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CADTH Reimbursement Recommendation

Tralokinumab (Adtralza)

Indication: 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. Tralokinumab can be used with or without topical corticosteroids.

Sponsor: LEO Pharma Inc.

Final recommendation: Do not reimburse

Summary

What Is the CADTH Reimbursement Recommendation for Adtralza?

CADTH recommends that Adtralza should not be reimbursed by public drug plans for the treatment of moderate to severe atopic dermatitis (AD) 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.

Why Did CADTH Make This Recommendation?

- Evidence from 4 clinical trials demonstrated that, in the short term, Adtralza treatment improved severity of AD, itch symptoms, and health-related quality of life (HRQoL) compared to placebo in adults and adolescents with moderate to severe AD; however, it is uncertain if the magnitude of benefit is clinically meaningful to patients and clinicians. Additionally, a clinical trial in adults with severe AD whose disease did not adequately respond to, or were deemed unsafe to receive, a systemic immunosuppressant showed that Adtralza treatment improved severity of AD but not itch, and its effects on other clinical outcomes are unclear.
- No evidence that directly compared Adtralza to currently available treatments for AD was submitted. The indirect evidence submitted was uncertain due to limitations of the analyses; therefore, it is unclear whether Adtralza offers a clinically meaningful benefit for patients compared to other treatments for AD.
- The evidence for the effectiveness of Adtralza use in the longer term and in patients who previously received dupilumab and/or Janus kinase inhibitors (JAKis) (i.e., currently existing treatments) was uncertain due to limitations of the study designs and analysis; therefore, the benefits of Adtralza in these scenarios cannot be determined.

Additional Information

What Is AD?

AD is a condition that affects the skin and causes dry, red skin that is extremely itchy. Constant scratching causes the skin to split and bleed, which can lead to infections. Oozing and weeping sores occur in more severe forms. Severe AD can be physically incapacitating and cause anxiety or depression. The lifetime prevalence of AD is estimated to be up to 17% in people in Canada.

Summary

Unmet Needs in AD

There is a potential need for additional treatment options that effectively reduce the severity and symptoms of AD, particularly in patients whose disease did not adequately respond to, or were deemed unsafe to receive, other biologics and/or the currently available JAKis.

How Much Does Adtralza Cost?

Treatment with Adtralza is expected to cost $22,802 per patient per year in the first year of treatment and then $21,958 in subsequent years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that tralokinumab not be reimbursed for the treatment of moderate to severe AD 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.

Rationale for the Recommendation

CDEC acknowledged the potential need for additional treatment options that effectively reduce the severity and symptoms of AD; however, based on the submitted evidence, CDEC could not determine whether tralokinumab would adequately meet this need because of the uncertainty around the magnitude of the treatment effect and the benefit of tralokinumab versus appropriate comparators and in patients who received prior dupilumab or JAKi treatment.

Three phase III randomized controlled trials (RCTs) (ECZTRA 1, N = 802; ECZTRA 2, N = 794; ECZTRA 3, N = 380) in adults with moderate to severe AD and 1 phase III RCT (ECZTRA 6, N = 301) in adolescents with moderate to severe AD demonstrated that treatment with tralokinumab resulted in statistically significant improvements in severity of AD, itch symptoms, and HRQoL compared with placebo at week 16 when used as a monotherapy or in combination with topical corticosteroids (TCSs); however, the magnitude of the treatment effect was uncertain considering expert opinion and that the minimal important difference (MID) was not consistently met for some of these outcomes in the trials.

The ECZTRA 7 trial (N = 277) in adults with severe AD whose disease was not adequate adequately controlled with, or who had contraindications to, oral cyclosporine A was the only RCT submitted that reflected the anticipated place in therapy of tralokinumab (i.e., for the treatment of patients whose disease is not adequately controlled with, or who have contraindications to, systemic immunosuppressants). The trial demonstrated that 16 weeks of treatment with tralokinumab in combination with a TCS resulted in a statistically significant improvement in Eczema Area and Severity Index 75 (EASI 75) score from baseline compared to placebo in combination with a TCS; however, the outcome of the Worst Daily Pruritus Numerical Rating Scale (NRS), which was tested first in the hierarchy, did not demonstrate a statistically significant difference between treatment groups. Therefore, it is not known whether tralokinumab would achieve statistically significant or meaningful results for other efficacy outcomes in the testing hierarchy of importance to patients in the ECZTRA 7 trial. Of note, no adolescents were included in this trial and only 21.2% of patients in the ECZTRA 6 adolescent trial had prior immunosuppressant treatment; therefore, evidence for the use of tralokinumab in the adolescent population in terms of the anticipated place in therapy was uncertain.

CDEC was unable to determine the comparative efficacy of tralokinumab versus other newer systemic treatments (i.e., dupilumab, upadacitinib, abrocitinib) as direct comparative evidence for tralokinumab against these existing treatments was not available. In addition, evidence from 3 indirect treatment comparisons (ITCs) in adults and 1 ITC in adolescents is uncertain due to important methodological

limitations (i.e., potential for intransitivity, residual confounding, imprecision). CDEC was also unable to draw conclusions regarding the comparative efficacy of tralokinumab beyond week 16 based on longer-term results from the submitted comparative evidence, and a single-arm long-term extension (LTE) study. CDEC recognized that there is a potential need for additional treatments for patients whose disease has inadequate clinical response and/or who are intolerant to the biologics and/or JAKis that are currently available; however, CDEC considered the evidence for the use of tralokinumab in patients who previously received dupilumab and/or JAKis based on 2 observational studies to be inconclusive given the small sample sizes and the open-label, noncomparative study designs.

The patient input received for this review identified a need for additional treatments for patients that can reduce the severity and symptoms of AD, improve sleep quality and HRQoL, have sustained benefits, and are safe. Based on the evidence reviewed, CDEC could not determine whether tralokinumab would adequately meet this need due to the uncertainty around the magnitude of the treatment effect and the benefit of tralokinumab versus appropriate comparators and in patients who received prior dupilumab or JAKi treatment.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse tralokinumab for the treatment of moderate to severe AD 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. There were 3 issues outlined by the sponsor in the Request for Reconsideration that were discussed by CDEC.
- During the initial and reconsideration meetings, CDEC discussed the magnitude of the treatment effect of tralokinumab observed in the RCTs in adults (the ECZTRA 1, ECZTRA 2, and ECZTRA 3 trials) and adolescents (the ECZTRA 6 trial) with moderate to severe AD. The committee considered the observed treatment effects with respect to the coprimary end points of the Investigator Global Assessment (IGA) 0 or 1 and EASI 75 to be modest based on expert opinion. For the key secondary outcomes with an identified MID estimate (i.e., change from baseline in Dermatology Life Quality Index [DLQI], Children's Dermatology Life Quality Index [CDLQI], and Scoring Atopic Dermatitis [SCORAD] scores), the difference between tralokinumab and placebo at week 16 did not consistently meet the MID estimate across the trials. Therefore, CDEC noted that there is uncertainty on the magnitude of benefit associated with tralokinumab. CDEC further discussed that optimal response to tralokinumab is usually expected 6 months after treatment initiation based on clinical expert input and that the insufficient duration of follow-up at 16 weeks had hindered the interpretation of the magnitude of benefit in the trials.
- During the initial and reconsideration meetings, it was discussed that although CDEC recognized the value that both patients and clinicians place in having a choice of treatment options, it is uncertain whether tralokinumab would address the unmet need for treatment options that are effective in reducing AD symptoms and severity, and improving HRQoL given the lack of robust comparative

evidence versus currently available treatments. CDEC noted that the combined ITC evidence in adults and adolescents is associated with uncertainty due to the potential for intransitivity in the network meta-analysis (NMA), potential residual confounding, and lack of precision in the matching-adjusted indirect comparisons (MAICs). Therefore, CDEC was unable to determine the comparative efficacy of tralokinumab versus dupilumab, abrocitinib, and upadacitinib.

- CDEC noted that AD is a chronic, relapsing condition in which patients often experience episodes of worsening symptoms throughout their lives. In the reconsideration meeting, CDEC re-examined the submitted evidence for tralokinumab beyond week 16 and noted that no definitive conclusion can be drawn on the longer-term comparative efficacy and safety of tralokinumab due to important limitations of the included studies. This includes a lack of control group in the maintenance phase (the ECZTRA 3 and 6 trials), inconsistent results between trials (the ECZTRA 1 and 2 trials), and evidence of imprecision in the longer-term results of the RCTs; risks of selection bias and confounding due to the noncomparative trial design of the LTE study (the ECZTEND trial); and potential residual confounding and imprecision associated with the long-term MAIC (the ECZTRA 3 trial versus the LIBERTY AD CHRONOS trial).
- During the initial and reconsideration meetings, CDEC considered that there is a potential unmet need for additional treatment options in patients whose disease has insufficient clinical response and/or those who are intolerant to dupilumab and are reluctant to receive a subsequent JAKi treatment due to safety concerns. CDEC discussed evidence from 2 observational studies assessing the efficacy and safety of tralokinumab in patients who previously received dupilumab and/or JAKis. CDEC considered the results to be inconclusive due to the methodological limitations associated with these studies (small sample size and open-label, noncomparative study design). Therefore, CDEC was unable to conclude if tralokinumab treatment could meet the unmet need for an effective treatment in patients who had prior treatment with dupilumab. During the reconsideration meeting, CDEC noted that the absence of robust comparative efficacy and safety data precluded assessment of all factors necessary to balance all outcomes and unmet needs (including improved safety). Thus, the place in therapy and sequence of using tralokinumab as first-line, second-line, or subsequent-line therapy is difficult to define.
- During the reconsideration meeting, CDEC discussed results from the economic analysis that suggested tralokinumab may be cost saving versus relevant comparators. The committee noted that this assessment was based on indirect comparative evidence that was associated with important methodological limitations and that the assumptions used in the model, such as no consideration of subsequent therapies, were not reflective of clinical practice. Both factors impact the costs associated with tralokinumab. Given the degree of uncertainty associated with the economic analysis, the results were not considered sufficiently robust to make conclusions regarding the cost-effectiveness of tralokinumab.

