CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

tralokinumab (TBC)

LEO Pharma Inc.

Indication: Tralokinumab is indicated for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. TRADENAME (tralokinumab) can be used with or without topical corticosteroids.

May 21, 2021

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting clinician group and all conflicts of interest information from individuals who contributed to the content are included in the posted clinician group submission.

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**SR0689-000**
Generic Drug Name (Brand Name)	**Tralokinumab**
Indication	**Moderate-to-severe atopic dermatitis**
Name of the Clinician Group	**Canadian Dermatology Association**
Author of the Submission	**Dr. Jason Rivers, President, Canadian Dermatology Association**
Contact information	**Name: Linda M. Jones** **Title: Chief Executive Officer** **Email:** [redacted] **Phone:** [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

The Canadian Dermatology Association, founded in 1925, is the national medical specialty association that represents Canadian certified dermatologists. The association exists to advance the science and art of medicine and surgery related to the care of the skin, hair and nails; provide continuing professional development for its members; support and advance patient care; provide public education on sun protection and other aspects of skin health; and promote a lifetime of healthier skin, hair and nails.

Clinical review and oversight is provided by the Canadian Dermatology Association's Pharmacy and Therapeutics Advisory Board and the CDA Board of Directors.

The Association's website address is www.dermatology.ca

2. Information Gathering

Please describe how you gathered the information included in the submission.

Information that was gathered came from clinical and trial experience, medical literature, published trials, and national and international meetings.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Most patients are initially treated topically with emollients, topical steroids, topical calcineurin inhibitors (pimecrolimus, tacrolimus) and/or phosphodiesterase inhibitors. Topical steroids are the most widely used. Topical treatment of moderate-to-severe disease may take upwards of 1-1.5 hours per application. The newer antihistamines bilastine and rupatadine are often used as adjunctive therapy to lessen itching. They have a better safety profile than the first generation antihistamines which cause dry mouth and impair sleep quality and work productivity. This initial approach may be sufficient for up to 90% of individuals. Those with recalcitrant disease are treated with phototherapy or systemic treatments often in addition to topical therapy. Multiple forms of phototherapy have been used including narrowband ultraviolet B (UVB), broad band UVB, ultraviolet A and psoralen plus UVA (PUVA). Due to an increase in skin cancer, PUVA is less commonly used now. There is only one approved systemic treatment, the biologic dupilumab which is given by subcutaneous administration every other week. It has helped many patients and has a good safety profile, yet it only clears approximately 1/3 of patients. Its side effects of conjunctivitis (inflammation of the eyes) and facial dermatitis result in morbidity and sometimes early treatment termination. The immunosuppressants methotrexate, cyclosporine, azathioprine and mycophenolate mofetil are used off label if there are no other alternatives. High-quality randomised, controlled trials in atopic dermatitis are lacking to support the use of these immunosuppressants and side effects limit their use. They all require frequent laboratory monitoring which is difficult for many patients, particularly in rural and small communities. In addition, the responses achieved are often not durable. Methotrexate and cyclosporine appear to be the most commonly used, however, it should be noted that due to nephrotoxicity and structural renal damage, cyclosporine is considered a short-term 3-6 month treatment rather than a long-term treatment. Cyclosporine may also cause a number of other adverse effects including malignancies, infection and hypertension. Methotrexate is teratogenic and may induce bone marrow suppression, hepatic toxicity, malignancies, infections and pulmonary fibrosis. Azathioprine is mutagenic and may cause bone marrow suppression and malignancies. Mycophenolate mofetil is also teratogenic and associated with serious infections and malignancies. In the COVID-19 era, immunosuppressants put our patients at increased risk. Systemic glucocorticoids are also used short-term as rescue treatment. Due to adverse effects, they are not considered for long-term therapy. Results are usually not durable and rebound is common after systemic glucocorticoids are discontinued.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

The treatment goals in atopic dermatitis are to provide long-term relief of itching and to clear skin in a safe, convenient and durable way. Secondary goals include improvement in depression, anxiety and quality of life, and restore the patients' ability to function again in society.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Approximately two thirds of patients treated with the only currently available biologic do not achieve clear skin. There is a need for additional systemic medications with different mechanisms of action for this heterogeneous complex disease so that more patients can obtain clear skin on treatment. Improved safety and less frequent dosing would also be convenient for patients. The only currently approved biologic is dupilumab which is dosed every two weeks.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

