Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Lebrikizumab (Ebglyss)

Indication: For the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab can be used with or without topical corticosteroids.

Sponsor: Eli Lilly Canada Inc.

Recommendation: Do Not Reimburse

Version: 1.0
Publication Date: July 2024
Report Length: 27 Pages

Single Technology

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 Canadian Drug Expert Committee (CDEC) recommends that lebrikizumab not be reimbursed for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg, 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 lebrikizumab would adequately meet this need due to the lack of comparative evidence as well as uncertainty about the place in therapy.

Three phase III randomized controlled trials (RCTs; ADvocate 1, N = 424; ADvocate 2, N = 427; ADhere, N = 211) in adults and adolescents with moderate to severe AD that was not adequately controlled with topical therapies provided evidence of lebrikizumab compared to placebo. ADvocate 1, ADvocate 2, and ADhere demonstrated that lebrikizumab induction therapy (with or without topical corticosteroids [TCS]) provided a clinically relevant improvement in physician assessed Eczema Area and Severity Index (EASI) and Investigator Global Assessment (IGA), and reduced patient-reported symptoms of itch relative to placebo at 16 weeks.

Dupilumab, upadacitinib, and abrocitinib were identified as comparators of interest for lebrikizumab. There was no direct evidence comparing lebrikizumab to other biologics or Janus kinase (JAK) inhibitors used to treat AD; however, one network meta-analysis (NMA) provided indirect evidence for the comparisons of interest. There was insufficient evidence to suggest a benefit with lebrikizumab relative to dupilumab and abrocitinib, with most estimates affected by serious imprecision. The NMA does suggest upadacitinib may be favoured over lebrikizumab for the proportion of patients with an EASI or Pruritus numeric rating scale (NRS) response, although differences were not consistently detected, and the clinical relevance of any differences is unclear.

The NMA did not assess any safety endpoints thus the comparative safety of lebrikizumab is unknown. The clinical trial evidence suggests lebrikizumab may increase the short-term risk of conjunctivitis relative to placebo. The longer-term safety and efficacy of lebrikizumab from the RCTs and extension study is uncertain due to limitations with the data which included an enriched population and carry-over effects for the 52-week data in the pivotal trials, and the lack of comparator group for the extension study.

Patient input received for this review identified a need for additional treatments for 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. Additional treatment options for patients who are refractory to or do not tolerate current biologic therapy, or who are concerned about the safety profile of JAK inhibitors, are also needed. Based on the evidence reviewed, CDEC could not determine whether lebrikizumab would adequately meet this need due to the uncertainty around the benefit of lebrikizumab versus appropriate comparators and in patients who received prior dupilumab or JAK inhibitor treatment.

Discussion Points

- Although CDEC recognized the value that both patients and clinicians place in having a choice of treatment options, the absence of comparative safety data as well as HRQoL outcomes preclude assessment of all factors necessary to balance all outcomes and unmet needs (including improved safety). Thus, place in therapy and sequence of using lebrikizumab as first-, second- or subsequent-line therapy is difficult to define.
- CDEC noted that lebrikizumab (with or without TCS) appears more efficacious than placebo in important EASI and IGA endpoints as well as patient reported Pruritis NRS for itch. There was no evidence to suggest lebrikizumab offered a benefit over other immunomodulator therapies, biologics or JAK inhibitors. The committee discussed the use of lebrikizumab in patients who are refractory to or do not tolerate current biologic therapy, which was identified as an unmet need by patients. Although some patients had exposure to other systemic therapies, the study populations were not required to have failed or experience intolerance to other immunomodulator therapies, biologics or JAK inhibitors, which is the population identified as having an unmet need. Therefore, whether treatment with lebrikizumab is an effective treatment for patients who had prior failure of treatment with dupilumab or a JAK inhibitor (i.e. as a second- or subsequent-line therapy) remains uncertain.

- CDEC discussed the CADTH GRADE assessment of outcomes selected for the review of lebrikizumab. The GRADE assessment applied to relevant outcomes included in placebo-controlled ADvocate 1, ADvocate 2, and ADhere trials, which demonstrated that lebrikizumab (with or without TCS) increased the proportion of patients with an IGA 0 or 1 response, EASI 75 response, or at least a 4-point improvement in the Pruritus NRS, relative to placebo with moderate to high certainty. The treatment effects for all 3 outcomes were considered clinically relevant; however, was based on clinical expert input and therefore is subject to some uncertainty. Also of note, outcomes related to HRQoL and safety, both of which were identified as outcomes that are important to patients, were assessed as having low to very low certainty.
- CDEC discussed the uncertainty of the comparative efficacy of lebrikizumab to dupilumab, upadacitinib and abrocitinib due to absence of direct comparative evidence. Although subject to limitations, the NMA signals that there may be differences in some outcomes, such as EASI response at week 16 and Pruritus/Itch NRS response at week 16, that suggests lebrikizumab may not be as effective as upadacitinib and abrocitinib.

Background

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory and non-contagious skin disease, which is commonly associated with other atopic expressions such as asthma, allergic rhinitis, and food allergy. The burden of disease and its impact on quality of life may be profound, particularly in case of moderate to severe AD. Itch or pruritus; soreness, pain, or tenderness; and skin dryness were the signs and symptoms that were most frequently cited as having a clinical impact. Itch is the major symptom which has negative impact on quality of life and is associated with mental distress and increased risk for suicidal thoughts. Depression, anxiety, and sleep disturbance are frequently reported comorbidities. Moreover, AD can result in embarrassment from appearance, and negative impact on self-esteem, and social life. Patients with AD are at an increased risk of skin infections because of excessive rubbing or scratching. Exacerbations or 'flares' are an integral part of the disease course and generally indicate a worsening of AD that requires escalation or intensification of treatment.

AD impacts approximately 15% to 20% of children and 1% to 3% of adults worldwide, and in high-income countries, AD affects around 20% of children, and up to 10% of adults. Most of the adult patients with AD have mild disease, and approximately 50% have moderate to severe disease based on clinical disease severity scales.

Initial treatment for most patients with AD is emollients (moisturizers) plus topical anti-inflammatory therapy, including topical corticosteroids (TCS) and topical calcineurin inhibitors. For patients with more severe AD or with AD that is refractory to topical therapy, advanced treatments including phototherapy and systemic treatment are considered. According to the American Academy of Dermatology and American Academy of Allergy, Asthma and Immunology clinical practice guidelines, biologics, and particularly dupilumab, are considered first line systemic therapy. Other options include tralokinumab (another biologic) and oral Janus kinase (JAK) inhibitors (upadacitinib, abrocitinib). According to the clinical expert consulted, off-label immunomodulators (cyclosporine, methotrexate, mycophenolate and azathioprine) are generally only used when mandated by a medication payer as step-through therapy or if the previously mentioned biologics and JAK inhibitors fail or are contraindicated. These drugs were not listed as first line systemic therapies in the 2023 American Academy of Dermatology clinical practice guidelines due to their lower certainty of evidence relative to newer drugs, the potential for serious adverse events (SAEs), the need for stringent laboratory monitoring, and lack of regulatory approval for use in AD.

