Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Do Not Reimburse

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that tralokinumab not be reimbursed 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.

Rationale for the Recommendation

CDEC acknowledged the 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 due to the uncertainty around the magnitude of 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 health-related quality of life (HRQoL) compared with placebo at week 16 when used as a monotherapy or in combination with topical corticosteroids (TCS); however, the magnitude of 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 who were not adequate adequately controlled with, or 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 TCS resulted in a statistically significant improvement in Eczema Area and Severity Index 75 (EASI75) score from baseline compared to placebo in combination with TCS; however, the outcome daily pruritus numerical rating scale (NRS), which was tested first in the hierarchy, did not demonstrate a statistically significant difference between treatment groups. Hence 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 ECZTRA 7. 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; evidence for the use of tralokinumab in the adolescent population as per the anticipated place in therapy was thus uncertain.

CDEC was unable to determine the comparative efficacy of tralokinumab versus other newer systemic treatments (dupilumab, upadacitinib, abrocitinib) since 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. CDEC recognized that there is a need for additional treatments for patients who have inadequate clinical response to newer systemic treatments currently available; however, CDEC considered evidence for the use of tralokinumab in patients who previously received dupilumab and/or Janus kinase inhibitors (JAKi's) based on 2 observational studies to be inconclusive given the small sample sizes, and the open-label, non-comparative study designs.

Patient input received for this review identified a need for additional treatments patients that can reduce severity and symptoms of AD, improve sleep quality and health-related quality of life (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

- CDEC discussed the magnitude of treatment effect of tralokinumab observed in the RCTs in adults (ECZTRA 1, ECZTRA 2, and ECZTRA 3) and adolescents (ECZTRA 6) with moderate-to-severe AD. The committee considered the observed treatment effects with respect to the co-primary endpoints of Investigator's Global Assessment (IGA) 0/1 and EASI75 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 interpretation of the magnitude of benefit in the trials.
- 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. CDEC noted that no conclusion can be drawn on the efficacy and safety of tralokinumab beyond week 16 based on the submitted evidence due to important limitations of the included studies, including inconsistent results between trials and evidence of imprecision in the longer-term results of the RCTs; and risks of selection bias and confounding due to the non-comparative trial design of the long-term extension study (ECZTEND).
- CDEC recognized that some patients have insufficient clinical response to currently available biologics and JAKi treatments. CDEC discussed evidence from 2 observational studies assessing the efficacy and safety of tralokinumab in patients who previously received dupilumab and/or JAKi's. CDEC considered the results to be inconclusive due to the methodological limitations associated with these studies (small sample size, and open-label, non-comparative 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 failure of treatment with dupilumab or a JAKi.

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 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 Janus kinase inhibitors [JAKi's]) are effective options that are currently available for patients who failed conventional treatments, although there are some patients who do 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 topical corticosteroids. Tralokinumab is a monoclonal antibody that inhibits interleutkin-13 receptors. It is available as a solution for subcutaneous injection (150 mg/1mL pre-filled syringe and 300 mg/2mL pre-filled 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 long-term extension 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 public drug plans that participate in the CADTH review process
- Two 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, the Canadian Dermatology Association
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

The Eczema Society of Canada and Eczema Quebec with 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 or caregivers/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', 'bugs crawling all over' leading 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 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 (dryness, flaking, inflammation, blistering, cracking), reduction in itch frequency and/or intensity, long-term improvement in quality of life (sleep, prevention of flares, discomfort, psychological burden), ability to carry out daily activities (work, school, leisure, personal hygiene), and are safe (reduced infection, 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 do not respond or are refractory to the newer systemic treatments (dupilumab, upadacitinib, abrocitinib) and that JAKi's 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 Investigator Global Assessment [IGA] in clinical trials), Eczema Area and Severity Index (EASI), Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), and Worst Daily Pruritus Numeric Rating Scale (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 have intolerable side effects. Tralokinumab could be prescribed by a dermatologist, allergist, immunologist, and pediatrician with expertise in the diagnosis, treatment, and monitoring of patients with AD, in the clinical experts' opinion.