The patients that have the greatest unmet need are those with moderate-to-severe atopic dermatitis who do not respond to topicals and phototherapy. Women of childbearing potential also have a greater need since most of the off-label systemics are teratogenic. Tralokinumab would meet their unmet need.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Tralokinumab is a biologic with a different mechanism of action to dupilumab, the only currently available biologic. Dupilumab is a monoclonal antibody directed against the α subunit of the Il-4 receptor (IL-4Rα) which is also a component of the Il-13 receptor, while tralokinumab is a monoclonal antibody against interleukin-13. It is expected that tralokinumab will be used for moderate-to-severe patients that have failed topical therapy and phototherapy. It would be used as a first systemic agent as well as after other systemics including dupilumab have failed. We have no data as to what the likelihood of a dupilumab failure responding to tralokinumab and vice versa. This would not be its primary use, however when dupilumab fails, another safe efficacious treatment is needed and tralokinumab will likely be tried in those cases. Tralokinumab will likely be used in combination with topical therapies that the patient is using, however once the atopic dermatitis improves, the topicals will likely only be used on resistant areas if any.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Patients should ideally have failed topical treatments and phototherapy since they are considerably less expensive yet reasonably safe. It is not appropriate to recommend that tralokinumab be used after significantly more toxic unapproved systemics, especially when there is little scientific support their use in atopic dermatitis and when one of the systemics, cyclosporine, may cause permanent structural renal disease if used long-term for this disease which usually requires long-term treatment.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Topicals will remain as first line therapy followed by phototherapy, then systemics including biologics. There are no data for use of tralokinumab in patients who have failed the other biologic dupilumab. It is conceivable that since their mechanisms of action are different, tralokinumab might work where dupilumab did not and vice versa. It is conceivable that patients that have conjunctivitis as a baseline atopic co-morbidity will be prescribed tralokinumab prior to dupilumab. Tralokinumab may be used before

more toxic systemic agents, but if tralokinumab and dupilumab don't work, patients will need to try something to relieve their suffering and this might mean that they use immunosuppressives after the biologics in the event that patients have insufficient improvement with the biologics.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients with moderate-to-severe atopic dermatitis affecting more than 10% body surface area, intense itching (NRS >4) and failure to respond to topicals and phototherapy are in most need of an intervention, although there is no evidence with the currently available trial data that there are any subtypes of moderate-to-severe atopic dermatitis patients that might respond better. With more therapies, patients who have not failed another agent respond better, but we do not know if that is the case for tralokinumab.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Patients with at least 10% body surface area, with an itch NRS of 4 and failure to respond to topical steroids, topical calcineurin inhibitors and phototherapy

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients with mild atopic dermatitis or a different disease state.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

A waterfall plot of patient response has demonstrated that most patients have some response to

tralokinumab. It is not clear how one might identify non-responders.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Itch NRS, body surface area and investigator global assessment are often used in clinical practice. In clinical trials, these are also used in addition to EASI and SCORAD and Dermatology Quality of Life Index. SCORAD is hard to calculate and is primarily a European instrument.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

A four point reduction in itch, reduction in IGA to mild or better and reduction in body surface area.
It is important to note that when patients are doing well and clearing, the lichenification often takes many months to resolve

6.10. How often should treatment response be assessed?

Response:

Treatment should be assessed at 6 months then yearly. Many patients with moderate-to-severe atopic dermatitis do not show maximal improvement until after 6 months.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease worsening or lack of improvement. There are no major safety concerns with tralokinumab. Injection site reactions and conjunctivitis infrequently lead to discontinuation.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

The treatment should be initially prescribed by a dermatologist or allergist. After 6 months, it could be

renewed by other physicians.
6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?
If so, which specialties would be relevant? ***Response:*** Most patients with moderate to severe atopic dermatitis are diagnosed, treated and monitored by dermatologists. Allergists also play a role in management.
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: Click here to enter response.

8. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

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. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr Jason Rivers*
Position	*President Canadian Dermatology Association*
Date	*10-May-2021*
☒	**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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
As the national medical speciality association representing Canada's certified dermatologists, the CDA does have various relationships with individuals including receipt of funding for programs				
AbbVie	☐	☐	☐	☒
Eli Lilly	☐	☐	☐	☒
LEO Pharma	☐	☐	☐	☒
Pfizer	☐	☐	☐	☒
Sanofi	☐	☐	☐	☒

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**Tralokinumab – moderate to severe atopic dermatitis in adults**
Generic Drug Name (Brand Name)	**No formal patient group.- I am a dermatologist who has created input on behalf of my Indigenous patients suffering from moderate to severe atopic dermatitis (Origins Dermatology Centre)**
Indication	**Rachel Asiniwasis MD, FRCPC**
Name of the Clinician Group	**Rachel Asiniwasis**
Author of the Submission	[redacted]
Contact information	Name: Rachel Asiniwasis Title: Dermatologist Email: [redacted] Phone: [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

Introduction:

Dear Committee, I apologize sincerely for the late submission (May 25 - but I submitted it on the wrong template so have re-submitted it May 31), please consider reviewing my information as below. I have also updated the COI. There is one involvement I had in an advisory board. Thank you!