Lebrikizumab is was approved by Health Canada for the treatment of moderate-to-severe AD in adults and adolescents 12 years of age and older with a body weight of at least 40 kg, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab can be used with or without topical corticosteroids. Lebrikizumab is available as a 250 mg per 2 mL solution in a prefilled pen or prefilled syringe with needle shield for subcutaneous (SC) injection. The recommended initial dose is 500 mg (two 250 mg injections) at week 0 and week 2, followed by 250 mg (one injection) every two weeks until week 16. Once clinical response is achieved, the recommended maintenance dose is 250 mg every 4 weeks starting at week 16. The product monograph states that continued therapy beyond 16 weeks should be carefully considered in a patient who does not show treatment benefit in this time period.

Sources of Information Used by the Committee

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

- a review of 3 randomized controlled trials (RCTs) in adults and adolescents with moderate to severe AD
- patients' perspectives gathered by patient groups, Eczema Quebec, Canadian Skin Patient Alliance and the Eczema Society of Canada
- input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with moderate to severe AD
- input from 2 clinician groups, including the Canadian Dermatology Association (CDA) and the Dermatology Association of Ontario (DAO)
- supporting evidence from 1 long-term extension study, and 4 other clinical trials addressing gaps in the systematic review evidence
- appraisal of a sponsor submitted network meta-analysis (NMA)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Three patient groups provided input to this submission. Eczema Quebec gathered information through review of scientific literature, informal conversations with patients, 'The Skin I'm In, 2022 Update' (a joint report by Eczema Quebec and Canadian Skin Patient Alliance [CSPA]), expert opinion from McGill University Health Centre's Center of Excellence for Atopic Dermatitis, 9 written patient testimonials, interviews with 14 patients and feedback from 3 patient group discussions. The CSPA gathered information from previous submissions to CADTH, data from the Canadian Institute for Health Information on AD-related emergency room (ER) visits, and hospitalizations from 2016 to 2020 as reported in the "The Skin I'm In" report, and guidelines. Eczema Society of Canada (ESC) gathered information through a survey, and one-on-one interviews from more than 3000 patients with AD and their caregivers who live in Canada.

According to the input from patient groups, symptoms of patients with AD include inflamed, painful, dry, and itchy skin that cracks, oozes, bleeds and in some cases involves thickening and/or infections of the skin. Conditions associated with AD include asthma, seasonal and environmental allergies, food intolerances, sleep disorders, anxiety, and depression. Patient groups stated that physical manifestations and visibility of the disease contribute to psychological distress through stigmatization which impacts self-esteem, professional commitments, and social engagements.

Based on patient groups input the burden of AD also extends to caregivers and family members. Caregivers reported feelings of anxiety, depression, helplessness, guilt, frustration, and a lack of control over the situation. Caregivers and family members also shared that their own health and emotional wellness, lifestyle, sleep, intimacy, social activities, and family dynamics were affected by the disease. Further, the cost of treatment and other skincare products can place financial stress not only on the patients but also on the family.

Important desired outcomes reported by patient groups included: better, fast and long-term control of the disease, reduction of flares, relief from itch, reduction of skin symptoms, pain and discomfort relief, improved psychological status, improved daily and social activities, increased productivity, improved emotional well-being, improved sleep quality, maintained intimate relationships, treatments covered by insurance or to be affordable, and treatments that are easy to use (i.e. those that are not administered by injection or topically).

Access to healthcare presents another challenge to patients with AD, with Canada's low ratio of dermatologists to the population, making specialized care difficult to obtain, particularly in remote areas. Additionally, 36% of caregivers reported feeling a lack of support from the health care system and 30% reported financial challenges related to managing their child's disease.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical expert consulted for this review, there is an unmet need for more treatment options for people who are refractory to or do not tolerate current biologic treatments for AD, as well as for people who are concerned about the safety profile of oral JAK inhibitors, particularly people with comorbidities and who are older.

Patients with moderate-severe AD refractory to topical therapy are most likely to respond to treatment with lebrikizumab, according to the clinical expert. The clinical expert anticipates lebrikizumab's use will be similar to other systemic medications with concomitant use of emollients and topical anti-inflammatory treatments (e.g., corticosteroids). Given the clinical experience with, and evidence supporting the use of dupilumab, the expert anticipated that lebrikizumab would be considered a second line biologic after dupilumab, and it may be chosen for patients for whom dupilumab is contraindicated, ineffective or not tolerated.

In clinical practice, the clinical expert stated that clinicians generally use a gestalt assessment of improvement in clinical signs and patients' history of change in symptoms (e.g., itch) and quality of life. Clinicians only use the tools used in clinical trials (e.g., EASI score) if mandated by a medication payer to obtain coverage. According to the clinical expert, a meaningful response to treatment would be an approximately 50% to 75% improvement in signs and symptoms; the specific proportion likely differs by clinician and by patient. The improvement should include a reduction in the severity and frequency of symptoms and is often accompanied by an improvement in quality of life and ability to perform household and work or school activities. A reduction in skin infections and disease flares are also important.

The clinical expert indicated that lebrikizumab would be discontinued if it is inadequately effective, if the patient experiences intolerable adverse effects, or the patient wishes to interrupt or discontinue therapy. The clinical expert noted that in most instances, a specialist (dermatologist, allergist, pediatrician) would be required to treat AD with a biologic, although in areas where access to specialty care is difficult, some family physicians could gain comfort with biologics for AD.

Clinician Group Input

CADTH received inputs from 2 clinician groups for this review. The Canadian Dermatology Association (CDA) submitted input from 3 clinicians from their Pharmacy and Therapeutics Advisory Board, and the Dermatology Association of Ontario (DAO) submission included input from 11 clinicians.

Clinician groups and the clinical expert consulted by CADTH agreed that lack of adequate response to treatment, incomplete effectiveness, adverse effects of treatments, lack of feasibility of some of treatments, and relapses are unmet needs of patients with AD. One of the clinician groups added that challenges in access to care, multi-tiered treatment regimens, treatment intolerance or contraindications, and co-morbid bacterial skin infections are unmet needs as well.

The CDA and the clinical expert consulted by CADTH agreed that the goals of treatment are improving quality of life and maximizing efficacy and safety. Regarding the place of lebrikizumab in therapy, the DAO and the clinical expert consulted by CADTH believe that lebrikizumab will not cause a shift in treatment paradigm and would be considered another treatment option. The CDA stated lebrikizumab contributes to an important shift in the current treatment paradigm towards a new era of focus on novel disease mechanism targeting and disease modification with favourable safety and efficacy profiles.

According to the DAO adult patients with moderate to severe AD who have failed topical therapies and those that have failed or do not have access to phototherapy would be best suited for the treatment with lebrikizumab. The CDA stated that patients best suited for treatment with lebrikizumab would be those with uncontrolled moderate to severe AD who are candidates for systemic therapy or meet criteria for biologic therapy. The CDA noted that dupilumab is indicated for patients with other severe forms of atopic or allergic conditions such as severe asthma or eosinophilic esophagitis, thus dupilumab may be chosen for these patients instead of the IL-13 inhibitors, such as lebrikizumab, which are not approved for use in these conditions.