Clinician group input

Three clinician groups, Atlantic Specialist Group Managing AD (7 clinicians), Dermatology Association of Ontario (16 clinicians), 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 (long-term and durable relief of chronic itch, minimize dry and inflamed skin, clear or almost clear skin, less oozing, scaling, cracking, or fissures), QoL (better sleep), and function (focus on work and school). The clinical experts added that 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 respond to or tolerate the existing systemic treatments. JAKi's have safety and contraindication issues (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 fail to respond to dupilumab and oral JAKi's. The clinician groups said the suitable patient population aligns with the reimbursement

request. They also noted that those who did not respond to biologics and/or JAKi's, have a history of conjunctivitis, risk factors associated with cardiovascular events, thrombosis, malignancy, serious infections, and/or significant drug-drug interactions, challenges to 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 (BSA) affected, pruritus NRS, PGA (in clinical practice) and/or EASI, if required by insurance company or payers, at 6 months after initiation of tralokinumab. According to the clinician groups, a lack of response or efficacy, worsening disease, deterioration of QoL, increased BSA affected, presence of adverse events (AEs), or unacceptable intolerance, and allergies would make clinicians to consider discontinuation of tralokinumab treatment. 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 requirement of trying off-label immunosuppressants with lower efficacy and increased risk before accessing newer systemic agents.

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 EASI75 (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 adolescent patients (ECZTRA 6, N = 301) and 4 of which included adult patients (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 was submitted for these studies in the current review. All enrolled patients had previously failed topical therapy for AD. Patients in ECZTRA 7, in addition, had previously failed or were deemed not a candidate for systemic cyclosporine A (CsA) treatment. Tralokinumab was compared with placebo, as monotherapy in ECZTRA 1, 2, and 6; tralokinumab with TCS was compared to placebo with TCS in ECZTRA 3 and 7. Proportion of patients with at least 4 points of reduction in Worst Daily Pruritus NRS, change from baseline in Scoring Atopic Dermatitis (SCORAD) score, and change from baseline in DLQI score (or CDLQI) were assessed at week 16 as key secondary endpoints in ECZTRA 1, 2, 3, and 6. In ECZTRA 7, these were assessed as secondary endpoints at week 16 and 26.

The mean age of the study population was 14.6 (standard deviation [SD] = 1.7) years in ECZTRA 6 and ranged between 36.5 (SD = 14.1) years and 39.1 (SD = 15.2) years in ECZTRA 1, 2, 3, and 7. The majority of patients were White and males in all studies. In ECZTRA 6, prior systemic immunosuppressant, monoclonal antibody, and phototherapy treatment for AD were reported in 21.1%, 2.4%, and 25.6% of patients, respectively. In ECZTRA 1, 2, 3, and 7, prior phototherapy was noted in 43.7% to 58.8% of patients. Prior systemic immunosuppressant treatment was notably more common in ECZTRA 7 than other studies in adults, with cyclosporine

being the most frequently used across studies (74.7% in ECZTRA 7; 31.1% to 36.4% in ECZTRA 1, 2, and 3). A small proportion of patients in ECZTRA 3 and 7 received prior monoclonal antibody treatment for AD (6.3% and 7.6%, respectively).

Efficacy Results – Initial Treatment Period

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

Investigator's Global Assessment (IGA) score of 0 or 1

Adolescents (12 to < 18 years old)

In ECZTRA 6, the difference between the tralokinumab 300 mg every 2 weeks (Q2W) group and the placebo group in the co-primary endpoint of IGA 0/1 (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 co-primary endpoint of IGA 0/1 at week 16 was 8.6% (95% CI, 4.1% to 13.1%; P = 0.002) in ECZTRA 1, and 11.1% (95% CI, 5.8% to 16.4%; P < 0.001) in ECZTRA 2, comparing tralokinumab Q2W with placebo; 12.4% (95% CI, 2.9% to 21.9%; P = 0.015) in ECZTRA 3 comparing tralokinumab Q2W+TCS with placebo+TCS; all of which were in favour of tralokinumab (or tralokinumab+TCS).

In ECZTRA 7, the between-group difference in the secondary endpoint of IGA score of 0/1 was [redacted] at week 16, and [redacted] at week 26 comparing tralokinumab Q2W+TCS with placebo+TCS. Both endpoints 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 (EASI)

Adolescents (12 to <18 years)

In ECZTRA 6, the between-group difference in the co-primary endpoint of EASI75 (i.e., proportion of patients with at least 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 Q2W over placebo. Analyses of EASI 90, EASI50 and change from baseline in EASI also showed results in favour of tralokinumab; however, these endpoints were not adjusted for multiplicity and at an increased risk of type 1 error (false positive results).

Adults

The between-group difference in the co-primary endpoint of EASI75 at week 16 was 12.1% (95% CI, 6.5% to 17.7%; P < 0.001) in ECZTRA 1, and 21.6% (95% CI, 15.8% to 27.3%; P < 0.001) in ECZTRA 2, comparing tralokinumab Q2W with placebo; 20.2% (95% CI, 9.8% to 30.6%; P < 0.001) in ECZTRA 3 comparing tralokinumab Q2W+TCS with placebo+TCS; all of which were in favour of tralokinumab (or tralokinumab+TCS).