My name is Dr. Rachel Netahe Asiniwasis and I am an Indigenous dermatologist based in my original hometown of Regina, Saskatchewan and have been working full time since 2014. One of my most recent passions is proactively addressing health disparities in remote Canadian Indigenous populations in a dermatologic context. Although my main practice is based in Regina, I offer remote clinics in northern and southern Saskatchewan in the form of virtual care/teledermatology, and in-person (drive-up, fly in) clinics with a focus on providing culturally safe care to Indigenous communities. My goal with this submission is to give a voice to and advocate for my Indigenous patients, and to discuss my own experience working first hand in remote Indigenous communities. The current outreach/remote communities under my care include:

Southern Saskatchewan:

- All Nations Healing Hospital (Fort Qu'appelle) and surrounding area
- Touchwood Agency Tribal Council communities:
    - George Gordon's

- Kawakatoose
- Muskokewan
- Day Star

Northern Saskatchewan:

- Pelican Narrows/Deschambault Lake
- Stony Rapids/Black Lake/Fond du Lac
- Ile a la Crosse, Buffalo Narrows and La Loche

My website is www.originsdermatology.com – See under "research" and "remote clinics"

This submission is in support of improved/unrestricted access to tralokinumab coverage for Indigenous patients in remote communities who suffer from moderate to severe atopic dermatitis and are candidates for tralokinumab.

2. Information Gathering

Please describe how you gathered the information included in the submission.

This was completed through conversations with patients during clinical care for their AD.

See below. I also have added some brief information on the clinician input template, although this was already submitted late (May 31) the correct portal. The first document was accidentally written on a patient input template submitted May 25.

Background:

A paucity of information exists on Indigenous skin disease in Canada. The skin is a manifestation of both internal and external health, and Indigenous populations face unique challenges and barriers compared to the general Canadian population. Complex health determinants in Indigenous communities exist, and addressing such skin disease must include a view of "the bigger picture". Research, although lacking on Indigenous skin disease and in particular the commonly seen disease of atopic dermatitis is desperately needed to raise awareness around these conditions in orer to inform policy and decision makers that there are issues that need to be recognized and addressed.

Working within Indigenous communities, I frequently encounter, **atopic dermatitis** (which I may refer to as AD or "eczema"), a chronic skin condition characterized by recurrently itchy, painful, oozing, inflamed and dry rashes on the skin ranging in severity from mild to severe, often starting in infancy to early childhood, and can have a hereditary component. Atopic dermatitis (AD), especially in its moderate to severe form, is a debilitating disease characterized by well documented significant functional impairment and wide reaching physical, psychosocial, academic, occupational and economic impact. When under poor control, it is frequently complicated by both short and long term problems such as secondary bacterial or viral skin infection (eg. impetigo, MRSA or eczema herpeticum), sleep disturbances and other physical and mental health comorbidities such as anxiety, depression, insomnia and suicidality and due to chronic itching, pain and discomfort (ESC 2017; Weidinger, 2016). Financial impacts include out-of-pocket expenses (in which costs are generally inflated in remote and northern Indigenous communities for basic, hypoallergenic skin care regimens and products used for hygiene and washing), as well as numerous medical service visits for eczema and its complications (eg. secondary infection), hospitalization, and consequences from absenteeism/loss of productivity. In my clinical experience, after seeing innumerable patients from remote Indigenous communities, those with AD have many AD complication-related health care practitioner visits. The impacts of AD are often magnified in these remote communities due to barriers and inherent health disparities.

The role of chronic itch can often be analogized to burdens of chronic pain. This can lead to daytime fatigue and irritability, and concentration and behavioural issues at school or work, for example, leading to lost productivity (Barbeau & Lalonde, 2004). The odds of having attention deficit hyperactivity disorder (ADHD) is significantly

increased in children with AD with a clear relationship between the prevalence of ADHD and the severity of the skin disease (Yaghmaie, Koudelka, & Simpson, 2013). The severity and impact on the mental health on patients suffering from skin conditions and the increased rates of anxiety and depression in both children and adults who suffer from AD cannot be understated. Estimations show that moderate to severe AD has a greater impact than diabetes on pediatric caregivers (Barbeau & Lalonde, 2004).