The DAO noted that a patient's response to treatment would be assessed via IGA, EASI, Pruritus NRS, and DLQI score systems at 4 to 6 months and then annually thereafter. The CDA stated that assessment of patient's response would be based on clinical exam, patient's history, physician-reported clinical scoring systems (EASI, body surface area [BSA], IGA,) and patient reported outcomes (DLQI, children's DLQI, and Pruritus NRS). The CDA added that in clinical practice, due to time limitations, only some of the scoring systems are used.

Clinician groups reported adverse events and poor efficacy of treatment as factors that should be considered when deciding to discontinue the treatment.

Based on clinician groups input, treatment and monitoring of patients on lebrikizumab should be limited to specialists trained in this area which would include dermatology, allergy, immunology or pediatrics.

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 lebrikizumab:

- considerations for relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation 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

Systematic Review

Description of Studies

Three double-blind randomized controlled trials (RCTs) met the inclusion criteria for systematic review (ADvocate 1, ADvocate 2 and ADhere studies). The objective of ADvocate 1 (N = 424) and ADvocate 2 (N = 427) studies were to evaluate the safety and efficacy of lebrikizumab as monotherapy in patients with moderate-to-severe AD. Eligible patients were adults or adolescents (aged 12 years to less than 18 years and weighing more than 40 kg) who had a diagnosis of chronic AD that was rated as moderate to severe based on Eczema Area and Severity Index [EASI] score of at least 16, Investigator Global Assessment (IGA) score of at least 3, and AD covering a body surface area (BSA) of 10% or more. All patients had history of inadequate response to topical therapies for AD. Both studies included a 16-week induction period (parallel design), followed by a 36-week maintenance period (randomized withdrawal design). The studies randomized patients in a ratio of 2:1 to receive double blind lebrikizumab 500 mg SC loading dose at week 0 and 2, and then 250 mg SC every 2 weeks or placebo for the 16-week induction period. At week 16, patients in the lebrikizumab group who responded to treatment (i.e., with an IGA score 0 or 1 or at least a 75% reduction in Eczema Area and Severity Index [EASI 75], and who did not receive rescue therapy) were randomly reassigned in a ratio of 2:2:1 to double-blind lebrikizumab 250 mg every 2 weeks., lebrikizumab 250 mg every 4 weeks or placebo for the 36-week maintenance period.

The objective of the ADhere study was to evaluate the safety and efficacy of the lebrikizumab in combination with low to mid-potency TCS, compared with placebo plus TCS in patients with moderate-to-severe AD. The study was a 16-week randomized, double-blind, parallel design trial (N = 211). Adults or adolescents (aged 12 years to less than 18 years weighing more than 40 kg) with moderate-to-severe AD (EASI ≥ 16, IGA score ≥3, AD covered a BSA of 10% or more) were eligible to enroll. Patients were randomized 2:1 to

receive 500 mg lebrikizumab SC loading dose at week 0 and 2 then 250 mg SC once every 2 weeks in addition to TCS, or placebo plus TCS for the 16-week treatment period.

In all trials the co-primary outcomes were the proportion of patients with an IGA score of 0 or 1 and at least a 2-point reduction from baseline to week 16, and the proportion of patients with an EASI 75 response at week 16. The IGA measures the investigator's global assessment of the patient's overall severity of AD at that visit, based on a static, numeric 5-point scale ranging from 0 (clear) to 4 (severe). The EASI is a composite index, based on the physician's assessment of 4 clinical signs of the disease (erythema, infiltration and/or papulation, excoriation and lichenification) and the extent of body surface area involved at that visit. It is scored from 0 to 72 with higher scores indicating greater disease severity and/or extent of disease. Other key outcomes reported were the proportion of patients with a Pruritus Numeric Rating Scale (NRS) score of at least 4 points at baseline who reported a at least a 4-point reduction from baseline at week 16, and the change from baseline to week 16 in the Patient Oriented Eczema Measure (POEM) score, the Dermatology Life Quality Index (DLQI) total score or the Children's Dermatology Life Quality Index (CDLQI) total score.

The patients enrolled in the trials had a mean age that ranged from 34.2 years (standard deviation [SD] =16.4) to 37.5 years (SD = 19.9) per treatment group. In the ADvocate 1, ADvocate 2 and ADhere studies, 13%, 11% and 22% of patients, respectively, were adolescents. There were roughly equal proportions of females and males in the studies. On average, the patients enrolled in the study had been diagnosed with AD for 20 or more years, with most patients (59% to 73%) classified as having disease of moderate severity based on an IGA score of 3 at baseline, whereas 27% to 41% were classified as having severe AD (i.e., IGA score of 4). Almost all patients enrolled had previously used TCS (97% to 100%) and 33% to 46% of patients had received topical calcineurin inhibitors. Systemic therapies were previously received by 43% to 56% of patients, and 12% to 24% of patients had used phototherapy before enrollment in the trials.

Efficacy Results

Induction Period

At week 16, the proportion of patients with an IGA score of 0 or 1 and at least a 2-point reduction from baseline favoured the lebrikizumab groups versus the placebo groups in all 3 studies. For the ADvocate 1 study, 43.1% versus 12.7% of patients attained an IGA 0 or 1 response in the lebrikizumab and placebo groups, respectively, with a risk difference (RD) of 29.7% (95% confidence interval [CI], 21.6 to 37.8, p value < 0.001). In the ADvocate 2 study, 33.2% versus 10.8%, attained an IGA 0 or 1 response (RD 21.9% (95% CI, 14.2 to 29.6, p <0.001) for the lebrikizumab versus placebo groups. The IGA 0 or 1 response also favoured lebrikizumab + TCS versus placebo +TCS in the ADhere study (41.2% versus 22.1%, RD 18.3% [95% CI, 5.1 to 31.5], [redacted]).

In all 3 studies a higher proportion of patients reported an EASI 75 response at week 16 in the lebrikizumab versus placebo groups. EASI 75 response was attained by 58.8% versus 16.2% of patients in the lebrikizumab versus placebo groups, respectively, in the ADvocate 1 study (RD 42.0% [95% CI, 33.3 to 50.6], p < 0.001), and 52.1% versus 18.1% of patients (RD 33.3% [95% CI, 24.4 to 42.2], p <0.001) in the ADvocate 2 study. In the ADhere study, 69.5% versus 42.2% of patients, attained an EASI 75 response at week 16 (RD 26.4% [95% CI, 12.1 to 40.8], p <0.001) in the lebrikizumab + TCS and placebo + TCS groups, respectively.