In ECZTRA 7, the between-group difference in the primary endpoint of EASI75 at week 16 was 14.1% (95% CI, 2.5% to 25.7%; P = 0.018), in favour of tralokinumab Q2W+TCS over placebo+TCS. The between-group difference in the secondary endpoint of EASI75 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 ECZTRA 1, 2, and 3, EASI90, EASI50, and change from baseline in EASI at week 16 were secondary endpoints. In ECZTRA 7, EASI90 at weeks 16 and 26 were exploratory endpoints; change from baseline in EASI at week 16 and week 26 were secondary endpoints. Results of these outcomes were in favour of tralokinumab (or tralokinumab+TCS); however, they were not adjusted for multiplicity and at an increased risk of type 1 error (false positive results).

Scoring Atopic Dermatitis (SCORAD)

Adolescents (12 to <18 years)

In ECZTRA 6, the between-group difference in the key secondary endpoint 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 Q2W over placebo. 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 endpoint of adjusted mean change from baseline in SCORAD at week 16 was -10.4% (95% CI, -14.4% to -6.5%; P<0.001) ECZTRA 1, and -14.0% (95% CI, -18.0% to -10.1%; P<0.001) in ECZTRA 2, comparing tralokinumab Q2W with placebo; and -10.9% (95% CI, -15.2% to -6.6%; P < 0.001) in ECZTRA 3 comparing between tralokinumab Q2W+TCS with placebo+TCS; all of which were in favour of tralokinumab (or tralokinumab+TCS). Results of the secondary (treatment policy) and tertiary (composite) estimands were consistent with the primary (hypothetical) estimand.

In ECZTRA 7, the between-group difference in the secondary endpoint 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 comparing tralokinumab Q2W+TCS with placebo+TCS. 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 endpoints were not tested for superiority due to prior failure in the testing hierarchy.

Worst Daily Pruritis Numeric Rating System (NRS) / Adolescent Worst Pruritis NRS

Adolescents (12 to <18 years)

In ECZTRA 6, the between-group difference in the key secondary endpoint of proportion of patients with at least 4 points of reduction in Adolescent Worst Pruritus NRS at week 16 was 21.7% (95% CI, 12.3% to 31.1%; P < 0.001), in favour of tralokinumab 300 mg Q2W over placebo.

Results of the responder analysis based on a 3-point reduction threshold (secondary endpoint) also showed results in favour of tralokinumab. The between-group difference with respect to the secondary endpoint of adjusted mean change from baseline in Adolescent Worst Pruritus NRS at week 16 was -1.5 (95% CI, -2.4 to -0.6). Both endpoints were not adjusted for multiplicity and at increased risk of type 1 error (false positive results).

Adults

The between-group difference in the key secondary endpoint of proportion of patients with at least 4 points of reduction in Worst Pruritus NRS at week 16 was 9.7% (95% CI, 4.4% to 15.0%; P = 0.002) in ECZTRA 1, and 15.6% (95% CI, 10.3% to 20.9%; P < 0.001) in ECZTRA 2, comparing tralokinumab Q2W with placebo; and 11.3% (95% CI, 0.9% to 21.6%; P = 0.037) in ECZTRA 3 comparing between tralokinumab Q2W+TCS with placebo+TCS; all of which were in favour of tralokinumab (or tralokinumab+TCS). Results of the responder analysis based on a 3-point reduction threshold (secondary endpoint) also showed results in favour of tralokinumab (or tralokinumab+TCS); however, this endpoint was not adjusted for multiplicity and at increased risk of false positive results.

In ECZTRA 7, proportion of patients with at least 4 points of reduction in Worst Pruritus NRS at week 16 and at week 26 were secondary endpoints. 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 Q2W+TCS and placebo+TCS. 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 endpoint of adjusted mean change from baseline in Worst Pruritus NRS at week 16 was -0.9 (95% CI, -1.4 to -0.4) in ECZTRA 1, and -1.3 (95% CI, -1.7 to -0.8) in ECZTRA 2, comparing tralokinumab with placebo; and -1.2 (95% CI, -1.7 to -0.7) in ECZTRA 3 comparing between tralokinumab Q2W+TCS and placebo+TCS. In ECZTRA 7, the between-group difference (exploratory endpoint) 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,

comparing tralokinumab Q2W+TCS with placebo+TCS. These endpoints were not adjusted for multiplicity and at increased risk of type 1 error (false positive results).

Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (CDLQI)

Adolescents (12 to <18 years)

In ECZTRA 6, the between-group difference in the key secondary endpoint of adjusted mean change from baseline in CDLQI at week 16 was -2.6 (95%CI, -4.5 to -0.7; P=0.007), in favour of tralokinumab 300 mg Q2W over placebo. Results of the secondary (treatment policy) and tertiary estimands (composite) were consistent with the primary (hypothetical) estimand.

Results of the responder analysis of proportion of patients with at least 6 points reduction in CDLQI from baseline at week 16 (secondary endpoint) were in favour of tralokinumab; however, this endpoint was not adjusted for multiplicity and at increased risk of type 1 error (false positive results).

Adults

The between-group difference in the key secondary endpoint of change from baseline in DLQI at week 16 was -2.1 (95% CI, -3.4 to -0.8; P = 0.002) ECZTRA 1, and -3.9 (-5.2 to -2.6; P < 0.001) in ECZTRA 2, comparing tralokinumab Q2W with placebo; and -2.9 (95% CI, -4.3 to -1.6; P < 0.001) in ECZTRA 3 comparing between tralokinumab Q2W+TCS with placebo+TCS; all of which were in favour of tralokinumab (or tralokinumab+TCS). Results of the composite estimand were consistent with the primary (hypothetical) estimand.

In ECZTRA 7, change from baseline in DLQI at weeks 16 and 26 were secondary endpoints. The between-group difference at week 16 was -1.5 (95% CI, -2.6 to -0.4). 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). Results of composite estimand were consistent with the primary estimand. Both endpoints were not tested for superiority due to prior failure of the testing hierarchy.

Proportion of patients with at least 4 points reduction in DLQI from baseline was a secondary endpoint (at week 16) in ECZTRA 1, 2, and 3, and an exploratory endpoint in ECZTRA 7. Results were in favour of tralokinumab (or tralokinumab+TCS) in ECZTRA 1, 2, and 3 [redacted]. These endpoints were not adjusted for multiplicity.

Other Efficacy Endpoints

Adolescents (12 to <18 years)

In ECZTRA 6, results of change from baseline in Eczema-related Sleep NRS (exploratory endpoint), Patient Oriented Eczema Measure (POEM; secondary endpoint), and Hospital Anxiety and Depression Scale (HADS) anxiety scores (exploratory endpoint) at week 16 were in favour of tralokinumab 300 mg Q2W over placebo; however, these endpoints were not adjusted for multiplicity and at increased risk of false positive results.

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

Use of TCS and number of days without topical treatment were not assessed in ECZTRA 6.

Adults

Results of change from baseline in Eczema-related Sleep NRS and POEM (exploratory endpoints) were in favour of tralokinumab (or tralokinumab+TCS) across the ECZTRA 1, 2, 3, and 7 trials; however, these endpoints were not adjusted for multiplicity and at increased risk of type 1 error (false positive results).

Results did not consistently suggest a difference between tralokinumab (or tralokinumab+TCS) and placebo (or placebo+TCS) across studies with respect to change from baseline in HADS anxiety and depression scores, proportion of patients with HADS

anxiety or HADS depression score of less than 8 (exploratory endpoints in ECZTRA 1, 2, 3, and 7), amount of TCS used, and number of days without topical treatment (secondary endpoints in ECZTRA 3; exploratory endpoints in ECZTRA 7). These endpoints were not adjusted for multiplicity.

Efficacy Results – Maintenance/Continuous Treatment Period

IGA score of 0 or 1 at week 52 (ECZTRA 1, 2, and 6) or week 32 (ECZTRA 3) among patients with IGA 0/1 at week 16

Adolescents (12 to < 18 years old)

In ECZTRA 6, the proportion of patients receiving tralokinumab 300 mg Q2W with IGA 0/1 at week 16 who maintained their IGA 0/1 response at week 52 was 37.5% (3 out of 8 patients, 95% CI, 13.7% to 69.4%) in the tralokinumab 300 mg Q2W/Q2W group, and 87.5% (7 out of 8 patients, 95% CI, 52.9% to 97.8%) in the tralokinumab 300 mg Q2W/Q4W group. No statistical analysis was conducted to assess the between-group difference.

