CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

tralokinumab (Adtralza)

(LEO Pharma Inc.)

Indication: Adtralza (tralokinumab injection) is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Adtralza can be used with or without topical corticosteroids.

June 19, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Group Input

CADTH Reimbursement Review - Patient Input Template

Name of the Drug and Indication	Tralokinumab (Adtralza) for the treatment of moderate-to-severe atopic dermatitis (AD) in patients aged 12 years and older
Name of the Patient Group	Eczéma Québec & Canadian Skin Patient Alliance
Author of the Submission	Charlie Bouchard, Eczema Quebec Rachael Manion, Canadian Skin Patient Alliance
Name of the Primary Contact for This Submission	Charlie Bouchard
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

Eczéma Québec, a Québec registered not-for-profit incorporated in 2020, is the only organization in Quebec dedicated to raising awareness, providing education, and advocating for patients with eczema. Our focus is on raising awareness, providing education, and advocating for patients affected by this condition. We are committed to partnering with patients, healthcare professionals, and experts living with atopic dermatitis, both adolescents and adults, to enhance the standard of care within the Quebec region. For more information about our work and initiatives, please visit our website at www.eczemaquebec.com.

The Canadian Skin Patient Alliance (CSPA) is a national non-profit organization with a mission to improve the health and wellbeing of people across Canada affected by skin, hair, and nail conditions, through collaboration, advocacy, and education. For more information, please visit www.canadianskin.ca.

2. Information Gathering

Eczéma Québec conducted a comprehensive information gathering process from February to May 2023 to ensure a wide range of perspectives and experiences for this patient input submission. Our approach included an online campaign to invite people to share their stories with Eczéma Québec via our newsletter, social media and website which resulted in six written patient testimonials, ten interviews and two group discussions (one with six participants, another with seven), including feedback from participants in the ECZTRA 2 Tralokinumab Monotherapy trial for moderate to severe. Testimonials were adapted and translated (where necessary) to more effectively convey the patients' intended messages in written form. Finally, insights for this submission were gleaned from the comprehensive expertise of the McGill University Health Centre (MUHC) Center of Excellence for Atopic Dermatitis (COE-AD), a renowned tertiary care centre dedicated to adult atopic dermatitis research and care.

We also drew insights from "The Skin I'm In: 2022 Update", a report jointly published by the CSPA and Eczéma Québec in November 2022. The report highlights the considerable impacts of AD on daily activities, emotional, and mental health, and emphasizes the need for safe and effective treatment options. The survey was open from November 1 to 30, 2021, and was supplemented with data from the Canadian Institute for Health Information (CIHI) on AD-related emergency room (ER) visits and hospitalizations from 2016 to 2020, to gain a fuller understanding of healthcare utilization associated with this condition. The survey team included members from the CSPA and Eczéma Québec, affiliated with the internationally accredited MUHC COE-AD. The report was supported by funding from AbbVie, LEO Pharma, Pfizer, and Sanofi, with survey incentives provided by Galderma (Cetaphil), Beiersdorf (Eucerin), and La Roche Posay.

3. Disease Experience

Atopic dermatitis (AD) is a chronic skin condition that presents a range of symptoms that can significantly interfere with daily life. These include dry, red skin, and intense itching; in some cases, there may be a thickening of the skin or skin infections. The burden of the disease, however, extends beyond the skin, and is often associated with related allergic conditions like asthma, seasonal

allergies, and allergies or intolerances to certain foods and environmental factors. AD is also linked to higher incidences of sleep disorders, anxiety, and depression.

Approximately 20% of children and 10% of adults in high-income countries are affected. This suggests that around 3,194,310 Canadians over the age of 15 suffer from this condition based on 2021 population data. While AD often develops before the age of 5 and was previously thought of as a disease of childhood, it's worth noting that the condition can also emerge in adulthood, highlighting the disease's diverse profile.

"From the earliest days I can remember, I have been locked in an unyielding battle against AD. As a child, brief periods of peace were punctuated by the mild eruptions of my symptoms, usually in response to moments of heightened stress. But, as I transitioned into adulthood, my eczema resurfaced with an unheralded intensity, a severe onslaught that infiltrated every facet of my existence. The persistent itch was, by far, the most incapacitating aspect." – 26-year old female AD patient

For adults and adolescents with moderate to severe AD, the symptoms can be so intense and constant that they become debilitating. For instance, the itching can be so severe that it disrupts sleep, affects concentration, and hinders routine activities.

"The itch is the last thing I feel before sleep and the first thing I notice when I wake up." – 38-year old female AD patient

"Some nights, it's like there's bugs crawling all over me. I know there's nothing there, but the itching is so intense, I can't help but check under the sheets." – 67-year old male AD patient

"I've had to stumble out of bed at 2am, desperate for relief, and practically scald myself in a hot shower just to numb the itch." - 25-year old female AD patient

Skin rashes can be not only painful but also a source of embarrassment and stigmatization, thus affecting self-esteem and social relationships. The results of the survey conducted for the '*The Skin I'm In Report: 2022 Update'* show that the physical and emotional toll of AD is significant, with 89% of respondents reporting that AD has a moderate to a lot of impact on their quality of life. Patients navigating the relentless discomfort and visibility of AD often face a profound emotional toll, manifested in heightened anxiety and depression levels. This correlation likely arises from the relentless itch and sleep disturbances associated with AD, which significantly impair quality of life and can induce emotional distress. Comprehensive treatment strategies that address both the physical and mental health aspects of AD management are still urgently needed.

"There are mornings when I wake up to find my eyes sealed shut. It's terrifying. The process of prying them open is beyond painful. It feels like I've been thrust into some gruesome horror film. The ordeal often results in my eyelids bleeding, so before I can even manage a good morning to my husband, I'm rushing off to the bathroom to apply a compress. It just makes everything difficult. And these thing happen way too frequently to call off work or take time off. So I've just learnt to push through it. But in bad periods, I cry myself to work most days." – 26-year old female AD patient

Such symptoms can significantly impact professional life, leading to frequent absences from work. Nearly 38.1% of patients surveyed at the MUHC COE-AD reported missing days of work in the past year due to their eczema. Among them, 18.4% missed work once, 23% twice, 23% 3-4 times, 8% 5-6 times, and 27.6% more than seven times. The reasons for these absences can vary from severe symptoms, frequent doctor visits, or lack of workplace support and accommodations.

"By May 2020, my doctor put me on medical leave. Even without washing my hands, they didn't improve. Plus, I couldn't sleep due to the itch and pain. I was suffering round the clock. I even thought about suicide because I felt so hopeless and didn't see a way out." – 42-year old female AD patient

"I've lost count of the number of jobs I've lost due to the sick leaves I needed because of my AD. Each job starts out with hope, but eventually, I hit a bad phase where I start coming in late because of the lack of sleep or the unpredictability of the mornings. I have to get excused from shifts to get to appointments. It's heartbreaking to feel like a failure because of something you have no control over." – 46-year old female AD patient

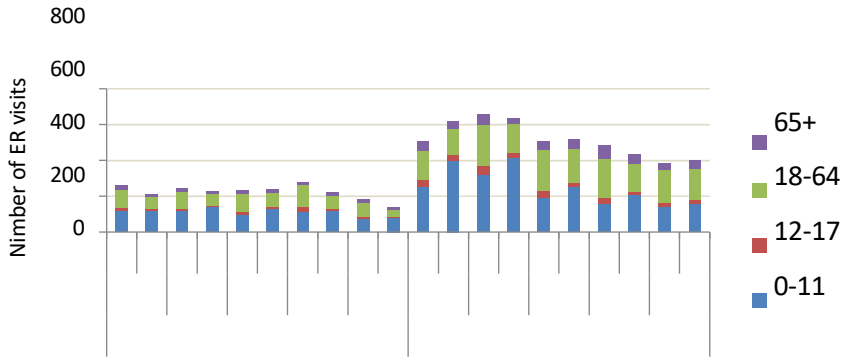
"I remember having to call in sick because my flare-up was so bad I couldn't wear clothes, let alone step outside. But I don't know how to explain it, it's like humiliating and hard to explain to someone that your skin feels like it's burning and that that's the reason you can't make it." – 48-year old male AD patient

Access to healthcare is a significant challenge. With a ratio of 1.62 dermatologists per 100,000 inhabitants in Canada in 2021, access to specialized care can be challenging, especially for those residing in remote areas. Treatments can be costly and require regular follow-ups, creating additional stress for patients.

"I've spent months on a waiting list, hoping to see a specialist. The wait is excruciating. And even when I get an appointment, there's always the anxiety over whether the prescribed treatment will work or if I'll have to start the process all over again. The treatments can be expensive, adding financial stress to an already challenging situation. The constant waiting - for appointments, for answers, for relief - is emotionally and physically draining. I often wonder if I'll ever find lasting relief from this condition that so deeply affects my daily life." – 25-year old female AD patient

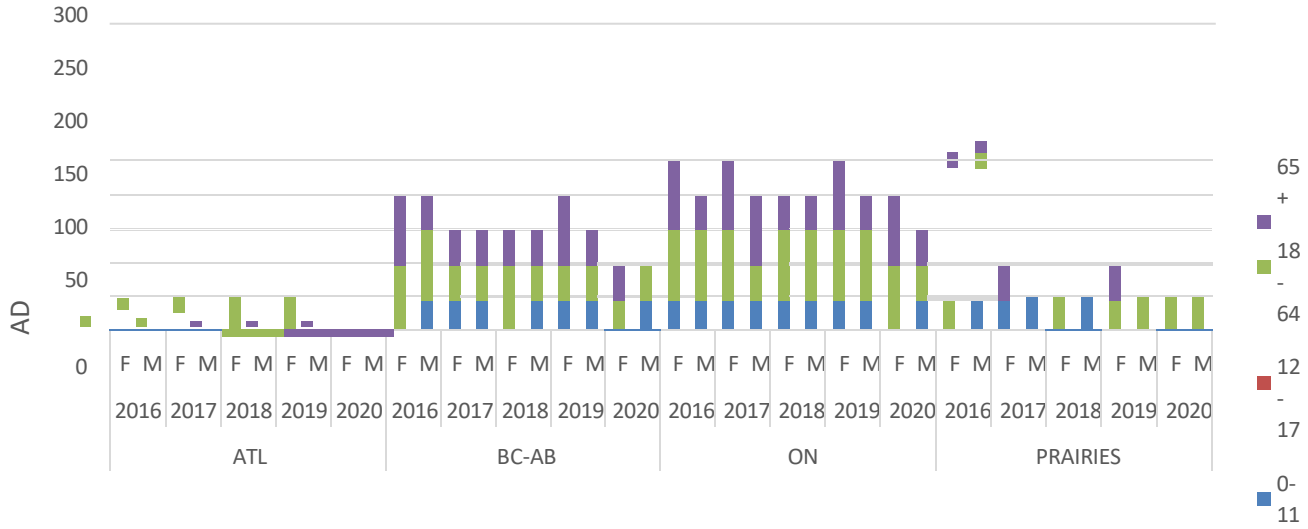
Eczéma Québec and the CSPA reviewed data obtained from the Canadian Institute for Health Information (CIHI) and found a considerable burden of disease with significant numbers of emergency room visits and hospitalizations associated with AD.