The severity of itch was assessed using the Pruritus NRS score, where patients rated their worst itch symptoms over the past 24 hours from 0, indicating "No itch" to 10, indicating "Worst itch imaginable". Among patients who had a Pruritus NRS score of 4 or more points at baseline, 45.9% versus 13.0% in the lebrikizumab versus placebo groups, respectively, reported at least a 4-point reduction at week 16 in the ADvocate 1 study (RD 32.9% [95% CI, 24.6 to 41.3], p < 0.001). The proportion of Pruritus NRS responders was 39.8% versus 11.5% in the ADvocate 2 study (RD 28.3% [95% CI 20.0 to 36.5], p < 0.001), favouring lebrikizumab. In the lebrikizumab + TCS group in the ADhere study, 50.6% met the Pruritus NRS response criteria compared with 31.9% in the placebo + TCS group (RD 19.2%, [95% CI, 4.3 to 34.1], [redacted]).

A secondary outcome in the pivotal trials was the change from baseline in the POEM score, a 7-item, self-reported questionnaire used to assess the frequency of disease symptoms (skin dryness, itching, flaking, cracking, sleep-loss, bleeding, and weeping) over the last week. It is scored from 0 to 28, with a higher score indicative of worse disease severity. A minimal important difference (MID) of 3.4 points was identified as the threshold for a clinically relevant between-group difference. The ADvocate 1 study reported a LS mean difference of [redacted]) in the POEM score change from baseline to week 16, for lebrikizumab versus placebo. The

LS mean difference was [redacted] for the lebrikizumab versus placebo groups in the ADvocate 2 study, and the ADhere study reported a LS mean difference of [redacted] for the lebrikizumab + TCS versus placebo + TCS groups. Of note, this outcome was potentially biased due to the extent of missing data and the analysis methods used to handle missing data. Moreover, the change in POEM score was not part of the graphical testing strategy used to control the family-wise type I error rate and thus this outcome should be interpreted as supportive evidence only.

In the pivotal trials, the DLQI was used to measure health-related quality of life (HRQoL) in patients 17 years and older, and the CDLQI was used for those who were 12 to 16 years of age. These instruments are scored from 0 to 30 with higher scores indicating poor HRQoL. An MID of 4 points for the DLQI and 6 points for the CDLQI were selected as the threshold for clinically relevant between-group difference. In the ADvocate 1 study, the LS mean difference in the change in baseline to week 16 in the DLQI total score was −5.8 points (95% CI, −7.1 to −4.5, p <0.001), and in the ADvocate 2 study, the LS mean difference was −4.9 points (95% CI, −6.3 to −3.5, p <0.001) for the lebrikizumab versus placebo groups. The ADhere study reported a LS mean difference in the change from baseline in the DLQI of −3.3 points (95% CI, −5.3 to −1.3, p = 0.001) for the lebrikizumab + TCS group versus the placebo + TCS group. These analyses included 75% to 86% of patients randomized to a treatment group who were 17 years or older at the start of the studies.

Among adolescents 12 to 16 years of age, the LS mean difference in the change from baseline in the CDLQI was [redacted] in the ADvocate 1 study[redacted]in the ADvocate 2 study, and [redacted] in the ADhere study for the lebrikizumab versus placebo groups at week 16. The change in CDLQI was not controlled for type I error rate and thus should be interpreted as supportive evidence only. Also of note, the number of patients per treatment group was small, ranging from 5 to 11 patients in the placebo groups, and 17 to 26 patients in the lebrikizumab groups.

Maintenance Period

At week 16 of the ADvocate 1 and ADvocate 2 studies, patients in the lebrikizumab group who met the treatment response criteria were re-randomized to placebo, lebrikizumab every 4 weeks or every 2 weeks for the maintenance period. This review focused on the results of the lebrikizumab every 4 weeks groups to be consistent with the Health Canada recommended maintenance dosing. The ADvocate 1 study reported 79.2% of patients in lebrikizumab every 4 weeks group maintained an EASI 75 response at week 52 compared with 61.3% of patients who were switched to placebo (RD of [redacted] In the ADvocate 2 study, 84.7% versus 72.0% maintained an EASI 75 response in the lebrikizumab every 4 weeks and placebo (i.e., lebrikizumab withdrawal) groups, respectively, (RD of [redacted]).

Harms Results

Induction Period

During the induction period of the trials, the proportion of patients who experienced 1 or more treatment emergent adverse events (TEAEs) was 46% versus 52%, 53% versus 66%, and 43% versus 35% in the lebrikizumab and placebo groups, respectively, of the ADvocate 1, ADvocate 2 and ADhere studies. The most common adverse events (AEs) in the lebrikizumab groups were conjunctivitis, headache and nasopharyngitis.

The frequency of SAEs was generally low, with 2.1% versus 0.7%, 0.7% versus 2.8% and 1.4% versus 1.5% reporting a SAE in the lebrikizumab versus placebo groups of the ADvocate 1, ADvocate 2 and ADhere studies, respectively. One patient who received placebo died of a myocardial infarction in the ADvocate 2 study. No other deaths were reported.

During the induction period, 1.1% versus 0.7%, 3.2% versus 2.8%, and 2.1% versus 0% of patients in the lebrikizumab versus placebo groups stopped treatment due to AEs in the ADvocate 1, ADvocate 2 and ADhere studies, respectively.

Conjunctivitis-related adverse events, which was also a notable harm, was reported by [redacted] of patients in the lebrikizumab groups and 0% to 3.5% of patients in the placebo groups. The RD for conjunctivitis in the lebrikizumab versus placebo groups was [redacted] for the ADvocate 1 study [redacted] for the ADvocate 2 study, and [redacted] in the ADhere study.

Maintenance Period

During the maintenance period [redacted] of patients experienced a TEAE in the lebrikizumab q.4.w versus placebo (i.e., lebrikizumab withdrawal) groups in the ADvocate 1 and ADvocate 2 trials, respectively. A total of [redacted] reported a SAE, including [redacted] in the lebrikizumab every 4 weeks group of the ADvocate 1 study, and [redacted] in the placebo group and [redacted] in the lebrikizumab every 2 weeks group of the ADvocate 2 study. No deaths were reported during the maintenance period.

Between week 16 and 52, 1 patient in each of the lebrikizumab every 4 weeks groups of the ADvocate 1 and ADvocate 2 studies stopped treatment due to AEs. No patients in the placebo groups stopped therapy due to AEs during the maintenance period. Overall, conjunctivitis was reported in [redacted] of patients in the lebrikizumab every 4 weeks versus placebo (lebrikizumab withdrawal) groups of the ADvocate 1 and ADvocate 2 studies, respectively.

Critical Appraisal

No major concerns were identified with the randomization, allocation concealment, blinding or statistical methods used in the trials included in the systematic review. The key outcomes tested (EASI 75, Pruritus NRS, POEM and DLQI) were important to patients and had evidence to support their validity and reliability in patients with AD or other dermatologic conditions. The primary estimand used for the EASI 75, IGA, Pruritis NRS and DLQI outcomes analyzed patients who discontinued due to lack of efficacy or who required rescue therapy as non-responders, and used multiple imputation methods to impute data for patients that discontinued due to other reasons. These methods should address any potential bias due to the differential use of rescue treatments in the lebrikizumab and placebo groups.