Adults

In ECZTRA 1 and 2, the proportion of patients with IGA 0/1 at week 16 (without use of rescue medication) who maintained their IGA0/1 response (without use of rescue medication) at week 52 was included in the statistical hierarchy. In ECZTRA 1, the difference between the tralokinumab Q2W group and the placebo group was 6.0% (95% CI, -21.8% to 33.7%; P = 0.68). Due to failure of this endpoint, no superiority testing was conducted for the difference between the tralokinumab Q4W group and the placebo group (lower in the testing hierarchy), which was -9.5% (95% CI, -37.1% to 18.0%). In ECZTRA 2, the difference between the tralokinumab Q2W group and the placebo group was 34.1% (95% CI, 13.4% to 54.9%; P = 0.004). The difference between the tralokinumab Q4W group and the placebo group was 19.9% (95% CI, -1.2 to 40.9; P = 0.084); due to failure of this endpoint, no superiority testing was conducted for the endpoint lower in the testing hierarchy (i.e., EASI75 at week 52 between tralokinumab 300 mg every 4 weeks [Q4W] and placebo).

In ECZTRA 3, the proportion of patients with IGA 0/1 at week 16 who maintained their IGA0/1 response at week 32 was 89.6% (95% CI not reported) in the tralokinumab Q2W+TCS group and 77.6% (95% CI not reported) in the tralokinumab Q4W+TCS group. No statistical analysis was conducted to assess the between-group difference. This endpoint was not assessed in ECZTRA 7.

EASI75 at week 52 (ECZTRA 1, 2, and 6) or week 32 (ECZTRA 3) among patients with EASI75 at week 16

Adolescents (12 to <18 years)

In ECZTRA 6, the proportion of patients with EASI75 at week 16 (without use of rescue medication) who maintained their EASI75 response 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 Q2W/Q2W group, and 53.8% (7 out of 13 patients, 95% CI, 29.1% to 76.8%) in the tralokinumab 300 mg Q2W/Q4W group. No statistical analysis was conducted to assess the between-group difference on these endpoints.

Adults

In ECZTRA 1, the proportion of patients with EASI75 at week 16 (without use of rescue medication) who maintained their EASI75 response (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 0/1 at week 16 who maintained their IGA0/1 response at week 52). The difference between the tralokinumab Q2W group and the placebo group was 21.2% (95% CI, -0.2% to 42.6%). The difference between the tralokinumab Q4W group and the placebo group was 11.7% (95% CI, -8.7% to 32.0%).

In ECZTRA 2, the difference in proportion of patients with EASI75 at week 16 who maintained their EASI75 response at week 52 between tralokinumab 300 mg Q2W and placebo were 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 EASI75 at week 16 who maintained their EASI75 response at week 52 between tralokinumab 300 mg Q4W and placebo were not tested for superiority due to failure of a prior endpoint in the statistical testing hierarchy (i.e., IGA 0/1 at week 52 between tralokinumab 300 mg Q4W and placebo).

In ECZTRA 3, the proportion of patients with IGA 0/1 at week 16 who maintained their IGA0/1 response at week 32 was 92.5% (95% CI not reported) in the tralokinumab Q2W+TCS group and 90.8% (95% CI not reported) in the tralokinumab Q4W+TCS group. No statistical analysis was conducted to assess the between-group difference. This endpoint was not assessed in ECZTRA 7.

Harms Results – Initial Treatment Period

Treatment-emergent Adverse Event (TEAE)

In the initial treatment period of ECZTRA 1, 2, 3, 6 and 7, 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+TCS) and between 61.7% and 78.8% in the placebo group (or placebo+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 TEAE

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

Withdrawals due to adverse events

No treatment withdrawal due to AE or death was reported in adolescent patients. In ECZTRA 1, 2, 3, and 7, the proportion of adult patients who withdrew from treatment due to AE ranged between 0.7% and 3.3% in the tralokinumab (or tralokinumab 300 mg Q2W+TCS) group, and between 0.8% and 4.1% in the placebo (or placebo+TCS) group.

Mortality

Two deaths (related to unknown cause and myocardial infarction) were reported in the tralokinumab group in ECZTRA 1, and 1 death (related to metastatic squamous cell carcinoma) was reported in the tralokinumab group in ECZTRA 2. 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 the placebo group (1.5% to 4.4%) across the studies in adults.

Harms Results – Maintenance/Continuous Treatment Period

Results in the maintenance (or continuous) treatment period of ECZTRA 1, 2, and 3 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 ECZTRA 3 and 6, 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) 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 0/1, EASI75, reduction of at least 4 points in (Adolescent) Worst Daily Pruritus NRS from baseline, change from baseline in SCORAD and DLQI outcomes were controlled for multiplicity, while the other endpoints (secondary and exploratory) were not and were at an increased risk of type 1 error (false positive results). Continuous secondary and exploratory endpoints (change from baseline in EASI, POEM, Worst Daily Pruritus NRS, Eczema-related Sleep NRS, 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 0/1 and EASI75 outcomes were adjusted for multiplicity in the ECZTRA 1 and 2 trial; however, results were uncertain due to a sizable reduction in sample sizes, wide CIs for IGA 0/1 and EASI75 outcomes, and inconsistent results between ECZTRA 1 and 2.