Background

AD, also referred to as eczema, is a chronic, heterogeneous inflammatory relapsing-remitting skin condition that is estimated to be present in 8.9% of adolescents (aged 13 to 14 years) and 3.5% of adults in Canada. An intense and debilitating itch and chronically relapsing eczematous lesions are the key clinical hallmarks of moderate to severe disease and could lead to sleep disturbances, psychosocial distress, and reduced quality of life (QoL) in patients and caregivers.

Conventional treatment options for moderate to severe AD include topical therapies, phototherapy, and off-label systemic immunosuppressants. Newer systemic treatments, including dupilumab (biologic), abrocitinib, upadacitinib (oral small molecules, known as JAKis), are effective options that are currently available for patients whose disease did not adequately respond to conventional treatments, although there are some patients whose disease does not achieve adequate response to dupilumab and JAKi treatments. As well, dupilumab is associated conjunctivitis, which may necessitate treatment discontinuation for some patients. Upadacitinib and abrocitinib treatments require baseline and routine laboratory monitoring and have black box warnings in the product monograph related to infections, malignancies, thrombosis, and major adverse cardiovascular events.

Tralokinumab has been approved by Health Canada for the treatment of moderate-to-severe AD 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. Tralokinumab can be used with or without TCSs. Tralokinumab is a monoclonal antibody that inhibits interleutkin-13 receptors. It is available as a solution for subcutaneous injection (150 mg/1mL prefilled syringe and 300 mg/2mL prefilled pen) and the dosage recommended in the product monograph is an initial dose of 600 mg followed by 300 mg administered every other week.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 5 double-blind, randomized placebo-controlled trials in patients with moderate to severe AD (4 in adults and 1 in adolescents), 1 LTE study, 4 ITCs (3 in adults and 1 in adolescents), and 2 observational studies
- patients perspectives gathered by 3 patient groups, including the Eczema Society of Canada, Eczema Quebec, and the Canadian Skin Patient Alliance — the last 2 provided a joint submission
- input from the public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with moderate to severe AD
- input from 3 clinician groups, including the Atlantic Specialist Group Managing AD, the Dermatology Association of Ontario, and the Canadian Dermatology Association
- a review of the pharmacoeconomic model and report submitted by the sponsor

- information submitted as part of the sponsor's Request for Reconsideration (described subsequently)
- stakeholder feedback on the draft recommendation.

Stakeholder Perspectives

Patient Input

The Eczema Society of Canada and Eczema Quebec with the Canadian Skin Patient Alliance submitted 2 separate patient group inputs. The Eczema Society of Canada's input was based on a survey (n = more than 3,000 patients, caregivers, and/or family members), questionnaires and 1-on-1 interviews (number not reported) with patients and caregivers. Eczema Quebec's input was based on patient testimonials (n = 6), interviews (n = 10), and 2 group discussions (n = 13 in total), as well as insights gleaned from the McGill University Health Centre's Centre of Excellence for Atopic Dermatitis and a report ("The Skin I'm in: 2022 Update") from 2021 to 2023. The groups noted that symptoms of moderate to severe AD include inflamed, red, and dry skin that cracks, oozes, bleeds, and in some cases involves thickening and/or infections of the skin. Often, patients experience "flare-ups" that are periods of worsening symptoms. Some patients experience remission, but some patients never experience relief. The input noted that itch is frequently reported as the most burdensome symptom and has been described as "incapacitating," "debilitating," and "bugs crawling all over," and leads to disrupted sleep, fatigue, decreased functionality, and significant impacts on daily life, work, and school. Also, skin rashes were reported to be not only painful but a source of embarrassment and stigmatization affecting self-esteem and social relationships. Family members and/or caregivers shared that they experience impacts on intimacy, family dynamics, and relationships, and experience feelings of anxiety, depression, and sleep loss. Patients with moderate to severe AD also reported that their choices of work, clothing, foods, environments, hobbies, regular activities, travels, and hygiene routine are limited due to AD. Some patients reported to have contemplated suicide due to uncontrollable AD. The joint input by Eczema Quebec and the Canadian Skin Patient Alliance quoted data from the Canadian Institute for Health Information, which showed that patients sometimes end up in the emergency department or become hospitalized when AD is not well controlled. Patients expressed a need for treatments that can result in improvement in symptoms (e.g., dryness, flaking, inflammation, blistering, cracking), reduction in itch frequency and/or intensity, long-term improvement in QoL life (e.g., sleep, prevention of flares, discomfort, psychological burden), ability to carry out daily activities (e.g., work, school, leisure, personal hygiene), and are safe (e.g., reduced infection, have minimal short-term and long-term adverse effects), affordable, flexible, and easy to administer.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts noted that there is an unmet need for more treatment options for moderate to severe AD that are effective and safe, given that some patients have disease that does not respond, or are refractory, to the newer systemic treatments (i.e., dupilumab, upadacitinib, abrocitinib) and that JAKis are associated with safety concerns. One clinical expert also noted that there is a need for treatment options that could improve

adherence and convenience of drug administration for patients who are averse to needles (dupilumab is a subcutaneous injection) or have difficulty adhering to daily administration of oral upadacitinib and abrocitinib.

The clinical experts expected tralokinumab to have the same place of therapy as dupilumab, serving as an additional biologic option for the treatment of moderate to severe AD after failure of off-label immunosuppressants. In the clinical experts' opinion, any patient with moderate to severe AD could be a candidate for tralokinumab treatment. The clinical experts noted that tralokinumab would most likely be used in patients with AD in the absence of comorbid conditions such as asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis, since these patients could benefit from dupilumab treatment instead given dupilumab is also indicated for the treatment of these conditions.

The clinical experts noted that in clinical practice, disease improvement is assessed using instruments such as Physician Global Assessment (PGA) (also referred to as IGA in clinical trials), EASI, DLQI, CDLQI, and Worst Daily Pruritus NRS. In the clinical experts' clinical experience, it takes approximately 6 months to observe optimal benefits from tralokinumab treatment. They noted that significant improvements in QoL and ability to perform daily activities are indicators for meaningful response to treatment even if the skin was not completely clear of all erythema or lichenification. The clinical experts noted that it would be appropriate to consider a switch of therapy in patients who have no improvement in clinical or patient-reported outcomes, or who have intolerable side effects. Tralokinumab could be prescribed by a dermatologist, allergist, immunologist, or pediatrician with expertise in the diagnosis, treatment, and monitoring of patients with AD, in the clinical experts' opinion.

Clinician Group Input

Three clinician groups, the Atlantic Specialist Group Managing AD (7 clinicians), the Dermatology Association of Ontario (16 clinicians), and the Canadian Dermatology Association (unknown number of clinicians) provided 3 separate inputs. The 3 clinician groups and the clinical experts consulted by CADTH agreed that the goals of therapy are to improve symptoms (i.e., long-term and durable relief of chronic itch; minimized dry and inflamed skin; clear or almost clear skin; and less oozing, scaling, cracking, or fissures), QoL (better sleep), and function (focus on work and school). The clinical experts added reduction of anxiety or depressive symptoms and caregiver burnout as goals of therapy. As for unmet needs, the clinician groups and the clinical experts consulted by CADTH all agreed that not all patients have disease that responds to, or can tolerate, the existing systemic treatments. JAKis have safety and contraindication issues (i.e., black box warnings for patients with risk factors for cardiovascular events, cancers, and infections), and dupilumab is associated with conjunctivitis. Therefore, new treatments are needed to provide more options for patients whose AD is not well controlled with existing systemic therapies. The clinician groups stated that tralokinumab would have the same place of therapy as dupilumab after phototherapy and/or off-label systemic therapies (if required by insurance or public plans) and may be trialed if patients' disease fails to respond to dupilumab and oral JAKis. The clinician groups said the suitable patient population aligns with the reimbursement request. They also noted that those whose disease did not respond to biologics and/or JAKis; who have a history of conjunctivitis; who have risk factors associated with cardiovascular

events, thrombosis, malignancy, serious infections, and/or significant drug-drug interactions; who have challenges adhering to stricter dosing schedules; and those over the age of 65 years would be best suited for tralokinumab treatment. The clinical experts added that tralokinumab would most likely be used in patients with "pure" AD without comorbid asthma or eosinophilic esophagitis and those with special site involvement. The 3 clinician groups and the clinical experts consulted by CADTH indicated that they would assess response to treatment based on body surface area affected, Worst Daily Pruritus NRS, PGA (in clinical practice), and/or EASI scores, if required by insurance company or payers, at 6 months after tralokinumab initiation. According to the clinician groups, a lack of response or efficacy, worsening disease, deterioration of QoL, increased body surface area affected, presence of adverse events (AEs), unacceptable intolerance, and/or allergies would make clinicians consider tralokinumab discontinuation. Lastly, the clinician groups and the clinical experts agree that a dermatologist, allergist, pediatrician, or immunologist well-versed in managing moderate to severe AD should be allowed to prescribe tralokinumab. The 3 clinician groups raised concerns regarding differential access to tralokinumab, which is currently only funded by private insurance, and the requirement to trying off-label immunosuppressants with lower efficacy and increased risk before accessing newer systemic drugs.

Drug Program Input

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

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- system and economic issues.