The key limitations of the change in POEM, DLQI and CDLQI were related to missing data. The analyses of the change in POEM and CDLQI scores were based on the supportive (hypothetical) estimand and the mixed model for repeated measure (MMRM) model, which assumed data are missing at random. These outcomes were not based on the true intention to treat (ITT) population as they excluded patients with missing data at baseline. In addition, there were differences between the groups in the frequency of missing outcome data at week 16 and it is unclear if the missing at random assumption is valid. Similar issues were noted with regards to missing data for the change in DLQI scores. Due to the missing data imputation methods and the extent and differential rate of missing data, there is potential for bias in the change in POEM and CDLQI scores. The change in POEM and CDLQI scores were not part of the graphical testing strategy used to control the family-wise type I error rate, therefore these results should be interpreted as supportive evidence only.

The 52-week data from the ADvocate trials were limited by the enriched population, carry over effects of lebrikizumab in the placebo group, and the small sample size. At week 16 of the ADvocate studies, lebrikizumab treated patients who met the response criteria were re-randomized to 3 groups. This represents an enriched population, and thus the 1-year treatment effects of lebrikizumab may overestimate the effects than would be observed in an unselected population. Given the long half-life of lebrikizumab (24.5 days), it is reasonable to assume there are substantial carry over effects for patients switched from lebrikizumab to placebo, which may impact efficacy assessments as well as the frequency of harms.

The clinical expert consulted for this review did not identify any major limits to the generalizability of the findings of the trials and baseline characteristics of patients enrolled were generally consistent with those who may receive systemic treatments for AD in clinical practice. However, the expert noted that the studies excluded some patients with comorbidities who may receive lebrikizumab for AD. Due to these exclusions the safety and efficacy of lebrikizumab is uncertain for patients with chronic conditions that may require treatment with oral corticosteroids, those with acute or chronic infections, severe mental or physical illnesses, or a history of immunosuppression. Given that 11% to 22% of patients enrolled were adolescents, the results are mainly reflective of adult patients. The dosing of lebrikizumab during the induction period of the trials was consistent with the Health Canada recommended dose, however the clinical expert anticipates that most patients using lebrikizumab will also use TCS as needed. Concurrent use of TCS was prohibited in the ADvocate studies, and thus the magnitude of effects observed in the ADhere study may be more consistent with what may occur in clinical practice. Also, the generalizability of the 52-week efficacy and safety data may be limited given the enriched population and the carry-over effects of lebrikizumab in patients switched to placebo. The results at 52 weeks are reflective of the effects of lebrikizumab maintenance therapy compared with lebrikizumab withdrawal among patients who initially tolerate and respond to treatment during the 16-week induction period.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment for the proportion of patients with an IGA 0 or 1 response, EASI 75 response, or at least a 4-point improvement in Pruritus NRS were based on thresholds informed by the clinical expert consulted for this review. The certainty of evidence assessments for the change in POEM, DLQI, and CDLQI were based on thresholds identified in the literature; and the certainty assessments for SAEs and conjunctivitis were based on the presence or absence of any (non-null) effect.

For the GRADE assessments, findings from ADvocate 1, ADvocate2 and ADhere studies were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Proportion of patients with an IGA score of 0 or 1 and at least a 2-point reduction from baseline
- Proportion of patients with an EASI 75 response
- Proportion of patients who reported at lest a 4-point reduction in the Pruritus NRS score
- Change from baseline in the POEM score
- Change from baseline in the DLQI, and CDLQI total score
- SAEs, conjunctivitis AEs

Table 1: Summary of Findings for Lebrikizumab Versus Placebo for Patients With Moderate to Severe Atopic Dermatitis

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
IGA response				
Proportion of patients with IGA score of 0 or 1 and ≥2-point improvement from baseline (95% CI)[a] Follow-up: 16 weeks	1,062 (3 RCTs)	ADvocate 1 • LEB: 431 per 1,000 • PBO: 127 per 1,000 • aRD (95% CI): 297 more per 1,000 (216 to 378 more per 1,000) ADvocate 2 • LEB: 332 per 1,000 • PBO: 108 per 1,000 • aRD (95% CI): 219 more per 1,000 (142 to 296 more per 1,000) ADhere • LEB + TCS: 412 per 1,000 • PBO + TCS: 221 per 1,000 • aRD (95% CI): 183 more per 1,000 (51 to 315 more per 1,000)	High	Lebrikizumab results in an increase in the proportion of patients with an IGA response when compared with placebo, with or without concomitant TCS.
EASI 75 response				
Proportion of patients with EASI 75 response (95% CI)[b] Follow-up: 16 weeks	1,062 (3 RCTs)	ADvocate 1 • LEB: 588 per 1,000 • PBO: 162 per 1,000 • aRD (95% CI): 420 more per 1,000 (333 to 506 more per 1,000) ADvocate 2 • LEB: 521 per 1,000 • PBO: 181 per 1,000 • aRD (95% CI): 333 more per 1,000 (244 to 422 more per 1,000) ADhere • LEB + TCS: 695 per 1,000 • PBO +TCS: 422 per 1,000 • aRD (95% CI): 264 more per 1,000 (121 to 408 more per 1,000)	High	Lebrikizumab results in an increase in the proportion of patients with an EASI 75 response when compared with placebo, with or without concomitant TCS.
Proportion of patients (95% CI) who maintained an EASI 75 response among patients who exhibited an EASI 75 response at week 16 with	172 (2 RCTs)	ADvocate 1 • LEB q.4.w.: 792 per 1,000 • PBO (LEB withdrawal): 613 per 1,000 • aRD (95% CI): [redacted] ADvocate 2	Moderate[c]	Among patients with an EASI 75 response to lebrikizumab induction therapy, lebrikizumab q.4.w. maintenance therapy likely results in an increase in the proportion of patients who maintain an EASI 75

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
lebrikizumab 250 mg q.2.w. induction therapy [b] Follow-up: 52 weeks		• LEB q.4.w.: 847 per 1,000 • PBO (LEB withdrawal): 720 per 1,000 • aRD (95% CI): [redacted]		response when compared to patients switched to placebo.
Pruritus NRS ≥4-point reduction				
Proportion of patients with Pruritus NRS ≥4-point reduction from baseline (95% CI)[d] Follow-up: 16 weeks	964 (3 RCTs)	ADvocate 1 • LEB: 459 per 1,000 • PBO: 130 per 1,000 • aRD (95% CI): 329 more per 1,000 (246 to 413 more per 1,000) ADvocate 2 • LEB: 398 per 1,000 • PBO: 115 per 1,000 • aRD (95% CI): 283 more per 1,000 (200 to 365 more per 1,000) ADhere • LEB + TCS: 506 per 1,000 • PBO +TCS: 319 per 1,000 • aRD (95% CI): 192 more per 1,000 (43 to 341 more per 1,000)	High	Lebrikizumab results in an increase in the proportion of patients with at least a 4-point reduction in the Pruritus NRS score when compared with placebo, with or without concomitant TCS.
Change in POEM total score				
POEM total score (0 [best] to 28 [worst]) LS mean change from baseline (95% CI)[e] Follow-up: 16 weeks	996 (3 RCTs)	ADvocate 1 • LEB: [redacted] • PBO: [redacted] • Difference[redacted] ADvocate 2 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADhere • LEB + TCS: [redacted] • PBO + TCS: [redacted] • Difference: [redacted]	Low[f]	Lebrikizumab may result in a reduction in the POEM score compared with placebo, with or without concomitant TCS.
Change in DLQI score				

