on people with SLE who are often over-burdened with managing their health and health care.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

(If not, what aspects are missing from the draft recommendation?)

We appreciate that CADTH and CDEC have recognized the heterogeneity of the disease and the need for multiple treatment options given that treatment responses can vary significantly among patients. Priority was also given to reducing corticosteroids which has been a long-term challenge for people with SLE given the limited treatment options. Going forward, we recommend that patient organizations and people with SLE be actively engaged with CADTH in developing and implementing real-world evidence in support of ongoing reviews of anifrolumab (Saphnelo) and other SLE medications and treatments.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

	Yes	☒

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717
Brand name (generic)	Saphenello
Indication(s)	Systemic lupus erythematosus
Organization	Lupus Ontario
Contact information[a]	Name: Linda Keill/June Alikhan

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		
Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
Please see attached CADTH Patient Feedback Anifrolumab Reimbursement Approval write-up addressing this item.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
Please see attached CADTH Patient Feedback Anifrolumab Reimbursement Approval write-up addressing this item.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*June Alikhan*
Position	*Vice President and Chair, Advocacy Committee*
Date	*05-01-2023*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☒
	Yes	☐

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☐	☐	☐	☒
GSK	☐	☐	☐	☒
Add or remove rows as required	☐	☐	☐	☐

Date: January 3, 2023

Submitted by: Linda Keill, President
June Alikhan, Chair Advocacy Committee

Re: Anifrolumab Draft Reimbursement Recommendation

Thank you for reconsidering your position and the recent recommendation on the reimbursement of Anifrolumab. This is one of the few new medications specifically designed for people living with lupus in the last decade and as such its approval is an important milestone for SLE treatment and a large step forward for the lupus community. CADTH's willingness to review new data submitted and to consider the patient voice in the process was very much appreciated.

However, we do have some concerns on the usage restrictions imposed in the draft recommendation. These relate to 1) after a year the patient must have attained an outcome of oral corticosteroid (OCS) levels of 7.5mg/day or less, and 2) only rheumatologists are allowed to prescribe the medication.

1) OCS levels of 7.5mg/day

Patients react differently to declines in OCS dosages and some patients need to decrease at a much more gradual rate than others. It is understandable that a positive outcome should be required to continue using the medication however I think setting a percentage decline target in order to assess effectiveness is more reasonable then setting a firm target of 7.5mg/day. For example, if the patient is on 15mg/day and then decreases their dosage to 10mg/day that is a decline of 33% and would be considered a substantial achievement in a year by the patient. Therefore, another year on the medication might allow the patient to reduce their OCS to below 7.5mg/day.

2) Prescription restricted to Rheumatologists

Lupus is a complex disease and often treated by a variety of specialist and sometimes a team of specialists. Therefore, Anifrolumab should be able to be prescribed by other specialists involved in the patients care such as a nephrologist, immunologist or a member of the health care team.

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0717
Brand name (generic)	Saphnelo™ (anifrolumab)
Indication(s)	Add-on to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE)
Organization	AstraZeneca Canada
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

- AstraZeneca (AZ) agrees with CADTH's draft recommendation that anifrolumab should be reimbursed for use in addition to standard therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE) based on statistically significant reduction in disease activity, maintenance of reduction in the oral corticosteroids (OCS) dose and reduction of 50% or more in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in TULIP-2 trial.
- AZ is also in alignment with CADTH proposed criteria for reimbursement and renewal. Furthermore, AZ agrees that anifrolumab addresses patient identified unmet needs by reducing SLE disease activity and OCS dose

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

- In the *'Prescribing'* section of Reimbursement Conditions and Reason (table 1; page 5), CADTH recommends that *"Patient should be under the care of a rheumatologist who has experience in the diagnosis and management of SLE"*. While AZ recognizes that Rheumatologists are the main healthcare professionals (HCPs) in the management of SLE and will represent the majority of the HCPs prescribing Anifrolumab, there are other HCPs such as dermatologists or internists who have clinical experience and expertise in managing and treating SLE patients[1-2] including prescribing biologics. It was noted in the consolidated patient input from ACE, Lupus Canada and Lupus Ontario, that "Lupus was described as a chronic disease characterized by inflammation in one or more parts of the body", it was also acknowledged by the clinical expert consulted by CADTH, "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" which

implies that there could be varied presentation of SLE and therefore, additional specialists with experience in SLE management need to be included as potential prescribers. Lastly, given the dissimilarities among provinces especially in remote areas pertaining to access to Rheumatologists, patients may experience difficulty in accessing a specific specialist care and consequently access to needed biologic treatment. Given that, internists and dermatologists are already managing SLE patients and that treatment effect with anifrolumab could be seen regardless of previous treatments with acceptable safety to patients, AZ proposes an update to the language in criteria and consideration during provincial implementation.

AZ proposed revisions:
AstraZeneca requests that CADTH update the prescribing criteria for anifrolumab as: Patient should be under the care of a **rheumatologist or a physician who has experience and expertise** in the diagnosis and management of SLE.