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

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

Five phase III, double-blind RCTs, which assessed whether tralokinumab increased the proportion of patients with an IGA score of 0 (clear) or 1 (almost clear) and the proportion of patients with EASI 75 (i.e., at least 75% reduction in EASI score from baseline) at week 16 compared to placebo in patients with moderate to severe AD, were included in the submission; 1 of which included adolescents (ECZTRA 6, N = 301) and 4 of which included adults (ECZTRA 1, N = 802; ECZTRA 2, N = 794, ECZTRA 3, N = 380; ECZTRA 7, N = 277). Note the 4 studies in adults were previously reviewed by CADTH and no new data were submitted for these studies in the current review. All enrolled patients had disease that had previously not adequately

responded to topical therapy for AD. In addition, patients in the ECZTRA 7 trial, in addition, had disease that had previously failed to respond to, or were deemed not a candidate for, systemic cyclosporine A treatment. Tralokinumab was compared with placebo as monotherapy in the ECZTRA 1, 2, and 6 trials; tralokinumab with TCS was compared to placebo with TCS in the ECZTRA 3 and 7 trials. The proportion of patients with at least a 4 point reduction in Worst Daily Pruritus NRS, change from baseline in SCORAD score, and change from baseline in DLQI (or CDLQI) score were assessed at week 16 as key secondary end points in the ECZTRA 1, 2, 3, and 6 trials. In the ECZTRA 7 trial, these were assessed as secondary end points at week 16 and 26.

The mean age of the study population was 14.6 (standard deviation [SD] = 1.7) years in the ECZTRA 6 trial and ranged between 36.5 years (SD = 14.1) and 39.1 years (SD = 15.2) in the ECZTRA 1, 2, 3, and 7 trials. The majority of patients were white and males in all studies. In the ECZTRA 6 trial, prior systemic immunosuppressant, monoclonal antibody, and phototherapy treatment for AD were reported in 21.1%, 2.4%, and 25.6% of patients, respectively. In the ECZTRA 1, 2, 3, and 7 trials, prior phototherapy was noted in 43.7% to 58.8% of patients. Prior systemic immunosuppressant treatment was notably more common in the ECZTRA 7 trial than other studies in adults, with cyclosporine being the most frequently used across studies (74.7% in the ECZTRA 7 trial; 31.1% to 36.4% in the ECZTRA 1, 2, and 3 trials). A small proportion of patients in the ECZTRA 3 and 7 trials received prior monoclonal antibody treatment for AD (6.3% and 7.6%, respectively).

Efficacy Results — Initial Treatment Period

The results presented in this section pertain to the primary estimand (i.e., COVID-19 modified composite in the ECZTRA 7 trial and composite estimand in other studies for binary end points; hypothetical estimand for continuous end points in all studies), unless otherwise specified.

IGA Score of 0 or 1

Adolescents (Aged 12 to < 18 Years)

In the ECZTRA 6 trial, the difference between the tralokinumab 300 mg every 2 weeks group and the placebo group in the coprimary end point of IGA 0 or 1 (i.e., proportion of patients achieving an IGA score of 0 [clear] or 1 [almost clear]) at week 16 was 13.8% (95% confidence interval [CI], 5.3% to 22.3%; P = 0.002) in favour of tralokinumab.

Adults

The between-group difference in the coprimary end point of IGA 0 or 1 at week 16 was 8.6% (95% CI, 4.1% to 13.1%; P = 0.002) in the ECZTRA 1 trial and 11.1% (95% CI, 5.8% to 16.4%; P < 0.001) in the ECZTRA 2 trial, which both compared tralokinumab every 2 weeks with placebo, and 12.4% (95% CI, 2.9% to 21.9%; P = 0.015) in the ECZTRA 3 trial, which compared tralokinumab every 2 weeks plus TCS with placebo plus TCS; all of which were in favour of tralokinumab (or tralokinumab plus TCS).

In the ECZTRA 7 trial, which compared tralokinumab every 2 weeks plus TCS with placebo plus TCS, the between-group difference in the secondary end point of IGA score of 0 or 1 was [redacted] at week 16

and [redacted] at week 26. Both end points were not tested for superiority due to prior failure in the testing hierarchy (i.e., reduction of Worst Daily Pruritus NRS of at least 4 points from baseline).

Eczema Area and Severity Index

Adolescents (Aged 12 to < 18 Years)

In the ECZTRA 6 trial, the between-group difference in the coprimary end point of EASI 75 (i.e., proportion of patients with at least a 75% reduction in EASI score from baseline) at week 16 was 22.0% (95% CI, 12.0% to 32.0%; P < 0.001) in favour of tralokinumab 300 mg every 2 weeks over placebo. Analyses of EASI 90, EASI 50, and change from baseline in EASI score also showed results in favour of tralokinumab; however, these end points were not adjusted for multiplicity and were at an increased risk of type I error (i.e., false-positive results).

Adults

The between-group difference in the coprimary end point of EASI 75 at week 16 was 12.1% (95% CI, 6.5% to 17.7%; P < 0.001) in the ECZTRA 1 trial and 21.6% (95% CI, 15.8% to 27.3%; P < 0.001) in the ECZTRA 2 trial, which both compared tralokinumab every 2 weeks with placebo, and 20.2% (95% CI, 9.8% to 30.6%; P < 0.001) in the ECZTRA 3 trial, which compared tralokinumab every 2 weeks plus TCS with placebo plus TCS; all of which were in favour of tralokinumab (or tralokinumab plus TCS).

In the ECZTRA 7 trial, the between-group difference in the primary end point of EASI 75 at week 16 was 14.1% (95% CI, 2.5% to 25.7%; P = 0.018) in favour of tralokinumab every 2 weeks plus TCS over placebo plus TCS. The between-group difference in the secondary end point of EASI 75 at week 26 was 14.1% (95% CI, 2.9% to 25.35%), for which superiority testing was not conducted due to prior failure in the testing hierarchy.

In the ECZTRA 1, 2, and 3 trials, EASI 90, EASI 50, and change from baseline in EASI score at week 16 were secondary end points. In the ECZTRA 7 trial, EASI 90 at weeks 16 and 26 were exploratory end points and change from baseline in EASI score at week 16 and week 26 were secondary end points. The results of these outcomes were in favour of tralokinumab (or tralokinumab plus TCS); however, they were not adjusted for multiplicity and were at an increased risk of type I error (i.e., false-positive results).

Scoring Atopic Dermatitis

Adolescents (Aged 12 to < 18 Years)

In the ECZTRA 6 trial, the between-group difference in the key secondary end point of adjusted mean change from baseline in SCORAD at week 16 was −19.7 (95% CI, −27.1 to −12.2; P < 0.001) in favour of tralokinumab 300 mg every 2 weeks over placebo. The results of the secondary (treatment policy) and tertiary (composite) estimands were consistent with the primary (hypothetical) estimand.

Adults

The between-group difference in the key secondary end point of adjusted mean change from baseline in SCORAD at week 16 was −10.4% (95% CI, −14.4% to −6.5%; P < 0.001) in the ECZTRA 1 trial and −14.0% (95% CI, −18.0% to −10.1%; P < 0.001) in the ECZTRA 2 trial, which both compared tralokinumab every 2 weeks with placebo, and −10.9% (95% CI, −15.2% to −6.6%; P < 0.001) in the ECZTRA 3 trial, which compared

tralokinumab every 2 weeks plus TCS with placebo plus TCS; all of which were in favour of tralokinumab (or tralokinumab plus TCS). The results of the secondary (treatment policy) and tertiary (composite) estimands were consistent with the primary (hypothetical) estimand.

In the ECZTRA 7 trial, which compared tralokinumab every 2 weeks plus TCS with placebo plus TCS, the between-group difference in the secondary end point of adjusted mean change from baseline in SCORAD was −8.6 (95% CI, −13.0 to −4.2) at week 16 and −8.9 (95% CI, −13.2 to −4.6) at week 26. The results of the secondary (treatment policy) and tertiary (COVID-19 modified composite) estimands were consistent with the primary estimand at weeks 16 and 26. Both end points were not tested for superiority due to prior failure in the testing hierarchy.

Worst Daily Pruritis NRS and Adolescent Worst Daily Pruritis NRS

Adolescents (Aged 12 to < 18 Years)

In the ECZTRA 6 trial, the between-group difference in the key secondary end point of proportion of patients with at least 4 points of reduction in Adolescent Worst Daily Pruritus NRS at week 16 was 21.7% (95% CI, 12.3% to 31.1%; P < 0.001) in favour of tralokinumab 300 mg every 2 weeks over placebo.

The results of the responder analysis based on a 3-point reduction threshold (secondary end point) also showed results in favour of tralokinumab. The between-group difference with respect to the secondary end point of adjusted mean change from baseline in Adolescent Worst Daily Pruritus NRS at week 16 was −1.5 (95% CI, −2.4 to −0.6). Both end points were not adjusted for multiplicity and at increased risk of type I error (i.e., false-positive results).

Adults

The between-group difference in the key secondary end point of proportion of patients with at least a 4-point reduction in Worst Daily Pruritus NRS at week 16 was 9.7% (95% CI, 4.4% to 15.0%; P = 0.002) in the ECZTRA 1 trial and 15.6% (95% CI, 10.3% to 20.9%; P < 0.001) in the ECZTRA 2 trial, which both compared tralokinumab every 2 weeks with placebo, and 11.3% (95% CI, 0.9% to 21.6%; P = 0.037) in the ECZTRA 3 trial, which compared tralokinumab every 2 weeks plus TCS with placebo plus TCS; all of which were in favour of tralokinumab (or tralokinumab plus TCS). The results of the responder analysis based on a 3-point reduction threshold (secondary end point) also showed results in favour of tralokinumab (or tralokinumab plus TCS); however, this end point was not adjusted for multiplicity and was at increased risk of false-positive results.