Number of ER Visits per Age Group and Sex, with AD as *main problem*



Emergency room visits for AD as the main problem were found mostly in the 0-11 and 18-64 age groups, reflecting the prevalence of AD in childhood and adulthood. Hospitalizations for conditions coded as dermatitis and eczema were primarily found among adults, indicating that the burden of these conditions extends beyond childhood. Interestingly, females were hospitalized more than males for eczema and dermatitis.

Hospitalizations by gender and age with dermatitis and eczema as *main diagnosis*



Another important aspect of the disease is its impact on family life. Relatives of people with moderate to severe AD are faced with a variety of emotional and psychological challenges. They may experience significant emotional distress, including worry, frustration, guilt, and despair, due to their loved one's illness. These feelings can be exacerbated by a sense of helplessness and a lack of control over the situation. In addition, the cost of treatments and necessary products patients need to buy to care for their condition can pose a financial burden on patients and their families. The sleep of relatives can also be affected, as the symptoms of AD can disrupt the child's sleep, requiring constant attention and care.

"The Skin I'm In: 2022 Update" report shows that caregivers reported several ways in which caring for a person with AD had a negative impact on various aspects of their lives. The emotional effect is clearly difficult, with the majority of respondents expressing feelings of despair and guilt. Two-thirds of caregivers also reported that their own health had been affected by anxiety and fatigue.

Comprehensive and personalized management of moderate to severe AD creates psychological and socio- economic burdens, including a profound impact on the day-to-day lives of patients, often restricting their engagement in regular activities and their enjoyment of life. Traveling, a joy for many, can turn into a stressful situation for those with AD, because of the unpredictability of the condition, potential exposure to unfamiliar allergens, and the necessity of maintaining a meticulous skincare routine. Sports and physical activities can be daunting. Sweat is often a trigger for AD flares and combined with potential irritants in sporting equipment or clothing, makes participation in these activities a minefield of potential discomfort.

"I used to love the gym, but now sweating is painful. Not being able to exercise messes with my head. It feels like my body is against me." – 50-year old male AD patient

"I found myself withdrawing from the physical activities that I once reveled in." – 26-year old female AD patient

Moreover, the daily dietary choices of AD patients can be heavily impacted as certain foods may trigger flare-ups. This dietary restriction can not only limit their nutrition but also create a constant state of alertness about what they consume, adding an additional layer of stress to their everyday lives.

4. Experiences With Currently Available Treatments

Patients suffering from AD are advised to use large volumes of moisturizing creams to seal the skin barrier. It is important to note that moisturizing creams are not covered for reimbursement and the annual cost can represent a significant sum. In addition to regular moisturizing and applying other topical products, other personal care habits can also help manage AD. Patients suffering from AD are often recommended to eliminate certain elements from their environment, such as perfumes, harsh soaps, and detergents, as well as certain fabrics that can irritate the skin, like wool and certain synthetic textiles.

Topical Corticosteroids (TCS): These drugs are often the first line of treatment for AD. They are effective in reducing inflammation and itching. However, their long-term use can lead to undesirable side effects. Common side effects of TCS include thinning of the skin, stretch marks, redness, pimples, and changes in skin color. More serious side effects, although rare, can include hormonal problems, an increase in intraocular pressure, and cataracts.

"I use steroid creams, and sure, they work to an extent, but they have this side effect of thinning out your skin. Over time, I've noticed my skin's become super delicate. I'm not kidding when I say that even the slightest scratch can cause bleeding. And once you have a wound, it takes forever to heal." – 32-year old female AD patient

Calcineurin inhibitors (TCI): These drugs are usually used when TCS are not effective or cannot be used. They are effective in reducing inflammation and itching but may take longer to act than TCS. Common side effects of TCI include burning and itching at the application site, redness, and rashes. More serious side effects, although rare, can include skin infection, lymphomas, and skin cancers.

"I stopped using [my TCI] when I saw that it could cause skin cancer" – 40-year old male AD patient

"I use [a TCI] for maintenance as part of my routine, but it's not always easy. There are days when it stings so badly on application, feels like it's just aggravating my skin rather than soothing it. And that's tough because I rely on it to keep my eczema in check." – 19-year old female AD patient

Phosphodiesterase 4 inhibitors (TPDE4i): These drugs are used to treat moderate to severe atopic dermatitis. They work by reducing inflammation and itching. Common side effects of TPDE4i include burning and itching at the application site, redness, and rashes.

That being said, TCS, TCI, and TPDE4i can be messy and can stain clothes, glasses, bedding, and block the shower drain due to accumulation of product in the pipes.

> *"it's not just about the skin anymore, it's also the mess that comes with it. My clothes are always catching stains, and the shower can get all blocked up because of the product buildup. Everything I touch seems to get a greasy smudge, from my glasses to my cellphone."* – 38-year old female AD patient

Off-label oral systemic medications are often used in the treatment of AD, especially in cases where conventional treatments have not provided sufficient relief, have side effects, or are contraindicated. These medications are not specifically approved for the treatment of AD, but they may help manage symptoms.

These off-label treatments include immunosuppressants like cyclosporine, methotrexate, and azathioprine, which work by suppressing the immune system's overactive response. However, these medications come with their own set of risks and side effects, including potential impacts on kidney function, liver function, and an increased risk of infections. These treatments are reserved for severe cases and used carefully.

> *"I tried methotrexate for 18 weeks, but it didn't help."* – 42-year old female AD patient

Another off-label treatment often used is **oral corticosteroids** (e.g., prednisone). These can be highly effective in reducing inflammation and controlling symptoms but not for long-term use due to the risk of serious side effects, including osteoporosis, hypertension, and diabetes.

> *"In times where I experienced severe, full-body flares, it was like my body was on fire, from head to toe. During these periods, the doctors would put me on prednisone. It helped short term, but once the medication was stopped, the intense itch and inflammation would come back."* – 67-year old male AD patient

Dupilumab (Dupixent): Dupilumab has been shown to reduce itching, clear skin, and improve the overall quality of life. Common side effects can include conjunctivitis and injection site reactions. The safety profile of dupilumab is better understood than oral Janus kinase inhibitors (JAKi), and it does not require the same level of monitoring as JAKi.

> "*I started Dupixent. It changed my life. Within the first few weeks, the itchiness decreased significantly. Gradually, my eczema almost entirely disappeared, and I was able to return to work. Unfortunately, the medication has lost some of its effectiveness, so some eczema has returned, but it's still manageable without the itch, so for now, I'm sticking with Dupixent. However, I had to change jobs because even with Dupixent, if I wash my hands too much, the eczema flares up on them. So, while Dupixent helps a lot, I still have to follow a routine of using mild soaps, unscented moisturizing creams, cortisone creams, and so on. I had no difficulty getting Dupixent because I was able to prove that I had tried other treatments without success, and I had a DLQI score of 22/30"* - 42-year old female AD patient

Janus kinase inhibitors (JAKi): These drugs are relatively new AD treatments, are taken on a daily basis orally and are generally used when other treatment options are not effective. They are effective in reducing inflammation and itching, but their long-term use is not yet well understood. JAKi are often associated with a higher risk profile and require continuous clinical monitoring.

> *"Starting [a JAKi] was a game-changer for me, honestly. I was scared at first, had some side effects right out of the gate, but I stuck with it. And let me tell you, I'm so glad I did. My skin has cleared up more than I ever thought possible, and within the first week, I started feeling less and less itchy".* – 46-year old female AD patient

But despite the use of advanced treatments, the burden of disease can remain considerable. The survey results from the *'the Skin I'm In: 2022 Update'* showed a majority of respondents (59%) rated their disease as moderate to severe even while under treatment and a majority of respondents (70%) reported dissatisfaction with their current treatment.

Reimbursement criteria imposed by payers can also have adverse impacts on AD patients. Although more tailored treatments are now available in Canada, there are still only a limited number of options, and some of them remain to this day in the evaluation process for reimbursement as the prices of these therapeutic options are considered high and are very challenging for individuals to afford out of pocket.

"Management wise, I found a promising ally in Dupilumab in 2019. My skin improved, the itching subsided, and my nights were filled with restful sleep. Yet, two years later, I faced a setback. Severe conjunctivitis and eczema on my eyelids began a cycle of unending inflammation. I found myself caught in a disconcerting position - should I trade the known for the unknown, considering the other available options came with more risks and uncertain long-term safety?" – 26-year old female AD patient

"Now my treatment regimen includes Dupixent and an immunosuppressor. But despite this, my AD is still very much present. I can still see the patches of dry, inflamed skin peeking out from under my sleeves. And the itch, it's always there, a constant reminder. It continues to impact my daily life; from the clothes I choose to wear to the activities I can engage in. It feels like a never-ending challenge." – 67-year old male AD patient

5. Improved Outcomes

When evaluating new therapies, patients, caregivers, and families have voiced a range of desired outcomes and improvements not currently met by existing treatments.

Safety: Safety is a paramount concern for patients when considering new treatments. Patients and caregivers want treatments that have minimal side short-term and long-term effects. The fear of potential side effects can often deter patients from trying new treatments, even if they promise better symptom control. The *'The Skin I'm In: 2022 Update"* report describes how the majority of survey respondents (57%) had stopped a treatment because it was not safe for long-term use.

"First and foremost, I'd love a treatment that could control the itching without causing more harm to my skin." – 35-year old female AD patient

Symptom Management: Patients hope for therapies that can decrease the negative feelings and physical discomfort associated with AD. This includes reducing itch intensity, sleep disturbances, skin bleeding, oozing, cracking, flaking, and dryness. Improvements in these areas would not only alleviate physical discomfort but also enhance overall mood, wellbeing, and daily functionality.

"I'm really hoping for something... something that gives real, long-lasting relief, you know? Not just a band- aid on the problem, but something that truly helps my skin heal. […] . I just want a chance to be in control again, not always feeling like my skin is calling the shots. That's what I'm really looking forward to in a new treatment." – 67-year old male AD patient

Reduction in Itch Frequency and Intensity: A decrease in itching would allow patients to better concentrate on their daily tasks and enhance their overall quality of life.

Improved Sleep: The constant itching and discomfort often interrupt sleep, leading to fatigue and diminished quality of life. A more restful night's sleep would improve their mood and productivity.

"I would love a treatment that would give me more than just temporary relief. Something that could help break the itch-scratch cycle, so I could have a good night's sleep, or focus on my work without constant discomfort." – 32-year old female AD patient

"The primary thing I'd hope for is an effective treatment that controls her severe itchiness and soothes her skin. It's heartbreaking to see her suffering from the constant irritation." – Caregiver to a 63 year old AD patient

Improved productivity: By effectively managing symptoms, patients would be able to focus better, not having to constantly deal with the itch or take frequent breaks to apply creams or ointments. This could lead to better performance at work or school, and less stress about completing tasks. Moreover, fewer sick days would be needed due to severe flare-ups, leading to better job or academic stability.

"*I had to change jobs because even with Dupixent, if I wash my hands too much, the eczema flares up on them. So, while Dupixent helps a lot, I still have to follow a routine of using mild soaps, unscented moisturizing creams, cortisone creams, and so on. I find it challenging that people don't know much about severe eczema, so they show little empathy."* – 42-year old female AD patient

Life Impact Reduction: By lessening the overall impact of AD on the patient's life, they would better be able to carry out daily activities, participate in leisurely activities, and manage work or school tasks without constant interruption from the condition.