The study population of the ECZTRA 7 trial (i.e., adults who had failed or 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 who failed who had failed topical therapy only. The study interventions of ECZTRA 3 and 7 (i.e., tralokinumab in combination with TCS) were also more reflective of the real-world use of tralokinumab compared with ECZTRA 1, 2, and 6 (i.e., tralokinumab monotherapy) based on clinical expert input that patients typically use biologics in combination with TCS for active lesions. The clinical relevance of SCORAD, POEM, HADS 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, since most patients would require at least 6 months of tralokinumab treatment to achieve optimal response in their clinical experience. Results of the maintenance treatment period (up to 52 weeks) are likely more generalizable but inconclusive due to 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, long-term extension (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., ECZTRA 1 to 8 and TraSki). Patients were eligible to participate in ECZTEND if they had completed the treatment period(s) 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 as per the product monograph by self-injection. Patients were permitted to use concomitant TCS or topical calcineurin inhibitors (TCI) and were required to use an emollient at least twice daily for at least 14 days prior to ECZTEND baseline and continue 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 (LOCF) or modified non-responder imputation (mNRI) 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 adult cohort for the reported interim analyses were April 30, 2021 (all participants from ECZTRA 1, 2, 3, 4, 5, and 7 enrolled in ECZTEND, n = 1,442, up to 3.5 years of follow-up; 3-year subgroup containing participants from ECZTRA 1 and 2, n = 347) and April 30, 2022 (4-year subgroup containing participants from ECZTRA 1 and 2, n = 347). The data cut-off date for adolescent cohort was April 30, 2022 (participants from ECZTRA 6, up to 3 years of follow-up, n = 127).

Efficacy Results

EASI-75

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

IGA 0/1

IGA 0/1 was achieved in 50.5% (244 of 483 patients, observed data) of patients at Week 104 in ECZTEND (i.e., up to 3 years of cumulative exposure to tralokinumab in the parent trials and ECZTEND) in the all participant adult cohort; in 52.6% (92 of 175 patients, observed data) of patients at Week 152 in ECZTEND in the 4-year adult subgroup; and in 61.5% (67 of 109 patients, observed data) of patients at Week 56 in ECZTEND (i.e., 2 years of cumulative exposure to tralokinumab in the parent trials and

ECZTEND) in the adolescent cohort. 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 (78.2%) patients experienced at least 1 TEAE. In the 3-year adult subgroup (n = 347), 295 (85.0%) patients experienced at least 1 TEAE. In adolescent cohort (n = 127), 83 (65.4%) patients 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 an SAE in these cohorts. Conjunctivitis was reported in 77 (5.3%) and 7 (3.6%) patients 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 cohorts. However, 1 death (0.8%) due to accident occurred in the adolescent cohort.

Critical Appraisal

Similar to other long-term extension studies, in ECZTEND, it is uncertain if the long-term effects observed could be attributed to tralokinumab treatment due to 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 transfer to the extension study. Similarly, long-term safety concerns may be underestimated since 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), 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 one of the parent trials regardless of treatment response. This is different from clinical practice where patients are expected to continue tralokinumab treatment only if they could demonstrate objective improvement of disease after an adequate trial of treatment. It is unclear what proportion of patients enrolled into the ECZTEND trial was a non-responder 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 since it is unclear what proportion of patients had prior failure of immunosuppressant therapy, which is the likely place in therapy of tralokinumab. Further, the use of concomitant TCS and rescue medications could influence treatment response; however, utilization of such medications was not reported in the study and the impact on generalizability of 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 indirect treatment comparisons (ITCs) indirectly comparing the treatment effect of tralokinumab to other treatment in patients with moderate-to-severe atopic dermatitis. Of the ITCs submitted, 2 were network meta-analysis (NMAs; one in adults and one in adolescents) and 2 were matching-adjusted indirect comparisons (MAICs; both in adults).

Network Meta-analyses

Description of studies

The sponsor submitted a 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 adult patients 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

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 since the treatment is currently not approved for use in Canada.