In the ECZTRA 7 trial, the proportion of patients with at least a 4-point reduction in Worst Daily Pruritus NRS at week 16 and at week 26 were secondary end points. The between-group difference at week 16 was 9.7% (95% CI, −2.0% to 21.4%; P = 0.106) at week 16, which did not show a difference between tralokinumab every 2 weeks plus TCS and placebo plus TCS. The results of the secondary (composite) estimand were consistent with the primary estimand. The between-group difference at week 26 was 7.3% (95% CI, −4.6% to 19.2%) and was not tested for superiority due to prior failure in the testing hierarchy.

The between-group difference in the secondary end point of adjusted mean change from baseline in Worst Daily Pruritus NRS at week 16 was −0.9 (95% CI, −1.4 to −0.4) in the ECZTRA 1 trial and −1.3 (95% CI, −1.7 to −0.8) in the ECZTRA 2 trial, which both compared tralokinumab with placebo, and −1.2 (95% CI, −1.7 to −0.7)

in the ECZTRA 3 trial, which compared tralokinumab every 2 weeks plus TCS and placebo plus TCS. In the ECZTRA 7 trial, which compared tralokinumab every 2 weeks plus TCS with placebo plus TCS, the between-group difference (exploratory end point) was −0.9 (95% CI, −1.4 to −0.4) at week 16 and −0.9 (95% CI, −1.4 to −0.3) at week 26. These end points were not adjusted for multiplicity and at increased risk of type I error (i.e., false-positive results).

Dermatology Life Quality Index and Children's Dermatology Life Quality Index

Adolescents (Aged 12 to < 18 Years)

In the ECZTRA 6 trial, the between-group difference in the key secondary end point of adjusted mean change from baseline in CDLQI score at week 16 was −2.6 (95% CI, −4.5 to −0.7; P = 0.007) in favour of tralokinumab 300 mg every 2 weeks over placebo. The results of the secondary (treatment policy) and tertiary estimands (composite) were consistent with the primary (hypothetical) estimand.

The results of the responder analysis of proportion of patients with at least a 6-point reduction in CDLQI score from baseline at week 16 (secondary end point) were in favour of tralokinumab; however, this end point was not adjusted for multiplicity and was at increased risk of type I error (i.e., false-positive results).

Adults

The between-group difference in the key secondary end point of change from baseline in DLQI score at week 16 was −2.1 (95% CI, −3.4 to −0.8; P = 0.002) in the ECZTRA 1 trial and −3.9 (−5.2 to −2.6; P < 0.001) in the ECZTRA 2 trial, which both compared tralokinumab every 2 weeks with placebo, and −2.9 (95% CI, −4.3 to −1.6; P < 0.001) in the ECZTRA 3 trial, which compared tralokinumab every 2 weeks plus TCS with placebo plus TCS; all of which were in favour of tralokinumab (or tralokinumab plus TCS). The results of the composite estimand were consistent with the primary (hypothetical) estimand.

In the ECZTRA 7 trial, change from baseline in DLQI score at weeks 16 and 26 were secondary end points. The between-group difference at week 16 was −1.5 (95% CI, −2.6 to −0.4). The results of the secondary (treatment policy) and tertiary (COVID-19 modified composite) estimands were not consistent with the primary (hypothetical) estimand and did not suggest a difference between the treatment groups. At week 26, the between-group difference was −1.6 (95% CI, −2.7 to −0.5). The results of the composite estimand were consistent with the primary estimand. Both end points were not tested for superiority due to prior failure of the testing hierarchy.

The proportion of patients with at least a 4-point reduction in DLQI score from baseline was a secondary end point (at week 16) in the ECZTRA 1, 2, and 3 trial, and an exploratory end point in the ECZTRA 7 trial. The results were in favour of tralokinumab (or tralokinumab plus TCS) in the ECZTRA 1, 2, and 3 trial [redacted]. These end points were not adjusted for multiplicity.

Other Efficacy End Points

Adolescents (Aged 12 to < 18 Years)

In the ECZTRA 6 trial, the results of change from baseline in the Eczema-Related Sleep NRS (exploratory end point), Patient-Oriented Eczema Measure (POEM) (secondary end point), and Hospital Anxiety and

Depression Scale (HADS) anxiety (exploratory end point) scores at week 16 were in favour of tralokinumab 300 mg every 2 weeks over placebo; however, these end points were not adjusted for multiplicity and at increased risk of false-positive results.

The results did not suggest a difference between treatment groups in change from baseline in HADS depression score (exploratory end point) at week 16. The 95% CI in the between-group difference in proportion of patients with a HADS anxiety or HADS depression score of less than 8 (exploratory end point) was wide, crossing the null.

Use of TCSs and number of days without topical treatment were not assessed in the ECZTRA 6 trial.

Adults

The results of change from baseline in Eczema-Related Sleep NRS and POEM scores (exploratory end points) were in favour of tralokinumab (or tralokinumab plus TCS) across the ECZTRA 1, 2, 3, and 7 trials; however, these end points were not adjusted for multiplicity and at increased risk of type I error (i.e., false-positive results).

The results did not consistently suggest a difference between tralokinumab (or tralokinumab plus TCS) and placebo (or placebo plus TCS) across studies with respect to the change from baseline in HADS anxiety and depression scores, the proportion of patients with HADS anxiety or HADS depression scores of less than 8 (an exploratory end points in the ECZTRA 1, 2, 3, and 7 trials), the amount of TCS used, and the number of days without topical treatment (secondary end points in the ECZTRA 3 trial; exploratory end points in the ECZTRA 7 trial). These end points were not adjusted for multiplicity.

Efficacy Results — Maintenance and/or Continuous Treatment Period

IGA Score of 0 or 1 at Week 52 (the ECZTRA 1, 2, and 6 Trial) or Week 32 (the ECZTRA 3 Trial) Among Patients With IGA 0 or 1 at Week 16

Adolescents (Aged 12 to < 18 Years)

In the ECZTRA 6 trial, the proportion of patients receiving tralokinumab 300 mg every 2 weeks with IGA 0 or 1 at week 16 who maintained their IGA 0 or 1 response at week 52 was 37.5% (3 out of 8 patients; 95% CI, 13.7% to 69.4%) in the tralokinumab 300 mg every 2 weeks/every 2 weeks group and 87.5% (7 out of 8 patients; 95% CI, 52.9% to 97.8%) in the tralokinumab 300 mg every 2 weeks/every 4 weeks group. No statistical analysis was conducted to assess the between-group difference.

Adults

In the ECZTRA 1 and 2 trials, the proportion of patients with IGA 0 or 1 at week 16 (without use of rescue medication) whose IGA 0 or 1 response was maintained (without use of rescue medication) at week 52 was included in the statistical hierarchy. In the ECZTRA 1 trial, the difference between the tralokinumab every 2 weeks group and the placebo group was 6.0% (95% CI, −21.8% to 33.7%; P = 0.68). Due to failure of this end point, no superiority testing was conducted for the difference between the tralokinumab every 4 weeks group and the placebo group (lower in the testing hierarchy), which was −9.5% (95% CI, −37.1% to 18.0%). In the ECZTRA 2 trial, the difference between the tralokinumab every 2 weeks group and the placebo group

was 34.1% (95% CI, 13.4% to 54.9%; P = 0.004). The difference between the tralokinumab every 4 weeks group and the placebo group was 19.9% (95% CI, −1.2 to 40.9; P = 0.084); due to failure of this end point, no superiority testing was conducted for the end point lower in the testing hierarchy (i.e., EASI 75 at week 52 between tralokinumab 300 mg every 4 weeks and placebo).

In the ECZTRA 3 trial, the proportion of patients with IGA 0 or 1 at week 16 who maintained their IGA 0 or 1 response at week 32 was 89.6% (95% CI not reported) in the tralokinumab every 2 weeks plus TCS group and 77.6% (95% CI not reported) in the tralokinumab every 4 weeks plus TCS group. No statistical analysis was conducted to assess the between-group difference. This end point was not assessed in the ECZTRA 7 trial.

EASI 75 at Week 52 (the ECZTRA 1, 2, and 6 Trials) or Week 32 (the ECZTRA 3 Trial) Among Patients With EASI 75 at Week 16

Adolescents (Aged 12 to < 18 Years)

In the ECZTRA 6 trial, the proportion of patients with EASI 75 at week 16 (without use of rescue medication) whose EASI 75 response was maintained at week 52 (without use of rescue medication) was 44.4% (4 out of 9 patients; 95% CI, 18.9% to 73.3%) in the tralokinumab 300 mg every 2 weeks/every 2 weeks group, and 53.8% (7 out of 13 patients, 95% CI, 29.1% to 76.8%) in the tralokinumab 300 mg every 2 weeks/every 4 weeks group. No statistical analysis was conducted to assess the between-group difference on these end points.

Adults

In the ECZTRA 1 trial, the proportion of patients with EASI 75 at week 16 (without use of rescue medication) whose EASI 75 response was maintained (without use of rescue medication) at week 52 was not tested for superiority due to prior failure in the testing hierarchy (the proportion of patients with IGA 0 or 1 at week 16 whose IGA 0 or 1 response was maintained at week 52). The difference between the tralokinumab every 2 weeks group and the placebo group was 21.2% (95% CI, −0.2% to 42.6%). The difference between the tralokinumab every 4 weeks group and the placebo group was 11.7% (95% CI, −8.7% to 32.0%).