- In the *Rationale for the Recommendation* (page. 3) and in the 'Pricing' section of the Reimbursement Conditions and Reasons table (page. 5, table 1), CADTH indicates that: "The ICER for anifrolumab + 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% would be required for anifrolumab to be able to achieve an ICER of $50,000 per QALY compared to best supportive care". AstraZeneca disagrees with the ICER reported by CADTH, which was based on inappropriate assumptions related to survival, discontinuation rate, and treatment efficacy waning. In its re-analysis, CADTH assumed an exponential survival distribution which commonly overestimates long-term survival; this overestimation was demonstrated in a comparison of different survival assumptions against the long-term Toronto Lupus Cohort data. AstraZeneca maintains that a log-logistic distribution produces the best-fit model and the most appropriate survival assumption using standard modelling criteria. In addition, CADTH acknowledged that sensitivity analyses, provided by AstraZeneca, showing that higher discontinuations in the TULIP 2 placebo arm did not result in attrition bias and reduced concerns regarding imbalance in discontinuation rates in the TULIP trials. Yet, CADTH adopted an alternate discontinuation rate from its scenario analysis in its base case ICER. AstraZeneca disagrees with this modelling approach and maintains that uncertainty in the discontinuation rate is represented alongside uncertainty in all model parameters in the probabilistic analyses submitted by the manufacturer in accordance with CADTH's *Guidelines for the Economic Evaluation of Health Technologies*.[3] Finally, CADTH assumed that waning of treatment effect would occur after 5 years. Data from the open-label extension of the MUSE trial and from the comparative TULIP Long-Term Extension (LTE) study showed no indication of treatment waning throughout the 3- and 4-year periods of the trials.[4,5] In addition, long-term real-world evidence with biologics used for patients with other rheumatic diseases, such as rheumatoid arthritis and psoriatic arthritis, demonstrate sustained efficacy for at least 10 years.[6-8] Given the long-term empirical evidence of anifrolumab and with biologics for other rheumatic diseases, AstraZeneca maintains that imposing a waning treatment effect after 5 years in the base case is not a reasonable assumption and should only be reported as a scenario analysis.

  AZ proposed revisions:
  AstraZeneca maintains the validity of the manufacturer-submitted ICER and requests that CADTH report its ICER using assumptions related to survival, discontinuation rate, and waning effect as scenario analyses.

- In the 'Economic Evidence' section (Cost and cost-effectiveness table, page. 17), Key limitations, CADTH states: "A difference among groups in baseline CLASI damage score was observed in

the treatment arm compared to BSC in TULIP 2 versus TULIP 1 trial, which could potentially allow for greater leaps in improvement in patients with more severe disease." AstraZeneca disagrees with this characterization of uncertainty across the TULIP trials. It is important to note that the CLASI damage score measures dyspigmentation and scarring damage caused by the disease, which is taken to be permanent. CLASI damage score was not used as an endpoint to measure improvement in the TULIP studies. It is, therefore, not plausible to expect any disproportionate improvement in damage among patients due to differences in CLASI damage scores. Nevertheless, AstraZeneca notes that the absolute differences in the number of patients with baseline CLASI damage score ≥10 in the treatment versus placebo arms was similarly small between TULIP 1 (n=3) and TULIP 2 (n=8). CLASI activity score, a more appropriate measure of disease activity, was used as a pre-specified secondary endpoint in TULIP trials. AstraZeneca further notes that the absolute differences in the number of patients at baseline with CLASI activity score ≥10 in the treatment versus placebo arms was again similarly small between TULIP 1 (n=5) and TULIP 2 (n=9) and therefore unlikely to drive any meaningful differences between the TULIP trials.

AZ proposed revisions:
AstraZeneca requests that CADTH remove the statement: "A difference among groups in baseline CLASI damage score was observed in the treatment arm compared to BSC in TULIP 2 versus TULIP 1 trial, which could potentially allow for greater leaps in improvement in patients with more severe disease" as the absolute differences in baseline CLASI scores (whether activity or damage scores) are not plausible drivers of any meaningful differences between the TULIP trials.

- In the 'Economic Evidence' section (Cost and cost-effectiveness table, page. 18), CADTH re-analysis results were based on scenarios using pooled data from TULIP-1 + TULIP-2 and data from TULIP-1 only. CADTH offers "…the different findings from the TULIP trials" as a rationale for this approach and reports that: "Based on the pooled data from TULIP trials, the ICER for anifrolumab + BSC compared with BSC is $224,736 per QALY, while the ICER was $354,355 per QALY when only TULIP-1 data was considered." AZ disagrees with using a scenario based on TULIP-1 data to address "different findings from the TULIP trials" instead of using the pooled analysis, which explicitly incorporates findings across the different TULIP studies. In addition, the presumed rationale for using only TULIP-1 data is based on smaller differences in CLASI damage scores between treatment and placebo arms in TULIP-1 versus TULIP 2. However, as noted in the previous point, CLASI damage score is not expected to improve and the absolute differences in number of patients with CLASI activity scores ≥10 at baseline are too small to drive any meaningful differences between the TULIP trials. Moreover, the *Rationale for Recommendation* highlights the clinically meaningful benefits of anifrolumab in reducing disease activity, reducing oral corticosteroid dose, and disease severity based on the TULIP-2 trial. Given that data from TULIP-2 underpins the rationale for recommendation, it would not be appropriate or justified to exclude it as the basis for a re-analysis of the ICER.

  AZ proposed revision:
  AstraZeneca requests that CADTH report ICERs using pooled TULIP-1 and TULIP-2 data to address the impact of different findings across the TULIP trials.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

References

1. Canadian Dermatology Association, Autoimmune Disease. Available online at: https://dermatology.ca/public-patients/resources/support-groups/autoimmune-diseases/
2. Lupus Foundation of America, Doctors who treat lupus. Available online at: https://www.lupus.org/resources/doctors-who-treat-lupus
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4. Chatham WW, Furie R, Saxena A, et al. Long-term safety and efficacy of anifrolumab in adults with systemic lupus erythematosus: results of a phase II open-label extension study. Arthritis & Rheumatology. 2021;73(5):816-825.
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7. Keystone EC, van der Heijde D, Kavanaugh A, et al. Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. J Rheumatol. 2013;40(9):1487-1497.
8. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther. 2019;21(1):89.