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
DLQI score (0 [best] to 30 [worst]) LS mean change from baseline (95% CI)[g] Follow-up: 16 weeks	856 (3 RCTs)	ADvocate 1 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADvocate 2 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADhere • LEB + TCS: [redacted] • PBO + TCS: [redacted] • Difference: [redacted]	Low[h]	Lebrikizumab may result in a reduction in the DLQI score compared with placebo, with or without concomitant TCS.
Change in CDLQI score				
CDLQI score (0 [best] to 30 [worst]) LS mean change from baseline (95% CI) [g] Follow-up: 16 weeks	[redacted] (3 RCTs)	ADvocate 1 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADvocate 2 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADhere • LEB + TCS: [redacted] • PBO + TCS: [redacted] • Difference: [redacted]	Very Low[i]	The evidence is very uncertain about the effect of lebrikizumab on the change in CDLQI when compared with placebo.
Serious adverse events				
Proportion of patients with SAE (95% CI) Follow up: 16 weeks	1,060 (3 RCTs)	ADvocate 1 • LEB: 21 per 1,000 • PBO: 7 per 1,000 • RD (95% CI): [redacted] ADvocate 2 • LEB: 7 per 1,000 • PBO: 28 per 1,000	Very low[j]	The evidence is very uncertain about the effect of lebrikizumab on the proportion of patients with 1 or more SAEs when compared with placebo, with or without concomitant TCS.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• RD (95% CI): [redacted] ADhere • LEB + TCS: 14 per 1,000 • PBO + TCS: 15 per 1,000 • RD (95% CI): [redacted]		
Proportion of patients with SAE (95% CI) among patients who met treatment response criteria at week 16 with lebrikizumab 250 mg q.2.w. induction therapy Follow up: 52 weeks	178 (2 RCTs)	ADvocate 1 • LEB q.4.w.: [redacted] • PBO (LEB withdrawal): [redacted] • RD (95% CI): [redacted] ADvocate 2 • LEB q.4.w.: [redacted] • PBO (LEB withdrawal): [redacted] • RD (95% CI): [redacted]	Very low[k]	Among patients who achieve a response to lebrikizumab induction therapy, the evidence is very uncertain about the effect of lebrikizumab maintenance therapy on the proportion of patients with 1 or more SAEs when compared with placebo (i.e., lebrikizumab withdrawal).
Conjunctivitis				
Proportion of patients with conjunctivitis AEs (95% CI) Follow up: 16 weeks	1,060 (3 RCTs)	ADvocate 1 • LEB: [redacted] • PBO: [redacted] • RD (95% CI): [redacted] ADvocate 2 • LEB: [redacted] • PBO: [redacted] • RD (95% CI): [redacted] ADhere • LEB +TCS: [redacted] • PBO +TCS: [redacted] • RD (95% CI): [redacted]	Moderate[l]	Lebrikizumab may result in an increase in the proportion of patients with 1 or more conjunctivitis events when compared with placebo, with or without concomitant TCS. The clinical importance of the increase is uncertain.
Proportion of patients with conjunctivitis AEs (95% CI) among patients who met treatment response criteria at week 16 with lebrikizumab 250 mg q.2.w. induction therapy	178 (2 RCTs)	ADvocate 1 • LEB q.4.w.: [redacted] • PBO (LEB withdrawal): [redacted] • RD (95% CI): [redacted] ADvocate 2 • LEB q.4.w:. [redacted] • PBO (LEB withdrawal): [redacted]	Very low[m]	Among patients who achieve a response to lebrikizumab induction therapy, the evidence is very uncertain about the effect of lebrikizumab maintenance therapy on the proportion of patients with 1 or more conjunctivitis events when

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Follow up: 52 weeks		• RD (95% CI): [redacted])		compared with placebo (lebrikizumab withdrawal).

AE = adverse event; aRD = adjusted risk difference; CDLQI = Children's Dermatology Life Quality Index; CI = confidence interval; DLQI = Dermatology Life Quality Index; EASI 75 = 75% reduction in Eczema Area and Severity Index; HRQoL = health-related quality of life; IGA = Investigator's Global Assessment for AD; LEB = lebrikizumab; LS = least squares; NR = not reported; NRS = numeric rating scale; PBO = placebo; POEM = Patient Oriented Eczema Measure; q.4.w. = every 4 weeks; RCT = randomized controlled trial; RD = risk difference; SAE = serious adverse event; TCS = topical corticosteroids.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] The IGA measures the investigator's global assessment of the patient's overall severity of AD at that visit, based on a static, numeric 5-point scale ranging from 0 (clear) to 4 (severe). Based on clinical expert input the threshold for a clinically important between-group difference was 100 per 1,000 for the proportion of patients with an IGA score of 0 or 1 and at least a 2-point reduction from baseline.

[b] The EASI is a composite index, based on the physician's assessment of 4 clinical signs of the disease (erythema, infiltration and/or papulation, excoriation and lichenification) and the extent of body surface area involved at that visit. It is scored from 0 to 72 with higher scores indicating greater disease severity and/or extent of disease. Based on clinical expert input the threshold for a clinically important between-group difference was 100 per 1,000 for the proportion of patients with at least a 75% reduction in the EASI score from baseline (EASI 75).

[c] EASI 75 response at week 52: −1 level for serious imprecision. The CI for differences between groups included the potential for little to no difference (based on the threshold for a clinically important between-group difference of 100 per 1,000 for the proportion of patients who maintained at least an EASI 75 response at week 52).

[d] The Pruritus NRS is a patient-reported, single-item, daily, 11-point scale. The scale is used by patients to rate their worst itch severity over the past 24 hours, with 0 indicating "No itch" and 10 indicating "Worst itch imaginable". Based on clinical expert input the threshold for a clinically important between-group difference was 100 per 1,000 for the proportion of patients with at least a 4-point reduction from baseline. This outcome was analyzed for the subgroup of patients who had a Pruritus NRS score of 4 or higher at baseline.

[e] The POEM is a 7-item, patient-reported questionnaire used to assess the frequency of disease symptoms in adults and children over the last week. The patients respond to 7 questions on skin dryness, itching, flaking, cracking, sleep-loss, bleeding, and weeping. The total score ranges from 0 to 28, with a high score indicative of worse disease severity. The MID of 3.4 points was selected as the threshold for a clinically important between-group difference based on the literature and clinical expert input.