In the ECZTRA 2 trial, the difference in proportion of patients with EASI 75 at week 16 whose EASI 75 response was maintained at week 52 between tralokinumab 300 mg every 2 weeks and placebo was included in the statistical testing hierarchy and was 33.7% (95% CI, 17.3% to 50.0%; P < 0.001). The difference in proportion of patients with EASI 75 at week 16 whose EASI 75 response was maintained at week 52 between tralokinumab 300 mg every 4 weeks and placebo was not tested for superiority due to failure of a prior end point in the statistical testing hierarchy (i.e., IGA 0 or 1 at week 52 between tralokinumab 300 mg every 4 weeks and placebo).

In the ECZTRA 3 trial, the proportion of patients with IGA 0 or 1 at week 16 whose IGA 0 or 1 response was maintained at week 32 was 92.5% (95% CI not reported) in the tralokinumab every 2 weeks plus TCS group and 90.8% (95% CI not reported) in the tralokinumab every 4 weeks plus TCS group. No statistical analysis was conducted to assess the between-group difference. This end point was not assessed in the ECZTRA 7 trial.

Harms Results — Initial Treatment Period

Treatment-Emergent Adverse Events

In the initial treatment period of the ECZTRA 1, 2, 3, 6 and 7 trials, the proportion of patients with at least 1 treatment-emergent adverse event (TEAE) ranged between 61.5% and 77.5% in the tralokinumab group (or tralokinumab plus TCS) and between 61.7% and 78.8% in the placebo group (or placebo plus TCS). No notable between-group difference in the proportion of patients who reported at least 1 TEAE in the initial treatment period was observed across studies. The most common TEAEs reported in the tralokinumab group (in at least 10% of patients) were upper respiratory tract infection (URTI), viral URTI, AD, conjunctivitis, and headache.

Serious TEAEs

The frequency of serious TEAEs in the initial treatment period ranged between 0.7% and 3.8% in the tralokinumab (or tralokinumab plus TCS) group and between 2.5% and 5.3% in the placebo (or placebo plus TCS) group in all pivotal studies.

Withdrawals Due to Adverse Events

No treatment withdrawals due to AE or death were reported in adolescents. In the ECZTRA 1, 2, 3, and 7 trials, the proportion of adults who withdrew from treatment due to an AE ranged between 0.7% and 3.3% in the tralokinumab (or tralokinumab 300 mg every 2 weeks plus TCS) group and between 0.8% and 4.1% in the placebo (or placebo plus TCS) group.

Mortality

Two deaths (1 related to an unknown cause and 1 related to myocardial infarction) were reported in the tralokinumab group in the ECZTRA 1 trial, and 1 death (related to metastatic squamous cell carcinoma) was reported in the tralokinumab group in the ECZTRA 2 trial. No deaths were reported in all other studies.

Notable Harms

There was no notable difference between the tralokinumab group and the placebo group in the frequency of eczema herpeticum, malignancies, skin infection requiring systemic treatment, and eye disorders reported in adolescents and adults, except that conjunctivitis was consistently more frequently reported in the tralokinumab group (3.0% to 11.1%) than in the the placebo group (1.5% to 4.4%) across the studies in adults.

Harms Results — Maintenance and/or Continuous Treatment Period

The results in the maintenance (or continuous) treatment period of the ECZTRA 1, 2, and 3 trials was overall consistent with the initial treatment period.

Critical Appraisal

The randomization and allocation concealment methods were adequate. Though there were some baseline imbalances in the ECZTRA 3 and 6 trials, these may have been compatible with chance and did not appear to consistently favour either treatment group. The trials were adequately blinded; however, there is a small potential for bias in measurement of patient-reported outcomes (i.e., [Adolescent] Worst Daily Pruritus NRS, Eczema-Related Sleep NRS, POEM, DLQI [or CDLQI], and HADS scores) leading to inflated efficacy

of tralokinumab due to possible unblinding in patients becoming aware of their assignments based on treatment response; however, the presence and extent of such potential bias is unknown. In the initial treatment period, IGA 0 or 1, EASI 75, reduction of at least 4 points in (Adolescent) Worst Daily Pruritus NRS score from baseline, change from baseline in SCORAD and DLQI score outcomes were controlled for multiplicity, while the other end points (secondary and exploratory) were not and were at an increased risk of type I error (i.e., false-positive results). Continuous secondary and exploratory end points (change from baseline in EASI, POEM, Worst Daily Pruritus NRS, Eczema-Related Sleep NRS, and HADS scores) were at a high risk of bias due to a large amount of missing data that were not appropriately accounted for in the statistical analysis. No conclusion can be drawn on subgroup analyses due to the lack of sample size consideration and control for multiplicity. In the maintenance (or continuous) treatment period, IGA 0 or 1 and EASI 75 outcomes were adjusted for multiplicity in the ECZTRA 1 and 2 trial; however, the results were uncertain due to a sizable reduction in sample sizes, wide CIs for IGA 0 or 1 and EASI 75 outcomes, and inconsistent results between the ECZTRA 1 and 2 trial.

The study population of the ECZTRA 7 trial (i.e., adults whose disease had failed to respond to, or who were deemed not a candidate for, topical therapy and cyclosporine) was more reflective of the anticipated place of therapy of tralokinumab compared with other included RCTs in patients whose disease had failed to respond to topical therapy only. The study interventions of the ECZTRA 3 and 7 trials (i.e., tralokinumab in combination with TCS) were also more reflective of the real-world use of tralokinumab compared with the ECZTRA 1, 2, and 6 trials (i.e., tralokinumab monotherapy) based on clinical expert input that patients typically use biologics in combination with TCSs for active lesions. The clinical relevance of SCORAD, POEM, and HADS score outcomes is unclear given that these instruments are not routinely used in clinical practice. The clinical experts considered the duration of follow-up in the initial treatment period (16 weeks) to be insufficient to adequately assess efficacy given that most patients would require at least 6 months of tralokinumab treatment to achieve optimal response in their clinical experience. The results of the maintenance treatment period (up to 52 weeks) are likely more generalizable but inconclusive because of issues with internal validity. The absence of direct comparative evidence between tralokinumab and relevant comparators (i.e., dupilumab, upadacitinib, abrocitinib) represents a gap in pivotal trial evidence in the treatment of patients with moderate to severe AD.

Long-Term Extension Studies

Description of Study

One ongoing, open-label, single-arm, multicenter, LTE trial, ECZTEND, was submitted by the sponsor. This study included patients with moderate to severe AD who previously participated in clinical trials for tralokinumab (i.e., the ECZTRA 1 to 8 and TraSki trials). Patients were eligible to participate in the ECZTEND trial if they had completed the treatment period in 1 of the parent trials, regardless of the type of previous treatment in the parent trials (i.e., tralokinumab or placebo) or treatment response. All patients received tralokinumab with dosing per the product monograph by self-injection. Patients were permitted to use concomitant TCSs or topical calcineurin inhibitors and were required to use an emollient at least twice daily for at least 14 days before the ECZTEND trial baseline and continue use throughout the trial. The primary

outcome was long-term safety, specifically the number of AEs experienced during the study. The secondary outcomes are for efficacy and included achieving an IGA score of 0 or 1 and achieving EASI 75, each measured at weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248. All analyses were descriptive and based on observed cases, with sensitivity analyses using last observation carried forward or modified nonresponder imputations to account for missing data. There are 2 major cohorts, namely adult and adolescent cohorts, for the outcomes analyses. The data cut-off dates for the adult cohort for the reported interim analyses were April 30, 2021 (all participants from the ECZTRA 1, 2, 3, 4, 5, and 7 trials enrolled in the ECZTEND trial [n = 1,442] up to 3.5 years of follow-up; 3-year subgroup containing participants from the ECZTRA 1 and 2 trials [n = 347]) and April 30, 2022 (4-year subgroup containing participants from the ECZTRA 1 and 2 trials [n = 347]). The data cut-off date for adolescent cohort was April 30, 2022 (participants from the ECZTRA 6 trial, up to 3 years of follow-up [n = 127]).

Efficacy Results

Eczema Area and Severity Index 75

EASI 75 was assessed relative to the baseline in the parent trials. EASI 75 was achieved in 85.1% of patients (411 of 483 patients, observed data) at week 104 in the ECZTEND trial (i.e., up to 3 years of cumulative exposure to tralokinumab in the parent trials and the ECZTEND trial) in the all-participant adult cohort; in 84.5% of patients (147 of 174 patients, observed data) at week 152 in the ECZTEND trial in the 4-year adult subgroup; and in 84.4% of patients (92 of 109 patients, observed data) at week 56 in the ECZTEND trial (i.e., 2 years of cumulative exposure to tralokinumab in the parent trials and the ECZTEND trial) in the adolescent cohort. The results of the sensitivity analyses were consistent with the primary analysis using observed data.

IGA 0 or 1

IGA 0 or 1 was achieved in 50.5% of patients (244 of 483 patients, observed data) at week 104 in the ECZTEND trial (i.e., up to 3 years of cumulative exposure to tralokinumab in the parent trials and the ECZTEND trial) in the all-participant adult cohort; in 52.6% of patients (92 of 175 patients, observed data) at week 152 in the ECZTEND trial in the 4-year adult subgroup; and in 61.5% of patients (67 of 109 patients, observed data) at week 56 in the ECZTEND trial (i.e., 2 years of cumulative exposure to tralokinumab in the parent trials and the ECZTEND trial) in the adolescent cohort. The results of the sensitivity analyses were consistent with the primary analysis using observed data.

Harms Results

In the adult cohort (all participants; n = 1,442), 1,127 patients (78.2%) experienced at least 1 TEAE. In the 3-year adult subgroup (n = 347), 295 patients (85.0%) experienced at least 1 TEAE. In adolescent cohort (n = 127), 83 patients (65.4%) experienced at least 1 TEAE. In all cohorts, the 3 most common AEs were viral URTI (13.4% to 28.8%), AD (10.2% to 19.6%), and URTI (7.0% to 10.1%). Between 2.4% and 8.9% of patients reported a serious AE in these cohorts. Conjunctivitis was reported in 77 patients (5.3%) and 7 patients (3.6%) from the all-participants adult cohort and the adolescent cohort, respectively. Frequency of treatment discontinuation was reported to be between 0.8% to 2.6%. No deaths were reported in the adult cohort. However, 1 death (0.8%) due to accident occurred in the adolescent cohort.