Atopic Dermatitis in Canadian Indigenous Populations:

In a Canadian context, limited published existing literature, health care practitioner experiences, and media all point to concerns involving **atopic dermatitis (eczema)** and skin and soft tissue infections (often secondary to AD) in remote Indigenous communities, with a poorly documented "crisis" seen. Canadian literature suggests that one year prevalence of AD on reserve may be up to 16.5% (Forsey, 2014), although more information is needed. A survey of remote health care practitioners in Saskatchewan Indigenous communities done by Asiniwasis et al. (2020) showed that the most commonly encountered dermatologic conditions include **atopic dermatitis (eczema) as #1**, followed by impetigo (MRSA/non-MRSA)/skin infections, scabies, diabetic skin complications or ulcers, lice, psoriasis and infestations. Barriers reported by survey participants include cost, transportation, long wait times, travel barriers, level of comprehension with skin instructions/reading instructions, supply and access, proximity, access to healthy water sources, and cultural barriers. In the Canadian First Nations Regional Health Survey (2012) of the National Report on Youth and Children Living in First Nations Communities, AD was among the top three commonly reported chronic health conditions. AD was also identified as ***the most common*** reason for accessing care among majority of the youth, children and caregivers, despite noted barriers. Several barriers to accessing care were reported included concepts of: "waiting list is too long", "felt health care provided was inadequate", "doctor or nurse not available in my area", and "service was not available in my area" (First Nation Health Survey, 2010/2012). It is important to note that AD is a chronic disease, often persisting into adulthood, and in my experience, this is a common disease seen in adults (although more formally literature is needed to document this issue in adults).

Although formal published literature is limited, AD is deemed a crisis by Canadian media in remote Indigenous communities, and I have attached media references as below. In my experience, this is a problem faced by adults, youth and children.

References:

Media:

- Abedi, M. and Russell A. (Feb 7, 2019). 'We're not bluffing': Ontario First Nation Urges Trudeau, O'Regan to Witness Housing Crisis. CBC News. Retrieved from https://globalnews.ca/news/4934630/cat-lake-first-nation-housing-health-crisis/
- CBC News (No Author listed). (2016, Mar 21.) Kashechewan children's skin lesions not caused by water: health minister. CBC News. Retrieved from https://www.cbc.ca/news/canada/sudbury/kashechewan-water-health-skin-rash-update-1.3500631
- Dehaas, J. (2016, Mar 23.) 'Social emergency': Kashechewan skin problems blamed on poverty, overcrowding. CTV News. Retrieved from https://www.ctvnews.ca/canada/social-emergency-kashechewan-skin-problems-blamed-on-poverty-overcrowding-1.2830199
- Dehaas, J. (2016, March 24.) Kashechewan skin infections exacerbated by 'social emergency'. CTV News. Retrieved from https://www.ctvnews.ca/canada/kashechewan-skin-infections-exacerbated-by-social-emergency-1.2831317
- https://cutoff.vice.com/updates/canada-is-evacuating-kids-from-this-first-nation-because-of-a-mysterious-rash

- https://www.cbc.ca/radio/thecurrent/the-current-for-march-25-2016-1.3507260/kashechewan-rash-outbreak-highlights-woeful-first-nations-health-care-say-critics-1.3507262
- https://www.theglobeandmail.com/news/national/doctors-treating-indigenous-childrens-rashes-cite-medical-crisis/article29414627/

Complications and Barriers Relevant to Remote Indigenous Communities:

Due to inherent skin barrier and cutaneous immune system dysfunction, those with uncontrolled AD are at elevated baseline risk for bacterial skin infections such as impetigo and cellulitis (Bieber, 2010; ESC 2021; Weidinger & Novak 2016; Silverberg 2017). This is extremely evident in my clinical experience working in both northern and southern Indigenous communities around Saskatchewan, and has also been reflected in discussions amongst my Canadian peers and colleagues working in other provinces. Environmental factors amongst other numerous barriers faced by remote Indigenous communities can play a role in exacerbation of skin disease (eg. crowded housing, poverty, communicable disease, cost/accessibility of basic skin care products such as soap, bleach, moisturizers or other hygiene fundmanetals, as well as water supply and access). Those with low incomes on or from reserve may not be able to afford expenses required to maintain basic skin (bathing/moisturizing/washing) regimes required to control AD, and on top of this, those in remote areas may even face higher costs of over-the-counter products. Crowded housing conditions can lead to increased transmission of contagious diseases such as scabies, impetigo, or MRSA. This further complicates care and management of patients with skin disease and compromised skin barrier as seen in AD, and in fact such infections may be worsened with traditional systemic immunosuppressants used in moderate to severe AD such as Methotrexate or Cyclosporine. In these situations, we need better options and better access to treatment, particularly for those with moderate to severe disease.