[f] Change in POEM score at week 16: -2 for levels for very serious study limitations. The extent of missing data was large and the method for accounting for missing data was potentially biased. Note: there was no control of type I error rate for this end point and thus should be interpreted as supportive evidence only.

[g] The DLQI (for 16 years and older) and CDLQI (for those younger than 16) are patient-reported, 10-item, HRQoL questionnaires that covers 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) over the "last week". The total score ranges from 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life). The MID of 4 points for the DLQI and 6 points for the CDLQI were selected as the threshold for a clinically important between-group difference based on the literature and clinical expert input.

[h] Change in DLQI at week 16: -1 level for serious imprecision (the CI for differences between groups included the potential for little to no difference based on a MID of 4 points.) -1 level for serious study limitations (due to missing data). Also considered was the possibility of inconsistency, given that the point estimate for 1 of the 3 trials falls below the MID, although a decision was made not to rate down for inconsistency.

[i] Change in CDLQI at week 16: -1 level for serious imprecision (the CI for differences between groups included the potential for little to no difference based on a MID of 6 points.) -2 levels for very serious study limitations. The extent of missing data was large and the method for accounting for missing data was potentially biased. Note: there was no control of type I error rate for this end point and thus should be interpreted as supportive evidence only.

[j] SAE at week 16: -2 for very serious indirectness (follow up duration limited to 16 weeks which may be insufficient to detect uncommon SAEs or those that may develop over time; the clinical expert noted that worsening AD may be reported as an SAE, whereas this more accurately reflects lack of efficacy). -1 for serious imprecision (CI for difference between groups includes the possibility of no difference, benefit (fewer harms) and increased harms.

[k] SAE at week 52: -2 for very serious indirectness (AE were reported for an enriched population who had received lebrikizumab 250 mg q.2.w. induction therapy and met the treatment response criteria at week 16; the AEs reported in the placebo group may be confounded due to the carry over effects of lebrikizumab prior to the switch to placebo; follow up duration and sample size may be insufficient to detect uncommon SAEs or those that may develop over time); -1 for serious imprecision (CI for difference between groups includes the possibility of no difference, benefit [fewer harms] and increased harms).

[l] Conjunctivitis at week 16: -1 for serious indirectness (the clinical expert stated that dermatologists may not have sufficient expertise to distinguish between eye disorders with a similar presentation, thus the reported conjunctivitis-related AEs may be flawed).

[m] Conjunctivitis at week 52: -2 for very serious indirectness (the clinical expert stated that dermatologists may not have sufficient expertise to distinguish between eye disorders with a similar presentation, thus the reported conjunctivitis-related AEs may be flawed; AE were reported for an enriched population who had received lebrikizumab 250 mg q.2.w. induction therapy and met the treatment response criteria at week 16; the AEs reported in the placebo group may be confounded due to the carry over effects of lebrikizumab prior to the switch to placebo); -2 for very serious imprecision (CI for difference between groups includes the possibility of no difference, benefit [fewer harms] and increased harms).

Source: Clinical Study Reports for ADvocate, CSR for ADvocate, CSR for ADhere, Additional information supplied by sponsor.

Long-Term Extension Study

Description of Study

One long-term extension study was summarized to provide evidence regarding the long-term (100-week) efficacy and safety of lebrikizumab among patients with moderate to severe AD who were enrolled in the ADvocate 1, ADvocate 2, ADhere, ADore and ADopt-VA studies (parent trials). This study was conducted at 199 centers that enrolled 999 patients in Australia, Bulgaria, Canada, Estonia, France, Germany, Latvia, Lithuania, Mexico, Poland, Singapore, South Korea, Spain, Taiwan, Ukraine, and the United States. This report presents interim safety data from ADjoin and limited efficacy data at Week 40 for a subset of patients who completed the 16-week ADhere study (i.e., up to 56 weeks of lebrikizumab treatment). [redacted]

Efficacy Results

Efficacy outcomes were assessed up to [redacted] (Week 16 to 104). Evaluation of efficacy in the interim report was conducted on a subset of the Main Cohort, which included [redacted] who were responders to lebrikizumab plus TCS in ADhere study.

At week 40, the proportion of patients with an IGA score of 0 or 1 was [redacted] in the lebrikizumab 250 mg every 4 weeks group and [redacted] in lebrikizumab 250 mg every 2 weeks group.

At week 40, the mean (standard error [SE]) percent change from baseline in EASI score in lebrikizumab 250 mg every 4 weeks and lebrikizumab 250 mg every 2 weeks groups were [redacted] respectively. The proportion of patients with an EASI 75 response at week 40 in the lebrikizumab 250 mg every 4 weeks and lebrikizumab 250 mg every 2 weeks groups was [redacted] respectively.

Among patients who had a Pruritus NRS score of 4 or more points at baseline, the proportion of patients who reported an improvement of at least 4 points at week 40 in the lebrikizumab 250 mg every 4 weeks and lebrikizumab 250 mg every 2 weeks groups was [redacted] and [redacted] respectively.

The mean (SE) percent change in POEM score from baseline to week 40 in the lebrikizumab 250 mg every 4 weeks and lebrikizumab 250 mg every 2 weeks groups was [redacted] respectively.

Harms Results

Overall [redacted] ([redacted]) discontinued study treatment due to AEs. Discontinuation due to an AE was noted in [redacted]

One death due to natural causes occurred in the lebrikizumab 250 mg every 2 weeks group.

The most frequently reported TEAEs were in the infections and infestations system organ class , with coronavirus disease 2019 [redacted] in lebrikizumab 250 mg every 4 weeks group and [redacted] in the lebrikizumab 250 mg every 2 weeks group) and nasopharyngitis [redacted] in lebrikizumab 250 mg every 4 weeks group and [redacted] in the lebrikizumab 250 mg every 2 weeks group) being the most common TEAE. A similar proportion of patients in the lebrikizumab 250 mg every 2 weeks group ([redacted] and the lebrikizumab 250 mg every 4 weeks group ([redacted] reported an AE of atopic dermatitis exacerbation. The proportion of patients experiencing 1 or more AEs in the conjunctivitis cluster (narrow terms) were similar in both the lebrikizumab 250 mg every 4 weeks group ([redacted] and the lebrikizumab 250 mg every 2 weeks group ([redacted]).

Critical Appraisal

Internal Validity

There is no randomized comparison to another treatment or a placebo, which limits the ability to draw inferences on the effects of lebrikizumab in the study population. The patients were aware they were receiving active treatment, thus their expectations of treatment may have influenced reporting of subjective patient-reported outcomes, such as the POEM, and subjective adverse events, or investigator reported IGA and EASI, which are measures that require subjective judgments. Discontinuation rates are [redacted] in the lebrikizumab every 4 weeks and [redacted] in the lebrikizumab every 2 weeks. Among the participants from ADhere (efficacy assessment)

the rates of discontinuation are [redacted] in every 4 weeks group and [redacted] in every 2 weeks group. Thus, there is potential bias due to missing data. All analyses were conducted descriptively without statistical comparisons between the cohorts or adjustment for multiple comparisons.