Critical Appraisal

Similar to other LTE studies, in the ECZTEND trial, it is uncertain if the long-term effects observed could be attributed to tralokinumab treatment because of a lack of comparison group and no adjustment for potential confounding. As well, there is a risk of selection bias that likely favours tralokinumab given that patients who perceived the treatment to be benefiting them during the parent trials were more likely to transfer to the extension study. Similarly, long-term safety concerns may be underestimated given that those who had experienced intolerable AEs in the parent trials were excluded from the ECZTEND trial. Given the open-label study design, there is also a risk of bias in the measurement of patient-reported outcomes (Worst Weekly Pruritus NRS and DLQI scores), potentially favouring tralokinumab. The results related to benefits findings are at risk of being overestimated given that they are interim findings.

The ECZTEND trial included patients who completed 1 of the parent trials regardless of treatment response. This is different from clinical practice in which patients are expected to continue tralokinumab treatment only if their disease demonstrates objective improvement after an adequate trial of treatment. It is unclear what proportion of patients enrolled into the ECZTEND trial had disease that did not respond in the parent trial and the extent of which could impact the generalizability of the study population. The generalizability of the study population was uncertain given that it is unclear what proportion of patients had prior failure of immunosuppressant therapy, which is the likely place in therapy of tralokinumab. Furthermore, the use of concomitant TCSs and rescue medications could influence treatment response; however, use of such medications was not reported in the study and the impact on generalizability of the study findings is thus unclear.

Indirect Comparisons

In the absence of head-to-head evidence comparing tralokinumab to other relevant therapies used in the management of AD, the sponsor submitted 4 ITCs indirectly comparing the treatment effect of tralokinumab to other treatment in patients with moderate to severe AD. Of the ITCs submitted, 2 were NMAs (1 in adults and 1 in adolescents) and 2 were MAICs (both in adults).

Network Meta-Analyses

Description of Studies

The sponsor submitted an NMA conducted by the Institute for Clinical and Economic Review (ICER), hereafter referred to as the ICER NMA, that aimed to evaluate the relative efficacy and safety of treatment with tralokinumab versus other therapies in adults with moderate to severe AD. It is not clear if this NMA was identified by way of a systematic literature search, and if so, how it was selected from the available literature. The ICER NMA was used to inform the sponsor-submitted economic model for the treatment effect of tralokinumab up to week 16. A sponsor-commissioned NMA, hereafter referred to as the LEO Pharma NMA, [redacted].

Efficacy Results

The efficacy results of the NMA are presented for monotherapy and combination therapy by population (i.e., adults and adolescents). The pairwise comparison against baricitinib is not presented as the treatment is currently not approved for use in Canada.

Eczema Area and Severity Index 50

Adult Population (the ICER NMA)

The treatment response to all included monotherapy interventions on the EASI 50 in adults were favoured over placebo. Treatment with upadacitinib 30 mg (relative risk [RR] = 1.75; 95% credible interval [CrI], 1.50 to 2.10), abrocitinib 200 mg (RR = 1.59; 95% CrI, 1.31 to 1.95), upadacitinib 15 mg (RR = 1.53; 95% CrI, 1.20 to 1.84), and dupilumab 300 mg (RR = 1.40; 95% CrI, 1.18 to 1.69) were favoured for achievement of EASI 50 compared to tralokinumab 300 mg. The point estimate for EASI 50 favoured abrocitinib 100 mg over tralokinumab 300 mg, but the CrI also included the potential of little to no difference between the treatments (RR = 1.21; 95% CrI, 0.95 to 1.53).

The treatment response of all included combination therapy interventions on the EASI 50 in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 1.45; 95% CrI, 1.27 to 1.71), abrocitinib 200 mg (RR = 1.32; 95% CrI, 1.14 to 1.57), upadacitinib 15 mg (RR = 1.32; 95% CrI, 1.15 to 1.57), dupilumab 300 mg (RR = 1.26; 95% CrI, 1.09 to 1.49), and abrocitinib 100 mg (RR = 1.20; 95% CrI, 1.02 to 1.43) were favoured for achievement of EASI 50 compared to tralokinumab 300 mg.

Adolescent Population (the LEO Pharma NMA)

[redacted].

Eczema Area and Severity Index 75

Adult Population (the ICER NMA)

The treatment response of all included monotherapy interventions on the EASI 75 in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 2.77; 95% CrI, 1.77 to 2.77), abrocitinib 200 mg (RR = 1.89; 95% CrI, 1.45 to 2.49), upadacitinib 15 mg (RR = 1.79; 95% CrI, 1.42 to 2.29), and dupilumab 300 mg (RR = 1.58; 95% CrI, 1.25 to 2.03) were favoured for achievement of EASI 75 compared to tralokinumab 300 mg. The point estimate for EASI 75 favoured abrocitinib 100 mg over tralokinumab 300 mg, but the CrI also included the potential of little to no difference between the treatments (RR = 1.29; 95% CrI, 0.93 to 1.76).

The treatment response of all included combination therapy interventions on the EASI 75 in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 1.90; 95% CrI, 1.53 to 2.45), abrocitinib 200 mg (RR = 1.58; 95% CrI, 1.25 to 2.07), upadacitinib 15 mg (RR = 1.48 95% CrI, 1.26 to 2.07), dupilumab 300 mg (RR = 1.46; 95% CrI, 1.15 to 1.90), and abrocitinib 100 mg (RR = 1.34; 9% CrI, 1.03 to 1.76) were favoured for achievement of EASI 75 compared to tralokinumab 300 mg.

Adolescent Population (the LEO Pharma NMA)

[redacted]

Eczema Area and Severity Index 90

Adult Population (the ICER NMA)

The treatment response of all included monotherapy interventions on the EASI 90 in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 2; 95.89% CrI, 2.19 to 3.95), abrocitinib 200 mg (RR = 2.36; 95% CrI, 1.65 to 3.39), upadacitinib 15 mg (RR = 2.17; 95% CrI, 1.60 to 3.00), and dupilumab 300 mg every 2 weeks (RR = 1.83; 95% CrI, 1.34 to 2.54) were favoured for achievement of EASI 90 compared to tralokinumab 300 mg. The point estimate for EASI 90 favoured abrocitinib 100 mg over tralokinumab 300 mg, but the CrI also included the potential of little to no difference between the treatments (RR = 1.39; 95% CrI, 0.91 to 2.09).

The treatment response of all included combination therapy interventions on the EASI 90 in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 2.74; 95% CrI, 1.98 to 3.97), abrocitinib 200 mg (RR = 2.01; 95% CrI, 1.41 to 2.98), upadacitinib 15 mg (RR = 2.01; 95% CrI, 1.43 to 2.96), dupilumab 300 mg (RR = 1.76; 95% CrI, 1.24 to 2.57), and abrocitinib 100 mg (RR = 1.54; 95% CI, 1.05 to 2.31) were favoured for achievement of EASI 90 compared to tralokinumab 300 mg.

Adolescent Population (the LEO Pharma NMA)

[redacted]

Investigator Global Assessment

Adult Population (the ICER NMA)

The treatment response of all included monotherapy interventions on the IGA in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 3.97; 95% CrI, 2.54 to 6.31), upadacitinib 15 mg (RR = 3.07; 95% CrI, 1.88 to 4.99), abrocitinib 200 mg (RR = 2.75; 95% CI, 1.54 to 4.95), and dupilumab 300 mg (RR = 2.15; 95% CrI, 1.31 to 3.60) were favoured for achievement of IGA 0 or 1 compared to tralokinumab 300 mg. The CrIs for the comparison between tralokinumab and abrocitinib 100 mg were too wide to draw any conclusions of certainty in IGA in adults receiving monotherapy for AD.

The treatment response of all included combination interventions on the IGA in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 2.83; 95% CrI, 1.90 to 4.27), abrocitinib 200 mg (RR = 2.24; 95% CI, 1.44 to 3.49), upadacitinib 15 mg (RR = 2.08; 95% CrI, 1.35 to 3.25), dupilumab 300 mg (RR = 1.85; 95% CrI, 1.20 to 2.88), and abrocitinib 100 mg (RR = 1.66; 95% CI, 102 to 2.68) were favoured for achievement of IGA 0 or 1 compared to tralokinumab 300 mg.

Adolescents Population (the LEO Pharma NMA)

[redacted]

Four or More Point Improvement in Peak Pruritus NRS Score

Adult Population (the ICER NMA)

The treatment response of all included monotherapy interventions on 4-point or greater improvement in Peak Pruritus (PP) NRS score in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 2.16; 95% CrI, 1.14 to 4.58), dupilumab 300 mg (RR = 2.12; 95% CrI, 1.06 to 4.43), and upadacitinib 15 mg (RR = 1.97; 95% CrI, 1.01 to 4.28) were favoured for achievement of a 4-point or greater improvement in PP NRS score in compared to tralokinumab 300 mg. The CrIs for the remaining comparisons were too wide to draw any conclusions of certainty in a 4-point or greater improvement in PP NRS score between tralokinumab and other active comparators among adults.