"My symptoms got worse, so much so it feels like I'm dealing with a whole new disease. I've always loved the outdoors, travelling, hiking, camping. But now, with the unpredictability of my skin and the demands of treatment, it's hard to enjoy these things..[…] *Now, it's just a reminder of how my skin holds me back. I can't even think about staying in a hotel without worrying about staining their clean white bedsheets with blood from scratching. It's embarrassing and makes me incredibly self-conscious. I'm hoping things will get better, but for now, it's tough."* – 56-year old male AD patient

Improved Personal Relationships: By gaining better control over the condition, patients would feel less anxious about physical intimacy, which would increase overall relationship satisfaction.

Enhanced Self-Esteem: Therapies that reduce the visible aspects of AD could lead to increased confidence and social engagement, improving comfort being in public without fear of judgment or stigma.

"Every comment on "how bad" it looked or "how painful" it seemed when referring to my raw patches of skin all over would only draw me back to the itching, stinging, burning, boiling feeling of my skin. Every well-meaning yet misguided advice confronted me with the thought of me failing to manage my condition. Alienation was profound and painful." – 26-year old female AD patient

Treatment Ease of Use: Treatment for AD should be as seamless as possible. An ideal treatment would be easy to use, have manageable side effects, and be something that patients can adhere to without it feeling like a burden. Improvements in this area would directly increase overall treatment satisfaction.

Flexibility in Treatment: AD patients often have to follow strict treatment schedules, which can be restrictive and interrupt daily routines. Greater flexibility in terms of administration and timing is sought that doesn't require multiple applications throughout the day or can be applied at any time without needing to avoid certain activities afterward. A treatment with more flexibility would lessen the burden of managing the condition. The *'The Skin I'm In: 2022 Update"* report's survey results highlighted that The majority of respondents (56%) reported that they had stopped a treatment because it was inconvenient to use.

"The time I need to put into my skin routine often feels like a part-time job." – 19-year old female AD patient

Long-lasting Effects: Many current treatments offer only temporary relief, leading to a cycle of symptom resurfacing and retreatment. A longer-lasting treatment effect would provide longer periods of comfort and relief and lessen the worry about when symptoms might return. A treatment with long-lasting effects could greatly improve patients' peace of mind and overall satisfaction with their treatment regimen.

Affordability: Treatments need to be affordable. Many patients struggle with the financial strain of current treatment options. An ideal new treatment would balance effectiveness and affordability, providing relief from symptoms without causing financial stress. In the *'The Skin I'm In: 2022 Update"* report, the majority of respondents (52%) reported having stopped a treatment because it was too expensive.

"I've had severe AD since I was around 15. Since moving out of my parents' home, it has become increasingly difficult to afford everything I need to manage my skin. Between the volumes of creams, the special soaps, cleaning products, unscented laundry detergent, cotton sheets, clothes that I ruin, the costs add up. I currently use dupilumab and it's helping so much, but it's another expense and with the current cost of living, it's hard for me to keep up." – 22-year old female AD patient

6. Experience With Drug Under Review

The testimonial shared with Eczema Quebec by participants in the ECZTRA 2 Tralokinumab Monotherapy trial for moderate to severe AD revealed that Tralokinumab addresses critical needs of AD patients. Compared to their previous therapies, which varied from patient to patient but often included TCS, TCI, and systemic immunosuppressants, Tralokinumab offered a substantial reduction in the unbearable itching, which patients consistently ranked as their highest priority.

"Tralokinumab has been a game-changer for me. For the first time in years, I felt like I had control over my skin." – 35-year old female AD patient

"When I started on the tralokinumab trial, I was desperate for a solution. The change was gradual, but I started to notice improvements in my skin and, most importantly, in my sleep. The constant itching started to decrease, and for the first time in years, I was able to sleep through the night." – 37-year old male AD patient

The patients also reported improvements in skin healing, with fewer new flare-ups and less severe symptoms when flare-ups did occur. The impact of these benefits on their daily lives was profound. Enhanced ability to focus on work, participate in social activities, and lead a less restricted lifestyle overall were frequently mentioned.

> *"It was just a matter of weeks before I noticed the itch had improved. And after a couple of months, it felt like I was living in a different skin – it was practically clear. It's not a cure, but it's the closest thing to relief I've had in a very long time."* – 35-year old female AD patient

Regarding side effects, patients either did not mention experiencing any side effects or found them to be tolerable and manageable. The occasional injection site reaction were significantly less distressing than the side effects of some of the previous treatments they had endured.

> *"Sometimes the injections can be a bit painful, and I've had some bruising and bleeding, but I can manage that. It's better than the constant itching."* - 19-year old female AD patient

> *"The side effects have been minimal and manageable, I had a couple of back-to-back weeks where I felt like I had caught a cold, but otherwise, nothing compared to the distress I was experiencing before. The itching started to fade, and my skin began to clear up. I've been able to participate more fully in my life. I'm more present in my relationships, more productive at work, and I've even started picking up old hobbies that I had given up because of my AD. It's like I'm finally living, and not just surviving."* – 37-year old male AD patient.

Patients expressed a preference for Tralokinumab's injection format compared to the labor-intensive application of topical treatments. They found it better than having to take a pill every day, as they didn't want to feel like they were constantly relying on medications. Additionally, some patients mentioned that attending multiple phototherapy visits in a week was laborious and inconvenient.

> *"I still get a bit of itch, but it's so more manageable and everything including the creams has become less demanding."* – 35-year old female AD patient

From the experiences shared, Tralokinumab appears to be particularly beneficial for patients whose symptoms are not adequately controlled by the current treatments, and for those who are affected by the distressing side effects of existing systemic therapies (e.g., conjunctivitis). The key values that are important to patients and caregivers concerning Tralokinumab are its ability to provide effective relief from symptoms, especially the distressing itch, its manageable side effects, and its relative ease of use. The hope that this drug brings for an improved quality of life cannot be overstated.

7. Companion Diagnostic Test

There is no companion test.

8. Anything Else?

Despite increased number of AD treatments in Canada, a considerable number of patients still find themselves underserved by the available options. Specifically:

a. **Patient Burden:** AD is far more than a skin condition. It impacts patients' physical, emotional, and social lives, disrupts sleep, mental health, work and school productivity, and quality of life.
b. **Existing Treatment Challenges:** Current treatment options often come with side effects that can be as distressing as the disease itself and are not accessible due to logistical and financial constraints.
c. **Tralokinumab's Potential:** Tralokinumab presents a promising option with meaningful benefits for patients. Its efficacy in improving symptoms and quality of life, with manageable side effects, is an important AD treatment option.
d. **Diverse Patient Experiences:** AD is a heterogeneous disease and some patients remain unserved with available treatments.

We extend our gratitude to CADTH for considering this submission. Your decision regarding the review and reimbursement of Tralokinumab can greatly influence the trajectory of many lives, offering hope and much- needed relief to those living with AD. We trust you appreciate the magnitude of your decision and the potential for positively impacting the lives of patients across the country. Thank you for your consideration.

Appendix: Patient Group Conflict of Interest Declaration

We have received assistance from entities outside of our patient group to complete this submission and want to transparently outline the support we've been given.

Completion of this submission:

We received substantial help from the McGill University Health Centre (MUHC) Center of Excellence for Atopic Dermatitis (COE AD) and the Canadian Skin Patient Alliance (CSPA). The MUHC COE AD provided a wealth of data, insights from scientific literature, medical and clinical expertise, insights from their research, and facilitated contact with patients. A patient committee also reviewed this submission.

Data collection or analysis:

For data collection and analysis, our collaboration with the MUHC COE AD has been invaluable. Their involvement extended to areas such as data gathering, analysis, and interpretation, lending invaluable insight from their research and practical clinical experience. The CSPA offered professional guidance, strategic planning assistance, and performed a review of our submission.

Companies or organizations that have provided Eczéma Québec 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 Canada				X
Leo Pharma			X	
Sanofi				X
Pfizer			x	

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.

On behalf of Eczéma Québec Name: **Charlie Bouchard**

Position: **Director**

Patient Group: **Eczéma Québec**

Date: **2023-06-16**

Companies or organizations that have provided the Canadian Skin Patient Alliance 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 Canada				X
Leo Pharma			X	

Sanofi			X	
Pfizer			x	

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.

On behalf of the Canadian Skin Patient Alliance

Name: **Rachael Manion**

Position: **Executive Director**

Patient Group: **Canadian Skin Patient Alliance**

Date: **June 21, 2023**

CADTH Reimbursement Review Patient Input Template

Name of the Drug and Indication	ADTRALZA (Tralokinumab) Manufacturer Requested Reimbursement Criteria: For the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and who had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available) and off-label immunosuppressants.
Name of the Patient Group	Eczema Society of Canada
Author of the Submission	Eczema Society of Canada
Name of the Primary Contact for This Submission	Amanda Cresswell-Melville Executive Director, Eczema Society of Canada
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

The Eczema Society of Canada (ESC) is a registered Canadian charity dedicated to improving the lives of Canadians living with eczema with a mission of support, education, awareness, and research. To learn more, visit www.eczemahelp.ca.

2. Information Gathering

ESC has gathered survey data from more than 3000 Canadians who live with atopic dermatitis (AD) on topics including quality of life impact, experience with systemic treatments, the AD patient journey, and experience with itch related to AD. Respondents included adults living with AD and their caregivers/family members. Information for this submission was also gathered via questionnaires and one-on-one interviews. In 2021, adult patients who shared their experiences using Adtralza accessed the drug through a clinical trial. In 2023, patients and caregivers who shared their experiences using Adtralza accessed the drug through a clinical trial, through private access to the drug, or through the manufacturer's compassionate supply program/support program.

3. Disease Experience

AD, commonly referred to as eczema, is a chronic, inflammatory skin condition. It is characterized by dry, itchy, inflamed skin that can crack, ooze, and bleed. AD patients experience "flares" which are periods of worsening of the condition and its symptoms. AD flares can be extremely itchy and painful and can lead to psychological distress and negatively impact the individual and their family.

AD can range from mild to severe, and while many people living with AD can experience periods of remission, some patients never experience relief from these life-altering symptoms, which is more likely among uncontrolled moderate and severe patients. Significant suffering, discomfort, and negative quality of life impact is commonly reported by patients with uncontrolled moderate or severe forms of AD.

Itch is frequently reported as the most burdensome symptom of AD. Adult survey respondents reported feeling itchy multiple times each day (reported by 72% of respondents with moderate AD, and by 95% of respondents with severe AD). As the severity of AD increases, so does the frequency of itch, as 44% of survey respondents with severe AD reported feeling itchy all the time. 71% of adult survey respondents with moderate or severe AD rated their overall itch as 7 out of 10 or greater, and at its worst, 42% of survey respondents rated it as 10 out of 10 – the worst itch imaginable. More than half (54%) of adult survey respondents with severe AD report rarely being able to control their urge to scratch their skin.

ESC survey data revealed that loss of sleep and poor sleep quality are reported as significant quality of life impacts due to AD. 63% of survey respondents with moderate AD and 86% of survey respondents with severe AD reported that itch negatively impacted their sleep. 50% of survey respondents with severe AD reported experiencing sleep loss 8 nights per month or more. Patients interviewed shared that the urge to itch is more pronounced at night, and the ability to sleep can be significantly affected. One patient interviewed reported they would scratch themselves all night long, and another reported that not only the itch, but the pain from scratching themselves so severely would interrupt their sleep.