EASI-50

Adult Population (ICER NMA)

The treatment response to all included monotherapy interventions on the EASI-50 in adult patients 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 adult patients were favoured over placebo. Treatments 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 (LEO Pharma NMA)

[redacted]

EASI-75

Adult Population (ICER NMA)

The treatment response of all included monotherapy interventions on the EASI-75 in adult patients were favoured over placebo. Treatments 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 adult patients were favoured over placebo. Treatments 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 (LEO Pharma NMA)

[redacted]

EASI-90

Adult Population (ICER NMA)

The treatment response of all included monotherapy interventions on the EASI-90 in adult patients were favoured over placebo. Treatments 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 Q2W (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 adult patients were favoured over placebo. Treatments 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 (LEO Pharma NMA)

[redacted]

IGA

Adult Population (ICER NMA)

The treatment response of all included monotherapy interventions on the IGA in adult patients were favoured over placebo. Treatments 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 0/1 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 adult patients receiving monotherapy for AD.

The treatment response of all included combination interventions on the IGA in adult patients were favoured over placebo. Treatments 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 0/1compared to tralokinumab 300 mg.

Adolescent Population (LEO Pharma NMA)

[redacted]

PP-NRS ≥ 4 Point Improvement

Adult Population (ICER NMA)

The treatment response of all included monotherapy interventions on PP-NRS ≥ 4-point improvement in adult patients were favoured over placebo. Treatments 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 PP-NRS ≥ 4-point improvement compared to tralokinumab 300 mg. The CrIs for the remaining comparisons were too wide to draw any conclusions of certainty in PP-NRS ≥ 4-point improvement between tralokinumab and other active comparators among adult patients.

The treatment response of all included combination therapy interventions on PP-NRS ≥ 4-point improvement in adult patients were favoured over placebo. Treatments 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 PP-NRS ≥ 4-point improvement compared to tralokinumab 300 mg. The point estimate for PP-NRS ≥ 4-point improvement 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 (LEO Pharma NMA)

[redacted]

CDLQI

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

[redacted]

POEMS

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

[redacted]

Harms Results

Adverse Events

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

[redacted]

Critical Appraisal

ICER NMA

The ICER NMA was based on studies identified from a systematic literature review of relevant randomized evidence of treatments for adults and adolescent with AD. The systematic literature search was based on a PICO defined a priori, 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 heterogeneity were identified which challenged the plausibility of the underlying transitivity assumption. These included variation in: patient age, duration of disease, disease severity, length of the washout period, timepoint of follow-up (12-16 weeks), methods of imputation for missing data. To account for differences in corticosteroids use across trials, separate NMAs were conducted for monotherapy and combination therapies. However, the treatment of patients in the control group (placebo + 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 three arm trials. Harms outcomes were not evaluated.

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 adolescent patients. The systematic literature search was based on a PICO defined a priori, 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: timepoint of follow-up, the pre-

determined duration of AD for study inclusion, exclusion criterion related to prior use of biologics, and protocol use for, 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 (ECZTRA 3) administered every two week (Q2W) and 300 mg every 4 weeks (Q4W) against dupilumab (LIBERTY AD CHRONOS) Q2W at 32 to 52 weeks of follow-up in adult patients with moderate-to-severe AD.

Efficacy Results

ECZTRA 7 vs. LIBERTY AD CAFÉ

[redacted]

ECZTRA 3 vs. LIBERTY AD CHRONOS

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

The results of the ECZTRA 3 vs. LIBERTY AD CHRONOS unanchored efficacy MAIC analysis between tralokinumab and dupilumab was in favour of tralokinumab for IGA score 0/1 (Risk Difference [RD], 13.9; 95% CI, 0.6 to 27.3) and change in DLQI (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 0/1; at week 52: percent change in EASI, change in worse daily pruritis NRS, percent change in SCORAD, change in POEM; at week 52 EASI-75, EASI-50, EASI-90, worst daily pruritis NRS improvement of at least 4 points, POEM improvement of at least 4 points, DLQI improvement of at least 4 points)

Harms Results

[redacted]

No harms endpoints were evaluated in the ECZTRA 3 vs. LIBERTY AD CHRONOS MAIC.

Critical Appraisal

ECZTRA 7 vs. LIBERTY AD CAFÉ

The comparison of ECZTRA 7 vs. LIBERTY AD CAFÉ was chosen after a review of [redacted] 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 [redacted] 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 post-matching 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 [redacted], in which [redacted] of enrolled patients in ECZTRA 7 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 CI favouring dupilumab. There was no assessment of residual confounding in the analysis.