The treatment response of all included combination therapy interventions on a 4-point or greater improvement in PP NRS score in adults were favoured over placebo. Treatment with upadacitinib 30 mg (RR = 2.37; 95% CrI, 1.75 to 3.29), abrocitinib 200 mg (RR = 2.04; 95% CrI, 1.47 to 2.89), upadacitinib 15 mg (RR = 1.91; 95% CrI, 1.34 to 2.74), and dupilumab 300 mg (RR = 1.79; 95% CrI, 1.28 to 2.55) were favoured for achievement of a 4-point or greater improvement in PP NRS score compared to tralokinumab 300 mg. The point estimate for a 4-point or greater improvement in PP NRS score favoured abrocitinib 100 mg over tralokinumab 300 mg, but the CrI also included the potential of little to no difference between the treatments (RR = 1.40; 95% CrI, 0.93 to 2.10).

Adolescent Population (the LEO Pharma NMA)

[redacted]

Children's Dermatology Life Quality Index

A network meta-analysis of the CDLQI scores was not reported in the ICER NMA.

[redacted]

Patient-Oriented Eczema Measure

A network meta-analysis of POEMS scores was not reported in the ICER NMA.

[redacted]

[redacted].

Harms Results

Adverse Events

A network meta-analysis of harms data was not reported in the ICER NMA.

[redacted].

Critical Appraisal

The ICER NMA

The ICER NMA was based on studies identified from a systematic literature review of relevant randomized evidence of treatments for adults and adolescents with AD. The systematic literature search was based on a population, intervention, comparator, and outcomes (PICO)-defined a priori design, with efficacy and safety outcomes predefined. The systematic literature search was comprehensive. The selection process was not clearly defined and data extraction was conducted by a single reviewer, increasing the risk of bias and error. While the risk of bias of the comparator trials was assessed, the method used was not reported, and risk of bias was not assessed by outcome. Several sources of clinical and methodological heterogeneity were identified that challenged the plausibility of the underlying transitivity assumption. These included variation in patient age, duration of disease, disease severity, length of the washout period, time point of follow-up (12 to 16 weeks), and methods of imputation for missing data. To account for differences in corticosteroid use across trials, separate NMAs were conducted for monotherapy and combination therapies. However, the treatment of patients in the control group (placebo plus TCS) were not consistent across the combination therapy trials. Statistical heterogeneity and consistency were not tested, despite the availability of several closed loops.

The networks were sparse (several comparisons with relatively few studies) and all comparisons to tralokinumab were indirect, which increased the uncertainty in the findings. No sensitivity analysis exploring possible assumptions made by the reviewers were reported. Moreover, there was no indication of model adjustment to account for the correlation in the 3-arm trials. Harms outcomes were not evaluated.

The LEO Pharma NMA

The LEO Pharma NMA was based on studies identified from a systematic review of relevant randomized evidence of treatment for moderate to severe AD in adolescents. The systematic literature search was based on a PICO-defined a priori design, with efficacy and safety outcomes predefined. The systematic literature search was comprehensive. The reasons for study exclusions were reported and the selection and data extraction processes were adequate to minimize the risk of bias and error. While the risk of bias of the comparator trials was assessed, the methods used were not reported and risk of bias was not assessed by outcome. Several sources of heterogeneity were identified across the included studies. These included variation in time point of follow-up, the predetermined duration of AD for study inclusion, exclusion criterion related to prior use of biologics, protocol use for biologics, and investigational drug discontinuation for rescue treatment.

No information was given on model fit and assessment of statistical consistency, despite the presence of closed loops. No sensitivity analysis exploring possible assumptions made by the reviewers were reported. All comparisons to tralokinumab were indirect, which introduces increased uncertainty in the findings. Due to small sample sizes, for several comparisons the CrIs were wide, which precluded conclusions about comparative efficacy and safety for those outcomes.

Matching-Adjusted Indirect Comparison

Description of Studies

The sponsor submitted 2 MAICs, conducted by a third-party on their behalf, comparing the relative efficacy of tralokinumab versus dupilumab in adults with moderate to severe AD. In both MAICs, evidence for tralokinumab was based on individual patient data, while evidence for dupilumab was based on published aggregate data. [redacted]. The unanchored MAIC based on the ECZTRA 3 and LIBERTY AD CHRONOS trials aimed to assess the long-term efficacy outcomes for tralokinumab 300 mg (the ECZTRA 3 trial) administered every 2 weeks and 300 mg every 4 weeks against dupilumab (the LIBERTY AD CHRONOS trial) every 2 weeks at 32 to 52 weeks of follow-up in adults with moderate to severe AD.

Efficacy Results

The ECZTRA 7 Trial Versus the LIBERTY AD CAFÉ Trial

[redacted].

The ECZTRA 3 Trial Versus the LIBERTY AD CHRONOS Trial

After matching, the reported baseline characteristics of the weighted patient population of the ECZTRA 3 trial were matched with those of the LIBERTY AD CHRONOS trial. A total of 106 patients were included in the dupilumab treatment group. The effective sample size (ESS) following match-adjustment was 123.4 for the tralokinumab treatment arm (49.36% of the original population).

The results of the ECZTRA 3 versus LIBERTY AD CHRONOS trials unanchored efficacy MAIC analysis between tralokinumab and dupilumab was in favour of tralokinumab for IGA score 0 or 1 (risk difference = 13.9; 95% CI, 0.6 to 27.3) and change in DLQI score (mean difference = −1.7; 95% CI, −3.0 to −0.3) at week 52. The CI were too wide to draw any conclusions of certainty on the remaining outcomes between tralokinumab and dupilumab (at week 32, EASI 75, EASI 50, EASI 90, and IGA score 0 or 1; at week 52, percent change in EASI score, change in Worst Daily Pruritis NRS score, percent change in SCORAD score, and change in POEM

score; at week 52, EASI 75, EASI 50, EASI 90, Worst Daily Pruritis NRS score improvement of at least 4 points, POEM score improvement of at least 4 points, and DLQI score improvement of at least 4 points).

Harms Results

[redacted]

No harms end points were evaluated in the ECZTRA 3 versus LIBERTY AD CHRONOS trials MAIC.

Critical Appraisal

The ECZTRA 7 Trial Versus the LIBERTY AD CAFÉ Trial

The comparison of the ECZTRA 7 trial versus the LIBERTY AD CAFÉ trial was chosen after a review of | trials evaluating the treatment of tralokinumab or dupilumab in patients with moderate to severe AD. There were no description of a literature search or selection criteria, or any indication of how the | trials were located. The sponsor noted that the decision to conduct a MAIC was based on substantial heterogeneity that precluded the conduct of a standard indirect comparisons (e.g., NMA or Bucher comparison). Of note, how the matching variables were selected for the MAIC was not described. Baseline characteristics postmatching were well balanced with almost perfect matching for the covariates included in the MAIC. However, the complete baseline demographic and disease characteristics for patients in both trials were not reported. The application of weights resulted in a reduced an ESS of [redacted], in which [redacted] of enrolled patients in the ECZTRA 7 trial were lost. The reduction of sample size in the primary analysis resulted in imprecision, leading to uncertainty of the results. Sensitivity analysis using a larger population by way of an unadjusted indirect comparisons were generally consistent with the primary MAIC, but with narrower CIs favouring dupilumab. There was no assessment of residual confounding in the analysis.

The ECZTRA 3 Trial Versus the CHRONOS Trial

The ECZTRA 3 trial versus the CHRONOS trial MAIC lacked description of a literature search or selection criteria, or any indication of how the trials were selected for the MAIC. There was also a lack of transparency in the data extraction process and quality assessment. Although both the ECZTRA 3 and LIBERTY AD CHRONOS trials included a placebo, an unanchored MAIC was conducted. The choice to conduct an unanchored MAIC was appropriately justified due to difference in trial design (rerandomized versus treat-through) that may have resulted in differences in treatment of placebo across the ECZTRA 3 and LIBERTY AD CHRONOS trials. Nonetheless, the ECZTRA 3 trial versus the LIBERTY AD CHRONOS trial MAIC was limited by heterogeneity between the dupilumab target population and the analysis set. First, the dupilumab target population in the LIBERTY AD CHRONOS trial was not the same analysis set for the results reported at week 32 and week 52. Consequently, the matched tralokinumab population may not be completely representative of the dupilumab population results reports at week 52. Next, the time point in which tralokinumab (week 32) and dupilumab (week 52) were compared at were different. The magnitude and direction of bias related to differences in analysis time point is uncertain. Although, input from the clinical experts suggests that better

results are expected for tralokinumab at week 52 versus week 32; therefore, analysis may be at risk of bias in favour of treatment with dupilumab. Unadjusted and match-adjusted baseline covariates were reported. Baseline characteristics postmatching were well balanced with almost perfect matching for the covariates included in the MAIC. However, the complete baseline demographic and disease characteristics for patients in both trials were not reported. The application of weights resulted in a reduced ESS of 123.4, in which 50.64% of enrolled patients in the ECZTRA 3 trial were lost. The reduction of sample size in the primary analysis resulted in imprecision, leading to uncertainty of the results. There was no assessment of residual confounding in the analysis.

Studies Addressing Gaps in the Pivotal and RCT Evidence

Description of Studies

Two observational studies were submitted by the sponsor to address the evidence gaps. There was no description about the search or selection methods used to identify these studies. Pezzolo and Naldi was an open-label, retrospective, 12-week case series conducted in Italy (N = 12) and published as a letter to the editor. This study included 12 adults who had disease that had previously failed to respond to dupilumab. Pereyra-Rodriguez et al. (N = 85) was a retrospective, 16-week study conducted in Spain. This study assessed 85 adults, including those who had previously been treated with either dupilumab (29.4%) or upadacitinib (8.2%). These 2 studies also assessed the clinical experience of tralokinumab in the real-world setting.