"At one point, I was covered with an itchy rash from head to toe [and]

I literally didn't sleep for three days straight, and went to the emergency room.

I was a mess and nothing I was doing was helping."

"*It was so severe that the pain would interrupt my sleep, which would lead to more inflammation and pain, which would further interrupt my sleep and my ability to heal. I was trapped in a destructive cycle."*

The burden of AD also extends to caregivers and family members. Partners and spouses reported loss of sleep due to their partner's sleep disruption, such as waking and scratching through the night. Family members have also reported feelings of helplessness, guilt, and frustration as it relates to the patient's condition. Intimacy, family dynamics, and relationships are affected by the condition, and many report experiencing feelings of anxiety and depression in addition to sleep loss.

Patients also reported skin damage, bleeding, and scarring due to scratching the skin, with 62% of survey respondents with moderate AD and 87% of survey respondents with severe AD having scars or marks on their skin from scratching. Others reported that they experienced deep cracks and blistered skin that would break or split from movements as minor as walking or signing their name. Patients report they have bled through their clothing and needed to change their sheets daily due to blood stains. Others reported they needed to vacuum daily to remove the dead skin that would flake from their bodies. These outcomes can be embarrassing, and significantly affect patients' confidence, sexual relationships, and intimacy. Episodes of itch can also be difficult for a non-AD sufferer to fully appreciate or understand. The intensity and drive to scratch the skin is described as overwhelming and uncontrollable.

"Living with eczema is like trying to run a race with an injury – people don't understand how bad it is and how much it's hurting you, and yet you're constantly trying to keep up with everyone else despite it."

The unpredictable patterns of flares and/or exacerbations, along with the physical symptoms of AD, can significantly impact mental health and cause stress (69% of survey respondents with moderate AD and 87% of survey respondents with severe AD reported that itch negatively impacts stress). Patients reported that the mental health impact of AD is a significant aspect of the condition and is often not understood by others, nor prioritized by health care providers. Feelings of depression and anxiety as well as poor self-esteem, low energy, and in some extreme cases, suicidal thoughts can be common among the more severe patients with AD. Itch can also be debilitating, with 46% of adult survey respondents with moderate or severe AD reporting this experience.

"People don't understand the reality of living with eczema.

It affects how you operate as a human being. Tasks as simple as bathing can be excruciating.

Falling asleep can be nearly impossible."

AD patients also report that their AD negatively impacts their hygiene, as bathing and hand washing can be excruciatingly painful. This cycle of poor hygiene is not only uncomfortable and socially disruptive, but it also perpetuates the cycles of infection and the need for systemic antibiotics and treatments. AD can negatively impact mood, work, school, and social interactions. 32% of adult survey respondents with moderate or severe AD have missed work events due to their condition, and 30% have had to change careers or give up certain activities. Patients report that their condition also impacts work including both productivity and contributions while at work. Pain and discomfort are a factor, and patients interviewed reported experiencing painful splitting of the skin during regular daily activities.

"I was in such bad shape that daily tasks became almost unbearable.

I couldn't work and wasn't able to play with my children without breaking my skin."

"You are scared to move your body – even if it's just walking or running errands – because a little drip of sweat can irritate you severely and make you stop everything to scratch."

Children and adolescents with AD can suffer significantly with itch and pain, however, the impact goes far beyond those symptoms. The daily life of 52% of the families in ESC survey data of moderate-to-severe disease is negatively impacted by AD. In the same moderate-to-severe disease data, 70% of children experience loss of sleep. 30% experience difficulty participating in sports or physical activities, and 21% avoid social activities. 30% of children experience anxiety related to their AD. The disease also impacts the child at school. 20% of children with moderate-to-severe disease miss school days specifically due to their AD, with 23% of those respondents missing 10 or more days of school per year, and 12% missing 20 or more days of school per year. The caregiver-reported rate of bullying of children related to moderate-to- severe AD is 14%.

"As a teenager, you're trying to get good grades, manage your emotions, and figure out your body, but there's a constant thrum of discomfort and pain in the background that just shoots down what you can do and the already precarious confidence you're trying to build."

"As a teenager, my severe eczema added another layer of challenge to an already full plate. There are so many doctor appointments to go to, and my treatment regimen was extensive and exhausting. It was too hard to balance it all with my school schedule and school was a non-negotiable item for me."

"*When our child went into high school, the bullying started. The name-calling, isolation, and nasty rumors about him being "contagious" all took an immense toll. It broke our hearts. It got so bad, we decided to keep him home while we desperately searched for something to save him, to give him hope."*

70% of children with moderate-to-severe disease experience sleep loss related to their AD, and 55% of caregivers also experience sleep loss related to their child's moderate-to-severe AD. 69% of caregivers report experiencing anxiety related to managing a child with moderate-to-severe AD, and 25% reported experiencing depression related to their child's moderate-to-severe AD. Caring for a child with moderate- to-severe AD can also take a toll on the caregiver's lifestyle, with 23% reporting having little or no time for social activities, 23% reporting having little or no time for intimacy, and 29% reporting having little or no time for exercise and physical activity. Additional challenges reported by caregivers include time management, stress, and feeling that they lack support to manage their child's disease. 62% report that time management is a challenge when trying to care for their child with moderate-to-severe AD, and 63% report experiencing physical, mental, or emotional stress. Caregivers of children with moderate-to-severe disease also report feeling a lack of support, with 36% report feeling a lack of support from the health care system, and 19% feeling a lack of support from family members and friends. Caring for a child with moderate-to-severe AD can also cause financial burden, with 30% of respondents reporting financial challenges related to managing their child's disease.

"Managing our child's eczema is exhausting and stressful. I try not to put my feelings of frustration and hopelessness onto our son, but it's hard, and the worst part is I know how much he is suffering."

4. Experiences With Currently Available Treatments

For some patients with AD, topical treatments work well to manage their flares. However, for other patients who live with uncontrolled moderate or severe forms of the condition, current available treatments are often inadequate, and there is a significant gap in treatments for these individuals. These patients report that even though they adhere to their prescribed topical treatment plans and follow instructions closely, they feel frustrated when the treatments don't work.

For some of these patients who are still uncontrolled after trying numerous topical treatments, they may be recommended systemic treatments by their dermatologist. Until recently, systemic treatments have been very limited for AD patients. These include off-label immune suppressing medications (such as methotrexate and cyclosporine), oral corticosteroids (e.g. prednisone), and phototherapy. Very recently, a biologic drug has been approved for AD, and some patients are now able to access this treatment, however access is a significant challenge despite the tremendous unmet need and potential benefit a biologic drug and other targeted therapies for

AD would provide for this patient population. As AD is a heterogenous diseases, not one single advanced therapy will meet the needs of all patients. Patients with AD would benefit from multiple advanced therapies being reimbursed.

Oral corticosteroids are commonly used as “rescue medications” for significant AD flares and were the most frequently used systemic treatment for AD according to a recent ESC survey. However, they also rated highest in safety concerns for patients, and they can only be used very short-term. Patients report frustration with this treatment as they are not a solution for a chronic condition. Patients also reported that the rebound flares experienced after taking oral corticosteroids can be devastating. Phototherapy is also sometimes used, however, some patients reported that it does not work well to control their AD in the long-term. In addition, access to phototherapy clinics can be a challenge for many patients depending where they are located in the country.

Patients with moderate-to-severe AD tell us:

“I have spent many years trying to get control of my eczema.

Many different drugs, topical creams and light therapy have had no effect on my AD.”

“I’ve been on cyclosporine as well as prednisone.

With prednisone, it helped with flares but there were all kinds of side effects. I gained weight and couldn’t sleep because my body was racing all the time. It is not a long-term solution.”

“My dermatologist kept prescribing me harsher and harsher creams, but my skin just kept getting worse.

I tried phototherapy, but it was more than 30 minutes away and my schedule couldn’t keep up.

You have to go often for it to work and I just couldn’t.”

Patients report frustration with the trial-and-error process of cycling through currently available treatments. Patients interviewed have tried many therapies with little success. They report having suffered for decades and commonly report now having little hope and low expectations when it comes to finding a treatment that will help to control their condition and bring them relief. This significant challenge highlights the need for improved treatments for this small population of patients who don’t respond to topical treatments.

5. Improved Outcomes

Patients interviewed expressed wanting a treatment that helped reduce symptoms like itch, dryness, flaking, inflammation, blistering, and cracked skin. These individuals who live with uncontrolled moderate or severe AD are seeking a long-term solution that allows them to sleep, to heal, and to avoid the relentless and debilitating cycle of flares. They also are seeking relief from the pain, discomfort, and psychological burden they live with each day. They want the ability to carry out simple daily activities, such as bathing, contributing at work, and exercise. They want to feel comfortable in their skin and establish and maintain intimate relationships, and also reduce or eliminate potential complications and secondary infections that often arise as a result of living with uncontrolled moderate or severe forms of the condition. Innovative treatments such Adtralza can offer these patients hope that they can experience control of their condition and achieve better quality of life.

Patients with moderate-to-severe AD shared:

“I would want something that is safe, effective, and help me heal from the trauma of living with this condition.”

“You just want a medication that works. You want to be able to sleep, to fit in with your peers, and to not feel hopeless anymore.”

6. Experience With Drug Under Review

ESC interviewed Canadian patients and caregivers about their experiences with Adtralza, and many reported that they experienced significant improvement in their symptoms after starting the treatment. The itch improved and patients reported being able to return to daily activities. For example, one patient reported they were finally able to exercise when previously, the first signs of overheating or sweating would trigger a flare. Other patients expressed relief that they could enjoy the outdoors, bathe, swim, and play with their children without discomfort and pain.

Adtralza was reported as not only effective at reducing the itch but reducing the frequency and intensity of flares. Patient reports varied on how quickly they experience improvement, ranging from some experiencing improvement in 4 to 6 weeks, to others seeing improvement within a few months.

Patients with Adtralza experience shared:

"This drug changed my life. I have not had an open wound, infection, or even a skin eruption since about the first six months of this trial.

I have only used topical ointment a handful of times since starting Adtralza"

"I can say if I had taken Adtralza when I was a young child/teen my life would have looked very different. It's impossible to predict the exact trajectory of where my life would be today, but I think it's safe to say that I would have been able to attend high school. I missed so much school due to my AD that I never graduated high school and am now in university in my mid 30's (as a mother to 3 young children) working and earning my degree."

"There are so many other areas of my life that are impacted by my AD and since taking Adtralza, decisions that I used to have to make are no longer relevant or less relevant. For example, the choice of clothes I wear and the ability to give my children a bath (as opposed to having my husband do it). Bathing creates bonding between a mother and her child, and you cannot put a price on it. I am very grateful to be able to do this now! The list of things that I am now able to do that I couldn't do before, or I can do with greater ease (like properly gripping a pen, opening a bottle of juice), goes on and on and this wouldn't be made possible without the incredible response my body has had to Adtralza." "*Adtralza worked for me after trying many, many medications for AD, including other advanced therapies.*

Finding the right treatment for AD is a lifelong journey and you have to keep trying."

As for side effects from the medication, some patients interviewed reported side effects such as fatigue and short-term redness/irritation of the injection site. Some patients experienced no side effects during the trial. In most cases, interviewees expressed that they were willing to accept potential risk of side effects in exchange for relief of their symptoms. In general, patients report to ESC that side effects and the risk-benefit profile is weighed carefully when deciding on a new treatment.