ECZTRA 3 vs. CHRONOS

The ECZTRA 3 vs. CHRONOS MAIC lacked description of a literature search or selection criteria, or any indication of the trials were selected for the MAIC. There was also a lack of transparency in the data extraction process and quality assessment. Although both ECZTRA 3 and LIBERTY AD CHRONOS included a placebo, an unanchored MAIC was conducted. The choice to conduct an unanchored MAIC was appropriately justified due to difference in trial design (re-randomized vs. treat-through) that may have resulted in differences in treatment of placebo across ECZTRA 3 and LIBERTY AD CHRONOS. Nonetheless, the ECZTRA 3 vs. LIBERTY AD CHRONOS MAIC was limited by heterogeneity between the dupilumab target population and the analysis set. First, the dupilumab target population in LIBERTY AD CHRONOS was not the same analysis set for 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, 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 timepoint is uncertain. Although, input from the clinical experts suggests that better results are expected for tralokinumab at week 52 versus week 32, and therefore, analysis may be at risk of bias in favour of treatment with dupilumab. Unadjusted and match-adjusted baseline covariates were reported. Baseline characteristics post-matching 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 ECZTRA 3 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 gaps in evidence. 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 adult patients who had previously failed dupilumab. Pereyra-Rodriguez et al. (N = 85) was retrospective, 16-week study conducted in Spain. This study assessed 85 adult patients, including those who had previously been treated with either dupilumab (29.4%) or upadacitinib (8.2%). These 2 studies also assessed 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 adult patients 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 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 (55.3%) patients with IGA score of 4. At the end of follow-up period, 18.8% (absolute number of patients was not reported) of patients had IGA 0/1.

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 naïve to advanced therapy with no prior eye-related adverse events. Moreover, 3 (3.5%) patients experienced worsening and generalized AD lesions, 2 (2.4%) patients developed reaction at the injection site, and 2 (2.4%) patients 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 due to 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; non-comparative 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 Pereyra-Rodriguez et al. which results in an increased risk of false-positive results. The duration 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 adolescent patients; therefore, the treatment effects in adolescents who had prior dupilumab and/or JAK inhibitor 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/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 be ineligible for each of the following therapies: 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)
Key data sources	ECZTRA 1, 2, and 3 for tralokinumab inputs; 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 versus comparators after week 16 is highly uncertain owing to a lack of direct or indirect comparative assessment, with naïve 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 0/1 was more often used in practice. • Maintenance dosing after week 16 for tralokinumab is highly uncertain. The sponsor assumed that [redacted] of responders on tralokinumab would switch from every 2 week to every 4 week (Q2W to Q4W) 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. Non-responders on biologic or JAK inhibitor treatments were expected to receive a utility benefit that was similar to that of responders for the 52-week induction period despite discontinuing treatment and not incurring treatment costs. • The expected proportion of patients on the higher dose of JAK inhibitors was underestimated. • Subsequent treatment after failing initial treatment 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 12-17), this analysis was also associated with substantial uncertainty due to limitations with the submitted

Component	Description
	indirect evidence, and it relied on several key inputs from adults. Therefore the cost-effectiveness of tralokinumab in adolescent patients 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 responders on tralokinumab switching to Q4W dosing after week 16; revised health state utility values; and, updated the proportion of patients on the high dose of JAK inhibitor 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 long-term comparative efficacy and drug acquisition costs of tralokinumab related to Q4W dosing.

AD = atopic dermatitis; BSC = best supportive care; EASI = Eczema Area and Severity Index; ICER = incremental cost-effectiveness ratio; IGA = Investigator's Global Assessment; JAK = Janus kinase; LY = life-year; NMA = network meta-analysis; QALY= quality-adjusted life-year; Q2W = every two weeks; Q4W = every four weeks.

Budget Impact

CADTH identified the following key limitations with the sponsors analysis: there was uncertainty surrounding the proportion of responders who would switch from Q2W dosing to Q4W maintenance dosing after 16 weeks, particularly given the sponsor's model did not account for non-responders 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 on high dose JAK inhibitors was likely underestimated. The CADTH reanalysis included restricting the proportion of patients switching to Q4W dosing after 16 weeks, adjusting market shares of tralokinumab and JAK inhibitors, and adjusting the proportion of patients on high dose of JAK inhibitors. CADTH's reanalysis found that funding tralokinumab for patients 12 and older with atopic dermatitis 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 Q4W maintenance dosing and the projected market shares of tralokinumab.

CDEC Information

Members of the Committee:

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.

Meeting date: October 25, 2023

Regrets:

Two expert committee members did not attend

Conflicts of interest:

None