Biologic therapy in moderate to severe AD is changing the treatment landscape in the form of new paradigm shifts in efficacy and safety compared to previously available limited options (beyond the scope of this discussion). Similar to dupilumab, coverage for tralokinumab for Indigenous patients suffering such health disparities should not require systemic immunosuppressants such as Methotrexate or Cyclosporine as a pre-requisite. In addition to this, phototherapy is not available in these remote communities and thus should not be used as a criteria.

Particularly during the pandemic, remote Indigenous patients are often hard to reach virtually and have limited lab as well as health care access, thus, it will be extremely difficult for safety monitoring of traditional systemic immunosuppressants, and this has been reflected in my own personal experience as patients often are lost to follow-up. If they do experience an emergent side effect of their traditional systemic immunosuppressant (eg. worsening of infection, cytopenias, liver damage), they often cannot see their primary health care practitioner in time as these areas are underserviced to begin with, and there may not even be a physician on site at the time. As a dermatologist who has a long waiting list in an underserviced area and already overwhelmed with clinical brudens, it is very challenging for me and my limited resources to also monitor these patients remotely who have an extra layer of barriers. Such issues have worsened during the pandemic. A therapy such as tralokinumab is not associated with the safety monitoring and concerns that are associated with such traditional systemic immunosuppressants (Methotrexate, Cyclosporine) and thus would be much better suited to these populations given the barriers they face. In addition to this, tralokinumab has been shown to decrease S.aureus colonization on the skin and is promising (as seen in ECZTRA 1), whereas traditional systemic immunosuppressants may indeed worsen secondary skin infection.

My concern is that many of these patients who present with moderate to severe AD have “given up” with the current treatment landscape, and unfortunately moderate to severe disease has become seemingly normalized in my experience.

Feedback from Patients:

I have asked some of my adult patients who suffer from moderate to severe AD or are caregivers for those with moderate to severe AD for feedback to CADTH on the current treatment landscape. Some inclusion themes are as below,

“How do I put these steroid ointments all over my body when my disease is everywhere? Are there side effects from that? My family doctors only give me small tubes and my pharmacy is kilometers away – it’s just not enough.”

“I have given up on my skin, no one seems to be able to help me. [this person suffers also from severe depression]”

“Soap and moisturizer are expensive, I can’t afford them when I need to be using them all over my body every day. One tub of Glaxal Base can be gone in a week if I am moisturizing twice daily as my doctor told me.”

“I have to drive to Prince Albert (400km one way) to get my skin care supplies, the roads are bad in the winter, I had slid into the ditch on the gravel road so we never got there.”

“I have lived like this since infancy (>50 years ago). I am used to living with my skin being this severe. I have been on too many steroids and am concerned with the side effects of Methotrexate and Cyclosporine.”

“I can’t get in to see my regular doctor.”

“I can’t use my hands. I’m off work. They ooze and the washing is worse during COVID. I am constantly in pain. I’ve tried various creams and they just don’t work”

Conclusion:

As many Indigenous communities are remote, they may experience many barriers to AD treatment including obtaining adequate health care including considerations around things such as transportation, crowded housing conditions on reserve, cost issues and health care provider resources (RHS 2010; Waldram et al., 2006). As noted in a referenced media article (Dehaas, 2016), general hygiene products including things such as body wash, moisturizer, laundry detergent and other cleaning products may be more costly in remote areas, and poorly accessible compared to urban populations. Other general factors may include health determinants such as the physical environment, support networks, education, literacy, income, and access to health services beyond the scope of this discussion but relevant to Indigenous people in general. All of these factors could be considered determinants of incidence, and can be discussed on a wider level surrounding social and economic considerations around health determinants that are unique to Indigenous populations in Canada and North America. In the end, given everything I have reviewed above, NIHB needs to streamline care with the safest treatment possible for those suffering from moderate to severe AD - a relatively common disease with a wide reaching impact. It is not “just a skin problem” and should never be dismissed as such.