Efficacy Results

In the study by Pezzolo and Naldi, the mean EASI score at baseline before any systemic therapy was 36.58 (range = 21 to 47). All 12 adults with AD reached EASI 75 within 8 weeks, with continuing improvement at 12 weeks. The mean EASI score was 27.58 (range = 20 to 35) at study baseline and 4.67 (range = 0 to 13) at week 12. The mean Itch NRS score was 8.42 (range = 7 to 10) at baseline and 2.92 (range = 0 to 7) at week 12. The mean Sleep NRS score was 7.0 (range = 3 to 10) at baseline and 1.92 (range = 0 to 5) at week 12. In the study by Pereyra-Rodriguez et al., the mean EASI score at baseline was 25.4 (SD = 8.1) and 7.5 (SD = 6.9) at week 16. The mean SCORAD score was 55.8 (SD = 13.3) at baseline and 20.0 (SD = 14.78) at week 16. The mean PP NRS was 8.1 (SD = 1.8) at baseline and 3.5 (SD = 2.4) at week 16. At baseline, there were 47 patients (55.3%) with an IGA score of 4. At the end of the follow-up period, 18.8% of patients (absolute number of patients was not reported) had an of IGA 0 or 1.

Harms Results

In the study by Pezzolo and Naldi, no serious AEs were reported. Also, the conjunctivitis that had been observed in 4 patients during the previous treatment with dupilumab did not recur. In the study by Pereyra-Rodriguez et al., the most frequent AEs were conjunctivitis and red face (5 patients; 5.9% each) with 1 patient having both events at the same time. Of those 5 patients, 2 patients had experienced conjunctivitis with prior dupilumab treatment, and 3 patients were naive to advanced therapy with no prior eye-related AEs. Moreover, 3 patients (3.5%) experienced worsening and generalized AD lesions, 2 patients (2.4%) developed reaction at the injection site, and 2 patients (2.4%) reported anxiety-depressive syndrome. One patient discontinued treatment due to severe conjunctivitis.

Critical Appraisal

It is not clear how the studies addressing gaps were selected; therefore, there is a potential for study selection bias (i.e., relevant studies may have been left out). There is a high level of uncertainty in the results because of the following study limitations common to both studies: small sample sizes (Pezzolo and Naldi, N = 12; Pereyra-Rodriguez et al., N = 85); potential selection bias in the absence of a clear description of patient selection methods; noncomparative study design with a lack of adjustment for confounding; a lack of clarity on whether the studies were designed a priori and if retrospective data collection was done in a systematic way. As well, no formal hypothesis testing was performed in the study by Pezzolo and Naldi. There was no control for multiple comparisons in the study by Pereyra-Rodriguez et al., which results in an increased risk of false-positive results. The durations of follow-up (Pezzolo and Naldi, 12 weeks; Pereyra-Rodriguez et al., 16 weeks) were also inadequate for assessing response to tralokinumab treatment according to the input of clinical experts consulted by CADTH. Neither of the studies included adolescents; therefore, the treatment effects in adolescents who had prior dupilumab and/or JAKi treatments were not addressed by these studies.

Economic Evidence

Cost and Cost-Effectiveness

Table 1: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree and Markov model hybrid
Target population	Patients aged 12 years and older with moderate to severe 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 are ineligible for both phototherapy (where available) and off-label immunosuppressants.
Treatment	Tralokinumab plus BSC (best supportive care; low- to mid-potency topical corticosteroids)
Dose regimen	The recommended dosage is an initial dose of 600 mg followed by 300 mg administered every other week.
Submitted price	Tralokinumab, 150 mg/1mL: $422.26 per syringe
Treatment cost	$22,802 annually per patient in year 1, $21,958 thereafter
Comparators	Dupilumab plus BSC Abrocitinib plus BSC Upadacitinib plus BSC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (maximum age 110)

Component	Description
Key data sources	The ECZTRA 1, 2, and 3 trials for tralokinumab inputs and the Institute for Clinical and Economic Review Evidence Report NMA for 16-week efficacy for all comparator treatments
Key limitations	• Evidence from the NMA informing treatment response at 16 weeks suggests all comparators are favoured in comparison with tralokinumab; however, limitations with the NMA render the magnitude of effect uncertain. • The comparative durability of treatment response, discontinuation, and safety of tralokinumab vs. comparators after week 16 is highly uncertain owing to a lack of direct or indirect comparative assessment, with naive comparisons used to inform these model parameters. Durability of response and discontinuation are key drivers of results and this introduces considerable uncertainty in estimated drug acquisition costs and effects in the sponsor's submission. • There is uncertainty surrounding whether the EASI 75 response definition is the most appropriate measure to inform treatment response in the submitted model. Clinical expert feedback obtained by CADTH indicated IGA 0 or 1 was more often used in practice. • Maintenance dosing after week 16 for tralokinumab is highly uncertain. The sponsor assumed that [redacted] of those who had disease that responded to tralokinumab would switch from every 2 week to every 4 week dosing and remain on this dosing regimen until treatment discontinuation or death; however, there is limited clinical evidence to support this assumption, which has a notable impact on the incremental costs associated with tralokinumab. • Health state utility values did not meet face validity. Those with disease that did not respond to biologic or JAKi treatments were expected to receive a utility benefit that was similar to that of those with disease that did respond for the 52-week induction period despite discontinuing treatment and not incurring treatment costs. • The expected proportion of patients on the higher dose of JAKis was underestimated. • Subsequent treatment after initial treatment failure was not modelled by the sponsor, which may not accurately reflect the clinical treatment pathway experienced by patients with AD. • While the sponsor conducted a scenario specific to the adolescent population (ages 12 to 17), this analysis was also associated with substantial uncertainty due to limitations with the submitted indirect evidence, and it relied on several key inputs from adults. Therefore, the cost-effectiveness of tralokinumab in adolescents is associated with uncertainty.
CADTH reanalysis results	• In the CADTH base case, CADTH adopted alternate estimates for the 52-week conditional response rate of abrocitinib, altered the proportion of those with [redacted] response to tralokinumab switching to every 4 week dosing after week 16, revised health state utility values, and updated the proportion of patients on the high dose of JAKi treatments. CADTH was unable to address uncertainty with the comparative clinical efficacy data for the reimbursement population at week 16 and beyond. • Tralokinumab was less costly and less effective (fewer QALYs) than all comparator treatments. • The key drivers of the cost-effectiveness estimates are the assumptions surrounding the long-term comparative efficacy and drug acquisition costs of tralokinumab related to every 4 week dosing.

AD = atopic dermatitis; BSC = best supportive care; EASI 75 = at least a 75% reduction in EASI score from baseline; IGA = Investigator Global Assessment; JAKi = Janus kinase inhibitor; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; vs. = versus.

Budget Impact

CADTH identified the following key limitations with the sponsors analysis: there was uncertainty surrounding the proportion of responders who would switch from every 2 weeks dosing to every 4 weeks maintenance dosing after 16 weeks, particularly given the sponsor's model did not account for those whose disease did not respond to induction therapy; there was uncertainty in the predicted market shares of tralokinumab, which were likely overestimated according to clinical expert input; the use of a claims-based approach was associated with uncertainty; use of abrocitinib was likely underestimated by the sponsor; the proportion of patients receiving high-dose JAKis was likely underestimated. The CADTH reanalysis included restricting the proportion of patients switching to every 4 week dosing after 16 weeks, adjusting market shares of tralokinumab and JAKis, and adjusting the proportion of patients receiving high-dose JAKis. CADTH's reanalysis found that funding tralokinumab for patients aged 12 years and older with AD resulted in cost savings of $1,418,549 in year 1, $2,256,300 in year 2, and $3,625,310 in year 3, for a cumulative savings of $7,300,159 across the 3-year time horizon. CADTH's reanalysis found that the reimbursement of tralokinumab is likely to result in substantially less cost savings than predicted by the sponsor's model. The estimated budget impact is sensitive to assumptions regarding every 4 weeks maintenance dosing and the projected market shares of tralokinumab.

Request for Reconsideration

The sponsor filed a Request for Reconsideration for the draft recommendation for tralokinumab indicated for the treatment of moderate to severe AD 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. In their request, the sponsor requested that CDEC reconsider its review of tralokinumab based on the following:

- The sponsor believes that the efficacy assessment at week 16 underestimates tralokinumab's magnitude of clinical benefits and that assessing tralokinumab's magnitude of clinical benefit solely on week 16 outcomes does not accurately reflect the heterogenous, chronic, and lifelong nature of AD.
- The sponsor believes that tralokinumab demonstrates savings and cost-effectiveness despite conservative efficacy assumptions. The sponsor noted that the cost-utility analysis incorporated the most pessimistic assumption of comparative efficacy of tralokinumab at week 16. They noted that, nonetheless, tralokinumab was more cost-effective than dupilumab or upadacitinib. The sponsor believes that dismissal of this evidence raises concerns regarding patient accessibility and payers' affordability needs of effective treatments.
- The sponsor believes that the CADTH recommendation is misaligned with patient, clinician, and expert input and this presents a critical issue.

In the meeting to discuss the sponsor's Request for Reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor

- feedback from 2 clinical experts with expertise diagnosing and treating patients with AD
- feedback on the drug recommendation from the public drug plans
- feedback on the draft recommendation from 3 clinician groups: the Dermatology Association of Ontario, the Atlantic Specialist Group Managing Atopic Dermatitis, and the Canadian Dermatology Association (1 joint submission)
- feedback on the draft recommendation from 1 patient group: Eczema Society of Canada
- feedback on the draft recommendation from the sponsor.

All stakeholder feedback received in response to the draft recommendation is available on the CADTH website.

CDEC Information

Members of the Committee at Initial Meeting

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Edward Xie, and Dr. Peter Zed

Members of the Committee at Reconsideration Meeting

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed

Initial meeting date: October 25, 2023

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Reconsideration meeting date: April 24, 2024

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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