In terms of medication delivery and impact on daily routines, patients interviewed generally reported that taking an injection was more simple and convenient when compared to the messy and painstaking nature of skin care routines and using topical treatment. Concerns and challenges with needle phobia were raised by a few individuals interviewed, however, they were all able to overcome this challenge.

Patients with moderate-to-severe AD shared:

"When I started the trial, it didn't matter what the side effects were.

At that point, Adtralza was my only option and I was willing to try anything."

"Once I started experiencing an improvement from the medication, it has relieved my eczema symptoms ever since. I scratch minimally during sleep instead of all night long. Not having any open areas on me has improved my mindset and has made my life considerably better."

"The drug means that I am almost completely symptom free and [it] has allowed for a significant new freedom in being in the outdoors… the drug did an excellent job of managing

itching, redness and inflammation."

7. Companion Diagnostic Test

N/A

8. Anything Else?

For the small group of patients who live with uncontrolled moderate-to-severe AD, access to new treatments like Adtralza can be life changing. This patient population has suffered immeasurably from the incessant itch and skin symptoms including blistering sores, infections, widespread crusting, flaking, and damaged skin. Many patients have diligently exhausted all their treatment options; they are adherent to their topical treatment plans, work closely with their health care providers, research and educate themselves about the condition, and still cannot find relief.

For some patients, they eventually lose hope that the possibility of relief is attainable. However, when new, breakthrough treatments come on the market which are reported as transformative, they find themselves hopeful that there might be something out there that can finally work for them. Then access becomes an issue, as patients fear they will not be able to afford or access these new therapies. These patients deserve the chance to access these new treatments.

Patients and caregivers impacted by AD shared:

"With my current job and benefits, I know that once I've completed the trial, I won't be able to afford the treatment. Adtralza is life changing, but unless it is affordable and available to those who need it, it is cruel to only allow the rich to access it."

"I hope that in the future Adtralza will be a medication Canadians will get financial assistance for so that nobody has to make the difficult choice to turn down a treatment that could so significantly change the quality of their life."

"I would like for doctors and politicians to realize the painful effects of severe AD are debilitating and chronic, but with the help of new drugs and therapies for people suffering with AD life can be great."

"Before my trial, I was 'existing', now I am a contributing member of my family and society. I hope that these drugs become covered by benefits for everyone (particularly when nothing else works)."

"Living with eczema isn't easy and searching for an effective treatment is a frustrating and difficult process. Improved access is a crucial step forward. Having access to proper treatment can help improve many facets of your quality of life with echoing benefits in your personal, academic, and work goals."

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.
   No.
2. Did you receive help from outside your patient group to collect or analyze data 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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Leo Pharma			X	

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.

Name: Amanda Creswell-Melville Position: Executive Director

Patient Group: Eczema Society of Canada Date: June 12th, 2023

Clinician Group Input

CADTH Project Number: **SR0787-000**

Generic Drug Name (Brand Name): **Tralokinumab (Adtralza)**

Indication: **Moderate-to-severe atopic dermatitis in adults and adolescents**

Name of Clinician Group: **Atlantic Specialist Group Managing Atopic Dermatitis**

Author of Submission: **Ian Landells, Wayne Gulliver, Bolu Ogunyemi, Martin Leblanc, Nicole Maillet-Lebel, Irina Turchin, Katherine Rodriguez**

1. About Your Clinician Group

We are a group of physicians including general practitioner, dermatology and allergy & immunology specialists managing patients with atopic dermatitis. We are located in various clinical settings across Atlantic Canada.

2. Information Gathering

A group of atopic dermatitis (AD) specialists from Atlantic Canada convened (dermatologists, an allergist, and a family physician) to consult on filling unmet needs in AD and broadening access to efficient treatment in AD (specifically newer biologics coming to market).

Over the course of a meeting, participants discussed Canadian regulatory processes, atopic dermatitis treatment options and recent updates, standards of care in AD, treatment goals in AD, AD patient burden and journey from different perspectives (e.g. patient, allergist, family physician), the ideal AD care pathway, and gaps needed to address in this care pathway. Following the meeting, we, a subset of the attendees, used the key discussion points to build this submission.

3. Current Treatments and Treatment Goals

The usual progression of treatment is emollients and lifestyle measures (types of clothing, moisturizing, bathing, avoiding skin irritants, minimizing stress, etc.), followed by topical steroids/topical non-steroidal anti-inflammatory creams/ointments, followed by systemic immunosuppressant therapies with/or without phototherapy. Most of these are prescribed long term (except for cyclosporine), with topicals and steroids used intermittently in some cases.

According to Canadian experts (Weinstein M et al, https://www.skintherapyletter.com/atopic-dermatitis/management-guide/):

- Patients are recommended to avoid triggers such as rough fabrics, as well as overheating and sweating
- Frequent and consistent moisturizing may sufficiently manage mild AD. However, moisturizing is still an important component of treatment even in cases of moderate to severe AD.
- Daily bathing is often recommended for patients with AD; however, there is no recommendation for specifying the frequency, duration, or method of bathing.
- Topical corticosteroids are considered safe and effective for the first-line treatment of the inflammatory components of AD.
- For refractory and severe AD, physicians may need to prescribe phototherapy, off label systemic immunosuppressant therapies, or biologic agents.

- Cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil are systemic immunosuppressant agents used off-label for moderate-to-severe AD by dermatologists

While off-label systemic agents target inflammation, which is an important component of AD's disease mechanism, the mechanisms are unknown. Further, these agents have safety concerns in long-term use, are not indicated for AD and provide low efficacy (van Der Schaft J et al. *Br J Dermatol.* 2015; 172(6):1621-1627; van der Schaft J et al. *Br J Dermatol.* 2016; 175(1):199-202; Politiek K et al. *Br J Dermatol.* 2015; 174(1): 201-203).

The first biologic agent approved for AD, dupilumab, inhibits IL-14 and IL-13 signalling via the receptor pathway, and targets inflammation, an underlying disease mechanism of AD. Similarly, the second biologic agent approved for AD, tralokinumab, inhibits only the IL-13 signalling via the cytokine, which also is an underlying mechanism behind inflammation. There is evidence that IL-13 is significantly overexpressed in AD lesional skin compared to IL-4 and is a key driver of AD (Beiber T, https://onlinelibrary.wiley.com/doi/10.1111/all.13954). The 2 injectable biologics have distinctly different mechanisms of actions and in practice, some patients respond better to one or the other and have different side effect experiences. Currently dupilumab is available to patients who have public or private insurance coverage – while tralokinumab is only available to patients who have private insurance coverage. Although dupilumab addresses the needs of some patients with moderate-to-severe AD, a large unmet need still exists in this population. In the dupilumab plus TCS phase 3 study (LIBERTY AD CHRONOS), almost one-third of patients failed to achieve EASI-75 after 16 weeks (Blauvelt A, et al https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31191-1/fulltext) – in clinical practice we also see similar outcomes. Additionally, in practice, some patients are unable to tolerate dupilumab due to conjunctivitis or persistent head and neck dermatitis – which do not appear to occur as frequently with tralokinumab.

Oral Janus kinase inhibitors (JAKi) like upadacitinib and abrocitinib are the newest systemic agents available and have shown short-term superiority over dupilumab at 12-20 weeks (Blauvelt A, et al https://jamanetwork.com/journals/jamadermatology/fullarticle/2782803, Bieber T, et al https://www.nejm.org/doi/full/10.1056/NEJMoa2019380, and Reich K, et al https://pubmed.ncbi.nlm.nih.gov/35871814/). Unlike the biologics, treatment with oral JAKi's requires patients to undergo regular lab monitoring and be aware of significant drug-drug interactions. As well, these therapies have black box warnings for patients with risk factors for cardiovascular events, cancers, and infections.

We believe that improving symptoms of AD such as chronic itch/dry and inflamed skin/sleep disturbances and quality of life and patient satisfaction (improve sleep, work/school disruption) are top priorities for treatment goals.

Other priorities include flare reduction and achieving disease control as reflected by Physician's Global Assessment (PGA) scores of clear or almost clear and Dermatology Life Quality Index (DLQI).

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The treatment goals described in Section 3 are still not being met for the subset of moderate to severe AD patients who, despite having access to the newer systemic therapies like dupilumab, upadacitinib, and abrocitinib, are unable to attain long-term disease control and remission. While these newer therapies have significantly improved the lives of patients, we observe many who require another treatment alternative due to:

- Failure to achieve response despite an adequate initial trial of treatment. We see this in practice and know from clinical trials that not every patient responds to the existing therapies, for example:
    - In the dupilumab plus TCS phase 3 study (LIBERTY AD CHRONOS), almost one-third of patients failed to achieve EASI-75 after 16 weeks (Blauvelt A, et al https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31191-1/fulltext).
    - In the upadacitinib plus TCS phase 3 study (AD UP), almost one-third of patients failed to achieve EASI-75 after 16 weeks (Reich K, et al https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00589-4/fulltext).
    - In the abrocitinib plus TCS phase 3 studies (JADE TEEN, JADE COMPARE, and JADE DARE), on average one-third of patients failed to achieve EASI-75 after 12 or 26 weeks (Eichenfield L, et al

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8374743/, Bieber t, et al https://www.nejm.org/doi/full/10.1056/NEJMoa2019380, and Reich K, et al https://pubmed.ncbi.nlm.nih.gov/35871814/).

- Intolerance, adverse events, and/or risk factors.
    - In practice, some patients are unable to tolerate dupilumab due to conjunctivitis or persistent head and neck dermatitis – which do not appear to occur as frequently with tralokinumab. Higher rates of conjunctivitis associated with dupilumab relative to tralokinumab have also been noted in clinical trials (Wollenberg A, et al https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.20810).
    - Patients who are frail and/or have a history of or risk factors for cardiovascular events, cancers, and infections are not well suited for oral JAKi (outlined in the black box warnings in the product monograph, upadacitinib https://pdf.hres.ca/dpd_pm/00070449.PDF and abrocitinib https://pdf.hres.ca/dpd_pm/00067858.PDF). Patients treated with oral JAKi may also develop adverse events that require discontinuation of therapy (examples include nausea, acne, herpes infection).

Other important unmet needs include:

- Phototherapy, which is often used in conjunction with systemic therapies, is associated with issues such as poor accessibility, long wait times, low efficacy, and exposure to UV radiation.
- Access to effective therapies in a suboptimal care pathway, which currently forces patients onto drugs that are not effective and not approved for AD and can be harmful to their health (methotrexate, cyclosporine, azathioprine, and mycophenolate).

5. Place in Therapy

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

The mechanism of action of tralokinumab (inhibition of IL-13 via the cytokine) means it would fit in the treatment paradigm in the same manner as dupilumab (inhibition of IL-14 and IL-3 via the receptor), after initial treatments such as lifestyle measures and topical steroids in moderate to severe AD patients. Where insurance or public drug plans require, these biologics would be used after off-label systemics, although this is not ideal as part of the care pathway due to their lack of efficacy and safety concerns. Tralokinumab, like dupilumab, is generally used in combination with topical therapies however some patients can stop topical treatment or reduce its usage as the condition improves after initiation of the biologic.