Many remote areas may have poor access to things such as moisturizers, body wash, or laundry products required as baseline, first-line proactive treatment as standardly recommended for management of AD. In addition to this, those with low incomes may not be able to afford expenses required to maintain this regime, and on top of this, those in remote areas may even face higher costs due to transportation and other issues.

Inter-population differences in diseases or illness can be attributed to range of exposures (Rose, 2001). For example, some remote Indigenous communities may have better access to certain health care resources, or cleaner water, whereas others may not. Although each remote Indigenous community may have different infrastructure and health care access, given the larger picture such communities in general are well reported to face similar challenges and barriers unique to colonized Indigenous populations (Waldram et al., 2006), and thus the bigger picture must always be kept in mind. Hereditary factors surrounding bloodlines in certain regional groups may also play a role, for example in the risk of development of AD leading to those who are at elevated baseline risk of skin and soft tissue infections to begin with. It is important to note that there appears to be a significant lack of information on this particular topic, thus warranting further epidemiologic investigation. It is unfortunate that most of the representation of this disease involves a media crisis.
Finally, Healthcare providers are essential in providing care to First Nation patients in rural and remote areas. However, these areas are historically underserviced. The COVID-19 pandemic has created an additional layer of barriers to these already underserved areas further jeopardizing all patients in need of healthcare and dermatology care in particular. Pandemic restrictions also appear to have exacerbated risks from crowded housing conditions and communicable skin disease, such as secondary skin and soft tissue infections in those with AD.

Thank you for considering this application RE: Tralokinumab for NIHB coverage in remote and northern Indigenous populations. Please do not hesitate to reach out if you have any questions or need further clarifications .

Sincerely,

Rachel Asiniwasis MD FRCPC

Dermatology

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3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Moderate to severe atopic dermatitis (AD) has no FDA approved systemic medications to date other than Dupilumab. Biologic therapy has changed the landscape and shifted the paradigm of treatment of this common and potentially debilitating disease. Current traditional systemic immunosuppressants such as MTX and CsA carry concerns for safety profile, especially in those who have inadequate access to health care in general.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

See in my notes above.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

See attached.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

See attached.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

It is likely that topical therapy would also be used for remaining dermatitis. However, the chronic inflammation must be addressed and it is not practical or safe for patients to be applying topical steroids, for example, on wide body surface areas daily.

Absolutely, there is a shift in treatment paradigm with this medication. Targeted, with both efficacy and superior safety profile.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

See above RE: Methotrexate/CsA.

These are potentially toxic immunosuppressants requiring ongoing safety monitoring and considerations around pregnancy, vaccines, etc.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

I would recommend tralokinumab as first line, cost permitting.,

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

See attached.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

See attached.

AD is a clinical diagnosis. Some criteria exist (eg. Hanifin and Rajka and UK working group) but have not been extensively validated.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Those with contraindications, such as hypersensitivity to ingredients.

Uncertain data in pregnancy and pediatrics.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Yes. However, it can be challenging to conduct virtual EASI and PASI scores. Thus, it may be difficult in remote patients. DLQI can be administered virtually easily.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

EASI, DLQI, IGA, BSA scoring.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

EASI 50 or EASI 75 response, drop in 2 IGA points, improvement in quality of life indices.

6.10. How often should treatment response be assessed?

Response:

Every 3 months approximately, maybe more until stable. Then if they are stable, annually could be considered due to superior safety profile.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Non-response, disease progression, AEs (serious AEs)

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

All as above.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?
If so, which specialties would be relevant? ***Response:*** Yes – should be prescribed by dermatology
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: See the attached which is the purpose of this submission. Thanks!

8. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

I received some references on psychogenic and psychosocial as well as economic impact by Leo Medical Science Rep. However, I wrote this all myself and this is all my own experience and literature I have looked at.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

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. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Rachel Asiniwasis*
Position	*Advisory Board – Leo – March 13 consultancy meeting (Tralokinumab)*
Date	*March 13, 2021*

☒	**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

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	☐	☐	☐	☐

Declaration for Clinician 2

Clinician 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 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

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	☐	☐	☐	☐

Declaration for Clinician 3

Clinician 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 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

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	☐	☐	☐	☐

Declaration for Clinician 4

Clinician 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 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				
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	☐	☐	☐	☐

Declaration for Clinician 5

Clinician 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 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				
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	☐	☐	☐	☐