Tralokinumab may also be used in patients who did not respond to or had an intolerance to the newer systemics like dupilumab and oral JAKi (given the current treatment gaps noted in the preceding section 4.1). These therapies have different mechanisms of action and therefore it makes good clinical sense to switch between them as alternatives – in practice we routinely see patients responding to tralokinumab despite prior therapy with the newer systemics.

As stated in Section 3, there is evidence that IL-13 is significantly overexpressed in AD lesional skin compared to IL-4, and is a key driver of AD (Beiber T, https://onlinelibrary.wiley.com/doi/10.1111/all.13954). The 2 injectable biologics have distinctly different mechanisms of actions and in practice, some patients respond better to one or the other and have different side effect experiences. In the dupilumab plus TCS phase 3 study (LIBERTY AD CHRONOS), almost one-third of patients failed to achieve EASI-75 after 16 weeks (Blauvelt A, et al https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31191-1/fulltext) – in clinical practice we also see similar outcomes.

Clinical trials tell us that tralokinumab shows maximum treatment effect closer to 6 months, where dupilumab and oral JAKi show maximum effect closer to 16 weeks. In practice, we observe no significant differences in clinical response between tralokinumab, dupilumab, and oral JAKi beyond 16 weeks. All these new systemic therapies produce similar clinically meaningful improvements in disease severity and symptoms for patients. The ability of tralokinumab to produce long-term disease control is also observed in practice and aligns with what is seen in the extension trial ECZTEND where recent interim analyses show patients maintain response after 3 years of treatment (Langley R, et al https://onlinelibrary.wiley.com/doi/10.1111/bjd.21666). While ECZTEND is not a blinded RCT (which would be unreasonable to conduct over a long period of time given the severity of the disease), it provides relevant evidence that patients who can tolerate therapy in the first 4-6 months have a good chance of achieve long-term disease control and meaningfully improving symptoms like itch. Members of this group continue to have ECZTEND trial patients achieving response years later who travel for hours to continue therapy in the trial.

We wish to also address the following commentary from the previous CADTH review on tralokinumab:

- CADTH commented that “Evidence from 3 clinical trials showed that after 16 weeks of treatment, Adtralza was only modestly effective in reducing AD symptoms”. As trialists and clinicians who treat these patients, our assessment is that the trial results are clinically meaningful and that extrapolating the 16-week results to conclude in absolute terms that the therapy is modest in efficacy is not accurate – given that it is clear in the clinical trial data and in practice that treatment effect continues to improve well beyond 16 weeks.
- CADTH commented “1 indirect comparison suggested that Adtralza is less effective than dupilumab”. It should be highlighted that the authors of the analysis state that “there is substantial uncertainty in these comparisons” given the significant differences in trial methods and baseline patient characteristics across all the trials (https://icer.org/wp-content/uploads/2023/02/atopic-dermatitis-RAAG-9AUG2021-1.pdf and https://icer.org/wp-content/uploads/2023/02/Atopic-Dermatitis_Final-Evidence-Report_Unmasked_02272023.pdf). As well, this indirect analysis is based on 16 weeks of data – it is difficult to make broad assessments on long-term efficacy and safety based on such short timeframes.
- CADTH also comments that the ECZTRA 7 trial shows tralokinumab “did not significantly improve itchy skin than placebo” – after years of treatment experience with tralokinumab it is evident that this finding is an outlier as it does not align with all other clinical trials nor the experience we have had with Canadian patients in practice.
- CADTH commented that the Q4W dosing schedule is “not reflective of likely Canadian clinical practice”. As we have been treating patients with tralokinumab in practice for over a year now, we can attest that the extended dosing schedule is very much a relevant consideration for our patients. Flexibility in dosing allows us to better individualize therapy for patients and gives the option to consume less medication while maintaining disease control.

In conclusion, tralokinumab may further shift the current treatment paradigm by providing an additional safe and effective option for patients with moderate-to-severe AD whose disease is not adequately controlled with lifestyle measures or topical corticosteroids.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Tralokinumab is best suited for patients who are also candidates for therapies like dupilumab, upadacitinib, and abrocitinib – namely, with moderate to severe AD who have not responded after initial treatments such as lifestyle measures and topical prescription therapies. It is also suited for patients who have not responded to or had an intolerance to newer systemic therapies like dupilumab and oral JAKi. Rationale described in section 5.1. If patients have the following characteristics and/or risk factors, tralokinumab would be the preferred 1st line systemic agent over dupilumab, upadacitinib, and abrocitinib:

- History of conjunctivitis.
- History of or risk factors for cardiovascular events, cancers, and infections.
- Risk for drug interactions.
- Risk for non-adherence due to dosing regimen + desire for more flexible and less strict regimen (every 4-week dosing).
- Cost concerns (for example insurance co-payments) – every 4-week dosing becomes more relevant in that scenario.

Patients with uncontrolled moderate to severe AD are in the most need of intervention as they lack long-term treatment options and are at high risk of disease progression. Once AD has progressed, patients are at higher risk of severe flare ups, skin infection, and hospitalization.

Patients least suited for tralokinumab are those who have mild atopic dermatitis that can be controlled with lifestyle changes and topical prescription therapies.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

In clinical practice, the PGA (Physician Global Assessment) is used instead of IGA (Investigator Global Assessment) although they are equivalent. Additional measures, including body surface area (BSA) affected, and the pruritus numerical rating scale (NRS), which ranges from 0 (“no itch”) to 10 (“worst imaginable itch”) are also used. EASI scoring is used if required by insurance or payers.

A clinically meaningful response to tralokinumab would include improvements in:

- 4-point reduction in itch NRS or scores of <3.
- DLQI score reduction of equal or more than 4.
- Patient-reported improvement in sleep quality and fewer AD-related disruptions at school and work.
- PGA score of 0 or 1
- EASI 50 by 16 weeks of therapy and EASI 75 by 6 months

Response to therapy should be assessed by 6 months after initiation of treatment in order to observe if the desired treatment effect is present.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The decision to discontinue treatment should be assessed based on lack of response, significant disease progression (i.e., lichenification, increased affected BSA and itching) and deterioration in quality of life.

Treatment should also be discontinued if the patient experiences adverse reactions or intolerance to the medication that are deemed to be unacceptable by the patient physician team.

The safety profile of tralokinumab is generally unremarkable and in practice there are no apparent adverse events that frequently lead to treatment discontinuation. The lack of required laboratory monitoring is a testament to the safety profile.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Patients with AD receiving tralokinumab would ideally be managed in any non-emergent setting that they have access to, and that has a dermatologist, allergist, pediatrician, or immunologist well-versed in managing moderate-to-severe AD. Referring family physicians, nurse practitioners, or other health care providers should be counseled on the appropriate referral process.

6. Additional Information

Half of our patients are currently receiving optimal care and have access to all new systemic therapies including tralokinumab; these are patients who have the means to pay for treatment and/or have private drug insurance coverage. Unfortunately, those who rely on public coverage are being denied access to a potentially life-changing therapy. Ultimately, tralokinumab is a therapy that works, is safe, and costs less. We ask CADTH to also consider the below examples of life-changing effects tralokinumab has had for some of our patients:

7. 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 <u>each clinician</u> who 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

Name: Ian Landells

Position: Dermatologist, Clinical Associate Professor Memorial University St. John's, NL

Date: 16-Jun-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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie		X		
Leo Pharma		X		
Pfizer		X		
Sanofi	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Wayne Gulliver

Position: Dermatologist, Clinical Professor Memorial University St. John's, NL

Date: 16-Jun-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.

Table 2: Conflict of Interest Declaration for Clinician 2

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				X
Amgen			X	
Aralez	X			
Bausch			X	
BI	X			
BMS			X	
Galderma	X			
Janssen			X	
Leo Pharma			X	
Lilly			X	
Novartis				X
Pfizer	X			
Sun			X	
UCB			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Martin Leblanc

Position: Dermatologist, Moncton NB

Date: 16-Jun-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.

Table 3: Conflict of Interest Declaration for Clinician 3

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		X		
Sanofi	X			

Leo Pharma	X			
Pfizer	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Katherine Rodriguez

Position: Dermatologist, Charlottetown, PEI

Date: 16-Jun-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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie	X			
Sanofi	X			
Leo Pharma	X			
Pfizer	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Bolu Ogunyemi

Position: Dermatologist, Clinical Assistant Professor Memorial University, St. John’s, NL

Date: 16-Jun-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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie		X		
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Nicole Maillet-Lebel

Position: Dermatologist, , Moncton, NB

Date: 16-Jun-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.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie	X			
Sanofi	X			
Leo Pharma	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Irina Turchin

Position: Dermatologist, Fredericton, NB

Date: 16-Jun-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.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie				X
Sanofi			X	
Leo Pharma				X
Pfizer		X		

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: **SR0787-000**

Generic Drug Name (Brand Name): **Tralokinumab (Adtralza)**

Indication: **Moderate-to-severe atopic dermatitis in adults and adolescents**

Name of Clinician Group: **Canadian Dermatology Association (CDA)**

Author of Submission: **Chair, CDA Pharmacy and Therapeutics Advisory Board**

1. About Your Clinician Group

The Canadian Dermatology Association, founded in 1925, represents Canadian 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. The association represents approximately 825 members.

2. Information Gathering

Information that was gathered came from clinical and trial experience, medical literature, published trials, and national and international meetings. The input provided here represents feedback from CDA membership.

3. Current Treatments and Treatment Goals

Initial treatment of adults or adolescents with moderate-to-severe AD consists of emollients, topical prescription therapies (such as topical steroids and/or topical calcineurin inhibitors) in the context of counselling regarding disease chronicity and appropriate utilization of large volumes of topicals needed.

Patients whose disease is not controlled by these initial therapies may then be treated with phototherapy or systemic treatments (usually with existing topical therapies).

Phototherapy is unfortunately not available across all parts of Canada. It is unavailable in most rural locations and certainly unavailable on indigenous reservations and in Nunavut. Access to treatment can also be excessively challenging for patients and costly due to the need to travel to clinics to receive therapy (patients typically require multiple sessions per week- usually a minimum 2-3 x per week appointments). This can often lead to employment issues due to the need to miss work.

Systemic treatment options include off-label therapies (cyclosporine and methotrexate), biologic therapies (such as dupilumab and tralokinumab), and oral Janus kinase inhibitors (JAKi) (such as upadacitinib and abrocitinib).

The off-label therapies are used if there are no other alternatives. High quality trials in atopic dermatitis are lacking to support their use and the side effect profile limit their use. In addition, they require frequent lab monitoring which can be difficult for patients, especially those living in rural and small communities.

Oral JAKi are the most recently approved therapies for moderate-to-severe AD and have head-to-head studies demonstrating short-term (12-16 week) superiority to dupilumab. These therapies have potential for significant drug-drug interactions (particularly through CYP3A4) and require regular lab monitoring. There is a black box warning for these therapies related to treatment of patients who have risks for cardiovascular events, thrombosis, malignancy, and serious infections.

Biologic therapies are subcutaneous injectables that are given every 2 weeks (in the case of tralokinumab, every 4-week dosing is an option for maintenance). No baseline workup and no lab monitoring is required, and the safety profile of the therapies lend

themselves well to being long-term treatment options. Although there are no head-to-head studies comparing tralokinumab to dupilumab, the rates of conjunctivitis in adult and adolescent trials were lower in the tralokinumab trials. In real life practice, conjunctivitis also occurs more frequently in dupilumab treated patients. While both dupilumab and tralokinumab are considered biologic molecules, they are not the same. Dupilumab is an anti-IL-4 and IL-13 mechanism and Tralokinumab is an anti-IL-13 mechanism. This difference in their mechanisms of action result in some patients responding better to one or the other and also leads to different side effects in different patients. Thus, having both options is important.

Systemic glucocorticoids can be used as short-term rescue treatments but due to their adverse effects (including a risk for rebound after discontinuation), are absolutely not suitable for long-term therapy.

Treatment goals in atopic dermatitis are to provide long-term relief of itching and to have clear skin in a safe, efficient, and durable manner. Additional goals include improvement in quality of life and restoring patients' ability to function again in society.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Not all patients respond to the available treatments (dupilumab, upadacitinib, and abrocitinib). Clinicians have observed patients who fail to achieve response with the current therapies and/or become refractory to current therapies, that go on to achieve good response with tralokinumab.

Safety considerations also limit some patients from using the currently available therapies:

- Some patients experienced significant conjunctivitis, allergic reactions, or treatment limiting side effects with dupilumab and had to discontinue therapy.
- Some patients may not be suitable for JAKi because of their baseline risks for cardiovascular events, thrombosis, malignancy, and serious infections and/or significant drug interactions. Some patients may be less well suited for JAKi therapy based upon age and frailty.
- Some patients who have been treated with JAKi's experienced significant nausea, acne, developed infections, and/or herpes infections, or other treatment limiting side effects and had to discontinue therapy.

Additional treatments that are well tolerated and can improve compliance (for example, through more flexible dosing regimens) are needed.

Additional treatments are ultimately needed because atopic dermatitis is a complex and heterogenous disease and not all patients will respond to or tolerate the currently available therapies. Atopic dermatitis is a complex disease that requires a breadth of therapeutic options to manage.

5. Place in Therapy

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

Tralokinumab is a targeted biologic therapy that binds to the IL-13 cytokine whereas dupilumab, the only other available biologic therapy, binds to the IL-4 receptor leading to inhibition of both IL-4 and IL-13 downstream signaling. There is a difference in mechanism of action, and it is observed that some patients in practice respond better to one or the other. They have a different MOA.

Phase 3 clinical trial data along with experience in practice suggests that tralokinumab typically requires more time (around 6 months instead of the 16 weeks typically used as the primary endpoint in trials) to show maximal effect compared to the newer systemic agents like dupilumab, upadacitinib, and abrocitinib. Overall, it is the experience of clinicians that there are no significant differences between tralokinumab and the newer systemic agents in potential to achieve long-term disease control. The results of the ECZTEND trial are significant as it reaffirms that tralokinumab can produce long-lasting disease control up to 3 or more years – in practice, this means that patients who tolerate therapy and produce early signs of response at 16-24 weeks are also likely to achieve long-term control.

Tralokinumab fits into the treatment paradigm the way it is currently being used in practice for patients who have private insurance coverage, which is in the same line of therapy as dupilumab. I.e., in patients who have moderate-to-severe disease that have failed topical therapy and phototherapy (if applicable) and where required by the insurance company, after they have failed an off-label therapy like methotrexate or cyclosporine.

While it is not its primary use, tralokinumab is also used in patients who have failed or could not tolerate other systemics like dupilumab, upadacitinib, and abrocitinib. In patients who are refractory to the existing systemics, a safe efficacious treatment is needed and tralokinumab is an appropriate option to turn to.

Like dupilumab, tralokinumab would typically be used in combination with the patient's current topical therapies. The topical therapies would likely be scaled back as the condition improves. In some patients, topicals can be discontinued.

Ideally, patients should only have to fail topical treatments and phototherapy before getting a newer systemic therapy like tralokinumab, dupilumab, upadacitinib, and abrocitinib. Recommending these therapies after a trial of an off-label therapy like methotrexate and cyclosporine is inappropriate given the toxicity of these drugs and minimal scientific support for their use in atopic dermatitis. Cyclosporine in particular, may cause permanent renal disease if used long-term – and atopic dermatitis is a lifelong condition.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As described above in 3.1, patients who are generally best suited for treatment with tralokinumab are patients who are also candidates and well suited for dupilumab. As well as patients who have failed to respond to or could not tolerate the existing newer systemic therapies.

Patients who have a history of conjunctivitis or have risk factors associated with cardiovascular events, thrombosis, malignancy, and serious infections and/or significant drug interactions, are better suited to receive tralokinumab over the existing therapies (dupilumab, upadacitinib, and abrocitinib).

Patients who may have challenges to adhering to stricter dosing schedules may also be better suited to receive tralokinumab given the option for every 4-week maintenance dosing.

Patients who have mild atopic dermatitis would not be suitable for tralokinumab.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Itch NRS, BSA, and IGA (and/or EASI if required by the insurance company) are typically used in clinical practice.

Clinically meaningful responses may look like one or more of the following:

- 4-point reduction in itch NRS
- Reduction in IGA to at least 'mild' (score of 2)
- Reduction in BSA
- EASI 50 (at earlier timepoints e.g., 16 weeks) or EASI 75 (at later timepoints e.g., 6 months)

Treatment should be initially assessed at 6 months and then yearly afterwards. Many patients with moderate-to-severe disease will not show maximal improvement until at least 6 months of therapy.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Disease worsening or lack of improvement over the initial 6 months. Tralokinumab is a very safe treatment. There are no major safety concerns with tralokinumab. Injection site reactions and conjunctivitis are not prevalent and rarely lead to discontinuation.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Treatment should be initially prescribed by either a dermatologist, allergist, clinical immunologist, or pediatrician to ensure equal and reasonable access to tralokinumab.

6. Additional Information

It is our understanding that tralokinumab has been adopted by clinicians internationally in regions that also rely on health technology assessments. In these geographies, patients with moderate-to-severe disease have the added option of tralokinumab in addition to dupilumab and JAK inhibitors. This represents optimal patient care and is also how nearly half of Canadian patients are currently treated today (those who have private insurance coverage). The overall clinical data and practice experience with tralokinumab continues to demonstrate it is a treatment alternative that is safe and has the same potential as recently recommended therapies (dupilumab and JAK inhibitors) to produce meaningful long-term disease control.

We reiterate the following key points with regards to CADTH's prior review of tralokinumab:

- The results from ECZTRA 1, 2, and 3 are considered clinically meaningful – particularly the observed EASI-75 response rates. Attaining even EASI-50 is considered to be a meaningful target at Week 16 in a moderate-to-severe population.
- The non-significant reduction in pruritus observed in ECZTRA 7 is likely the result of lack of statistical power and trial methodology considerations – it is the outlier in the clinical data. The results from ECZTRA 1, 2, 3, 6, longer-term data from ECZTEND, and experience in clinical practice with Canadian patients who can access tralokinumab all demonstrate that treatment does meaningfully improve itch for patients.
- ECZTEND is a meaningful trial that gives confidence that patients who tolerate therapy and produce early signs of response at 16-24 weeks (which is when drug plans ask for evidence of response) are also likely to achieve long-term control.
- Despite the availability of dupilumab, upadacitinib, and abrocitinib – there continues to be a place in therapy for tralokinumab as noted in 5.2 above – there are patient profiles that make tralokinumab the most appropriate 1st line systemic therapy.

7. 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 <u>each clinician</u> who 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

Name: Susan Poelman, MD, FRCPC

Position: Chair, CDA Pharmacy and Therapeutics Advisory Board

Date: June 19, 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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sanofi-Genzyme	x			
Abbvie		x		
Pfizer	x			
Leo Pharma	x			

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: **SR0787-000**

Generic Drug Name (Brand Name): **Tralokinumab (Adtralza)**

Indication: **Moderate-to-severe atopic dermatitis in adults and adolescents**

Name of Clinician Group: **Dermatology Association of Ontario (DAO)**

Author of Submission: **Dr. David N. Adam**

1. About Your Clinician Group

The DAO provides broad representation for Ontario dermatologists. The DAO membership consists of community dermatologists as well as national and internationally recognized experts in the treatment of atopic dermatitis.

2. Information Gathering

Information gathered for this submission is based on published literature, clinical trial experience, and clinical practice experience from the members of DAO.

3. Current Treatments and Treatment Goals

Atopic dermatitis is a chronic debilitating disease that can have profound effect on not only the individual but the family. Atopic dermatitis (AD) is initially managed with topical therapies (emollients, prescription topical steroids and/or topical calcineurin inhibitors). Unfortunately, these therapies alone usually fail to control moderate to severe disease. Prior to the approval of specific AD therapies, patients that failed topical therapies were forced to use off-label systemic immunosuppressants like methotrexate or cyclosporine in addition to topical treatments. However, neither are approved for the treatment of AD. Moreover, for many patients these therapies are either contraindicated due to safety, are not tolerated, or do not provide durable efficacy. Phototherapy treatments may also be added to topical therapies however access to phototherapy is inconsistent across the province (and the country) and treatment can be burdensome to patients who may have to travel long distances to access care. Phototherapy is also very disruptive to working patients or school aged patients as phototherapy clinics primarily operate during business hours and require patients to attend three times per week for minimum two to three months at a time.

Newer systemic agents, biologics and oral JAK inhibitors (JAKi), are approved for AD and have become the mainstay of therapy for moderate to severe AD in those who do not have disease control after topical therapies or phototherapy.

Rather than immunosuppression with older off-label systemic therapies, biologics for AD are immunomodulating that normalize the cytokine milieu leading to impressive durable efficacy with greater safety particularly as demonstrated with decreased risk of cutaneous infection. Dupilumab was the first new systemic agent approved and is an injectable biologic that inhibits IL-4 receptor and downstream IL-4 and IL-13 signaling. Subsequently, tralokinumab, another injectable biologic, was approved in Canada and inhibits the IL-13 cytokine and downstream signaling. While the mechanisms of action are similar, they are not the same and in practice, we will look to trial one biologic if the other is not tolerated or fails to achieve the treatment effect we are looking for. Dupilumab is a receptor blocker while tralokinumab binds soluble IL-13. These are fundamentally different strategies. The differences in mechanism of action also may explain why we see a difference in adverse event rates between the two biologics e.g., in practice we observe a greater rate of conjunctivitis among dupilumab treated patients compared to tralokinumab treated patients. Both therapies are generally well tolerated and do not require laboratory monitoring. Tralokinumab is currently used where patients have access to therapy (namely through private insurance) and we observe no significant long-term efficacy or safety differences between tralokinumab and dupilumab – particularly after 6 months of initial treatment.

Oral JAKi's, upadacitinib and abrocitinib, are also treatment options for moderate to severe AD patients who are refractory to conventional therapies and are alternatives to the injectable biologics. Head-to-head RCTs suggest that these therapies produce

significantly greater response rates over the initial treatment period (<24 weeks) however, clinical trials and practice experience suggest that these therapies yield similar rates of long-term control like the injectable biologics. Unlike the biologic therapies, oral JAKi's require routine lab work and it may not be suitable for some patient populations if they have risk factors highlighted by black box warnings in the product monograph (cardiovascular events, thrombosis, malignancy, and serious infections).

Treatment goals include achieving clear or almost clear skin, long-term itch relief, and meaningfully improving patients' quality of life.

4. Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The previous negative CADTH recommendation for Adtralza is disappointing and discriminatory as it resulted in patients who rely on public drug coverage not getting the benefit from the same treatment options as patients who have private insurance coverage.

Since the previous CADTH recommendation, it has become more apparent that treatment gaps exist for patients without access to tralokinumab as an additional treatment option.

There are safety considerations that also create treatment gaps for patients who could have their needs addressed by tralokinumab. Literature and clinical practice validate that conjunctivitis and facial erythema occurs more frequently with dupilumab treated patients compared to tralokinumab treated patients. Patients who must discontinue dupilumab due to these adverse events are typically trialed on tralokinumab, where we rarely see a recurrence of the conjunctivitis or facial erythema. Additionally, there are patients that are not suitable for oral JAKi therapy based on risk factors highlighted by black box warnings in the product monograph (cardiovascular events, thrombosis, malignancy, and serious infections) or who must also discontinue due to adverse events (acne, herpes infections, GI upset, dyslipidemia, hepatitis). Furthermore, and consistent with Health Canada product monographs of biologics as first-line therapy, many patients are reticent to try JAKi because of the safety profile and prefer biologic therapy.

These treatment gaps persist for patients who rely on public drug coverage where tralokinumab can address the unmet need.

5. Place in Therapy

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

Tralokinumab is currently used as a first-line systemic option for patients who have the benefit of private insurance coverage – in a manner like dupilumab – for moderate to severe AD in adults and adolescents who have not achieved disease control after initial therapies like topical steroids, phototherapy. Clinical trial evidence and practice experience support positioning of tralokinumab as a first-line systemic option in the treatment paradigm and this should apply not only for patients who have private insurance coverage but for those who rely on public insurance too.

Clinical trial evidence and practice experience supports tralokinumab being a first-line systemic option alongside dupilumab and oral JAKi:

I. The significant improvements in AD severity, symptoms, and health-related quality of life from the phase III trials ECZTRA 1, 2, 3, 6 and 7 are clinically meaningful. Achieving significant improvements in EASI 75 and IGA 0/1 in particular, (endpoints which regulators require in AD trial designs because of their meaningfulness) is especially meaningful at a 16-week timepoint given we typically see tralokinumab exert its full treatment effect closer to 24-weeks (or 6 months).
    - We note that in the previous CADTH review it was stated that there was uncertainty on whether tralokinumab improved itch due to the results from ECZTRA 7. CADTH should consider that ECZTRA 7, unlike the other pivotal trials included more pre-treated patients, had a smaller sample size, was impacted by COVID-19, and did not include any Canadian patients. When we consider the data from all the pivotal trials, there is consistency in the findings demonstrating that tralokinumab does address itching in patients. Feedback from our patients who have been treated with tralokinumab also confirms this.

II. The clinical trials demonstrate that the Q4W maintenance dosing is a relevant dosing consideration as there are clearly patients who can maintain long-term control with half the injections. In practice, we regularly have patients who have achieved disease control and ask about reducing the dose to manage cost and/or medication burden. Tralokinumab has the option for Q4W dosing,

and we do explore this with patients where appropriate – this benefits not only the patient but the healthcare system in the form of cost savings.

III. There is long-term safety and efficacy data supporting the use of tralokinumab as an initial therapy. The open-label single arm ECZTEND extension trial clearly demonstrates that patients who tolerate initial therapy are very likely to achieve and maintaining long-term disease control. This mirrors what we see in practice. Importantly, having many years of data collection through ECZTEND gives us further confidence of the safety of tralokinumab. The main purpose of extension trials is to provide evidence of safety, and this is exactly what ECZTEND does. A source of rich data collection like this is unavailable for many other AD therapies, particularly off-label immunosuppressant systemics which is endorsed as part of the treatment paradigm by CADTH and public drug plans (although counter to the Health Canada approved indication of biologics).

IV. There are no head-to-head trials comparing tralokinumab to the other newer systemic agents like dupilumab and oral JAKi. Available indirect comparisons are difficult to interpret for evidence of long-term efficacy and safety as they rely on short- term (≤16 weeks) evidence and are limited by trial heterogeneity. We point out that the authors of the ICER network meta- analysis, cited by CADTH in the previous tralokinumab review, state that "Conclusions regarding the long-term efficacy of tralokinumab compared to the active comparators relevant to this review cannot be drawn from the ICER NMA, as the NMA used study results collected over a relatively short duration compared to the chronic nature of AD". The analysis also did not consider safety. We also point out that in the ICER report, their cost-effectiveness analysis shows there is a 0.18 QALY difference between tralokinumab and dupilumab suggesting that there is a minimal clinical difference between the therapies.

    - As summarized above, clinical trial data and practice experience demonstrates that the full treatment effect of tralokinumab is apparent closer to 24 weeks/6 months – meaningful indirect comparisons using shorter term data are not contributing meaningful results to any assessment. Our practice experience reaffirms that there does not appear to be obvious differences in long-term efficacy or safety between tralokinumab and dupilumab. In practice, we do not evaluate full response to a biologic treatment until at minimum 6 months. AD is a chronic disease as such achieving long-term safe disease control is paramount rather than speed of response.

Beyond being a potential first-line systemic therapy, tralokinumab is also used as a second-line therapy in patients who fail to achieve disease control or who cannot tolerate dupilumab or the oral JAKi. Given the heterogenous patient profiles, it is not unexpected to see some patients being a better fit for one therapy over another (efficacy and safety reasons summarized in Section 4.1). In practice, we see clear evidence of tralokinumab meeting unmet needs for patients who were refractory to or intolerant of dupilumab or the oral JAKi.

5.2 Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Tralokinumab is best suited for adults and adolescents with moderate to severe AD who remain refractory or are contraindicated to topical therapies and/or phototherapy. It would be an alternative to dupilumab or the oral JAKi and preferable to other off-label immunosuppressant systemic treatments. It is also best suited for those who have not responded to or were intolerant of newer systemic therapies like dupilumab and oral JAKi.

Tralokinumab may also be preferred over dupilumab, upadacitinib, and abrocitinib if patients present with:

i. History of conjunctivitis.
ii. Risk factors for cardiovascular events, thrombosis, malignancy, and serious infections.
iii. History of eczema herpeticum, herpes zoster or herpes simplex
iv. Significant risk for drug-drug interactions.
v. Cost concerns and/or desire for less frequent injections.
vi. Age > 65

Tralokinumab is least suitable for patients with mild AD.

While there may be a perception that patients would be more inclined to choose an oral therapy over an injection, in practice, we observe that many patients are desperate to control their condition and as a result, are amenable to anything – even if they have needle phobia. This reflects how poorly managed some moderate to severe AD patients are and how devastating the condition is on their lives.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Patient response is assessed via:

- PGA/IGA score of 0 or 1.
- EASI improvement (50% by 12-16 weeks or 75% by 24 weeks/6 months).
- Itch NRS reduction of 4 or more points.
- Patient feedback (Are they happy with the treatment? Has their outlook on life improved? Etc.).

Initial treatment response is typically assessed at 6 months and then annually thereafter.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

- Lack of response to treatment / disease progression despite treatment (typically at 6 months we will assess this).
- Intolerable adverse events or allergies (the safety profile of tralokinumab is very clean, this is not a common reason for discontinuation in practice).

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Patients can be managed with therapy in the community setting. A specialist such as a dermatologist, allergist, or pediatrician should be diagnosing/treating/monitoring patients who receive therapies like tralokinumab.

6. Additional Information

On behalf of the DAO and our difficult to treat AD patients, we strongly urge you to consider recommending tralokinumab be made available to patients who rely on public insurance coverage. It is discriminatory that patients who rely on public insurance are only given access to off-label immunosuppressants with lower efficacy and increased risk while those that are privileged enough to have a private drug plan can access first-line safe, effective, and durable biologic therapies. Coverage of tralokinumab will give those public-relying patients the same standard of care that is currently available to patients with private insurance coverage where we see clear benefits of therapy. Tralokinumab is an important addition to our therapeutic arsenal that demonstrates it is capable of producing long-term disease control with an unremarkable safety profile that also costs less than some of the new systemics.

7. 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 <u>each clinician</u> who 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

Name: Dr David Adam

Position: Dermatologist and President, Dermatology Association of Ontario Date: <11-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie			x	
Leo			x	
Pfizer		x		
Sanofi			x	

Declaration for Clinician 2

Name: Dr Wei Jing Loo

Position: Dermatologist

Date: <11-03-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Abbvie			x	
Leo	x			
Pfizer		x		
Sanofi		x		

Declaration for Clinician 3

Name: Dr Salvatore Cammisuli

Position: Dermatologist

Date: <11-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie			x	
Leo	none			
Pfizer	x			
Sanofi	none			

Declaration for Clinician 4

Name: Dr Sameh Hanna

Position: Dermatologist

Date: <11-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 4

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			x	
Leo	x			
Pfizer			x	
Sanofi	x			

Declaration for Clinician 5

Name: Dr Carrie Lynde

Position: Dermatologist

Date: <10-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 5

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		x		
Leo		x		
Pfizer		x		
Sanofi		x		

Declaration for Clinician 6

Name: Dr Maxwell Sauder

Position: Dermatologist

Date: <07-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie			X	
Leo			X	
Pfizer			X	
Sanofi			X	

Declaration for Clinician 7

Name: Dr John Kraft

Position: Dermatologist

Date: <06-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie		X		
Leo		X		
Pfizer		X		
Sanofi		X		

Declaration for Clinician 8

Name: Dr Perla Lansang

Position: Associate Professor, University of Toronto, Dermatologist

Date: <11-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie			X	
Leo		X		
Pfizer		X		
Sanofi			X	

Declaration for Clinician 9

Name: Dr Paul Adam

Position: Dermatologist

Date: <11-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie	none			
Leo				
Pfizer				

Sanofi	

Declaration for Clinician 10

Name: Dr. Patrick Fleming

Position: Assistant Professor of Medicine, University of Toronto, Dermatologist & Investigator, York Dermatology & Research Centre, Consultant Dermatologist, University Health Network

Date: 11-06-2023

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie				X
Leo	X			
Pfizer	X			
Sanofi				X

Declaration for Clinician 11

Name: Dr. Caroline Horgan-Bell

Position: Dermatologist, HB Well Derm

Date: <11-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Abbvie	N/a			
Leo				
Pfizer				
Sanofi	X			

Declaration for Clinician 12

Name: Dr. Geeta Yadav

Position: Dermatologist

Date: <12-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 12

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		x		
Leo	x			
Pfizer	x			
Sanofi		x		

Declaration for Clinician 13

Name: Dr. Fiona Lovegrove

Position: Dermatologist

Date: <12-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 13

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			X	
Leo			X	
Pfizer		X		
Sanofi			X	

Declaration for Clinician 14

Name: Dr. Jennifer Lipson

Position: Dermatologist (The Ottawa Hospital, The University of Ottawa)

Date: <13-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 14

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		x		
Leo	x			
Pfizer	x			
Sanofi		x		

Declaration for Clinician 15

Name: Dr. Lyne Giroux

Position: Dermatologist

Date: <13-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 15

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			x	
Leo	x			
Pfizer	x			
Sanofi	x			

Declaration for Clinician 16

Name: Dr. Denise Wexler

Position: Dermatologist

Date: <12-06-2023>

☒**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.

Table 1: Conflict of Interest Declaration for Clinician 16

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	none			
Leo				
Pfizer				
Sanofi				