External Validity

Only the responders of ADhere study were included in the efficacy assessment. Patients were excluded if during their participation in the parent trial, they developed a SAE deemed related to lebrikizumab; developed an AE that was deemed related to lebrikizumab and led to study treatment discontinuation; or had conditions in the parent trial which led to investigator or sponsor-initiated withdrawal from the study. This is a select population such that the results apply only to patients who initially tolerate and respond to lebrikizumab. The proportion of patients with concomitant TCS use and systemic rescue therapy was higher in every 4 weeks group compared to every 2 weeks group. The effect of these differences between groups on the efficacy results remains unclear.

Indirect Comparisons

Description of Studies

The sponsor-submitted indirect treatment comparison (ITC) first conducted a systematic literature review (SLR) to identify evidence for inclusion in a network meta-analysis (NMA). The relative efficacy of lebrikizumab (with or without TCS) from the ADvocate 1, ADvocate 2, J2T-DM-KGAF, ADhere, ADhere-J, ADopt-VA, and ADvantage trials was indirectly compared to alternative treatments for AD via Bayesian NMA. Comparators of interest for the sponsor-submitted NMA included abrocitinib, dupilumab, and upadacitinib. All networks in the sponsor submitted NMA also included baricitinib and tralokinumab as comparators. However, baricitinib does not have Health Canada approval for the treatment of AD, and tralokinumab is not currently reimbursed by public drug plans in Canada. As such, results comparing lebrikizumab to baricitinib or tralokinumab were not included in this report. Outcomes of interest included EASI Response, IGA 0/1 Response, and greater than or equal to 4-point reduction in Pruritus/Itch NRS at Week 16, and greater than or equal to 4-point reduction in Pruritus/Itch NRS at Week 4.

Efficacy Results

The SLR identified a total of [redacted] citations. A total of [redacted] unique studies identified by the SLR were assessed for eligibility to be included in NMAs. Three studies of lebrikizumab were not identified as part of the SLR were also assessed for inclusion. In total, [redacted] studies were eligible for inclusion in NMAs: [redacted] monotherapy studies, and [redacted] combination therapy studies.

Networks were generated for all eligible interventions as monotherapy and combination therapy for the outcomes of EASI response, IGA 0/1 response, and pruritus/Itch NRS response at timepoints of interest. In all cases, the baseline risk-adjusted random effects model was selected as the favoured model based on the deviance information criterion (DIC) and residual deviance.

Primary Analysis

<u>EASI Response (Week 16)</u>

In the primary analysis for EASI response at week 16 in the monotherapy network, there was insufficient evidence to show a difference between lebrikizumab and dupilumab 300 mg every 2 weeks and abrocitinib 100 mg daily. Abrocitinib 200 mg daily (probit difference, [redacted] and upadacitinib 15 mg daily (probit difference, [redacted] and 30 mg daily (probit difference, [redacted] were favoured over lebrikizumab.

[redacted]

<u>IGA Response 0/1 (Week 16)</u>

In the primary analysis for IGA 0/1 response at week 16 in the monotherapy network, there was insufficient evidence to show a difference between lebrikizumab and dupilumab 300 mg every 2 weeks, abrocitinib 100 mg daily or 200 mg daily, or upadacitinib 15 mg daily. Upadacitinib 30 mg daily was favoured over lebrikizumab [odds ratio [OR], [redacted]]).

[redacted]

Greater than or Equal to 4 Point Reduction in Pruritus/Itch NRS (Week 16)

In the primary analysis for Pruritus/itch NRS response at week 16 in the monotherapy network, there was insufficient evidence to show a difference between lebrikizumab and dupilumab 300 mg every 2 weeks, abrocitinib 100 mg daily or 200 mg daily, or upadacitinib 15 mg daily. Upadacitinib 30 mg daily was favoured over lebrikizumab [redacted]

[redacted]

Greater than or Equal to 4 Point Reduction in Pruritus/Itch NRS (Week 4)

In the primary analysis for Pruritus/itch NRS response at week 4 in the monotherapy network, there was insufficient evidence to show a difference between lebrikizumab and dupilumab 300 mg every 2 weeks, and abrocitinib 100 mg daily. Abrocitinib 200 mg daily [redacted] upadacitinib 15 mg daily [redacted] and upadacitinib 30 mg daily [redacted] were favoured over lebrikizumab.

[redacted].

Secondary Analysis

Phase III Studies Only – Monotherapy Networks

[redacted]

Meta-Regression Analysis

[redacted]

[redacted]

Harms Results

Harms were not evaluated in the sponsor-submitted NMA.

Critical Appraisal

The sponsor-submitted NMA was informed by a SLR that included comprehensive searches (updated to April 2023) of multiple databases, conference proceedings, clinical trial databases, and HTA websites. Additionally, the risk of bias assessment conducted by the sponsor was not indicative of serious risk of bias in the included studies. However, it should be noted that methods for risk of bias appraisal were incompletely reported (i.e., it is not clear how many reviewers were involved and whether they worked independently). As such, the risk for bias and error in the appraisals could not be ascertained. Further, the risk of bias appraisal was undertaken at the study level, rather than at the level of the reported effects. Appraisals undertaken at the study level do not account for differences in the risk of bias that can exist across reported results (within and across outcomes) within trials. Additionally, there is

a risk of bias due to missing results in the networks, because trials of relevant comparator treatments without a placebo control group were excluded[redacted]

A feasibility assessment was conducted, evaluating potential heterogeneity in study design; patient baseline characteristics; interventions; and outcomes, timepoints, and placebo response. The sponsor noted that some heterogeneity was observed across studies in both the monotherapy and combination therapy networks. Studies for abrocitinib used a 12-week time of assessment as opposed to the 16-weeks for other trials. The effect of the difference in time of assessment was not evaluated in the NMA and remains unknown. There were also differences in age across studies, with the mean age [redacted]. There was also heterogeneity in the proportion of patients [redacted] Adjustment for baseline EASI and IGA did not bring about improvements in model fit and conclusions were considered to be comparable to the primary analysis. Other differences were noted by the CADTH review team in weight, and ethnicity across studies, though the impact of these differences remains unclear. The sponsor also noted heterogeneity in other features such as race and time since AD diagnosis, though it is not clear whether these are important treatment effect modifiers. No formal search for potential treatment effect modifiers was conducted; instead, the sponsor relied on internal clinical opinion, only including AD severity measured by EASI and IGA, and weight, which the clinical expert consulted by CADTH agreed with, though there was a risk of bias in the selection of treatment effect modifiers, and it was not clear whether the list was comprehensive. Additionally, the sponsor also highlighted differences in the [redacted] Differences in TCS treatment may bias reported response rates and limit the reliability of comparing responses on the active interventions, however, baseline risk adjusted analysis models were included to mitigate the potential for bias. No scenario analyses were conducted to compare the difference between adjusted and unadjusted results; thus, it is unclear what effect not adjusting for baseline risk had on the results. Overall, the notable heterogeneity in the baseline characteristics raises concern about the plausibility of the transitivity assumption, whereby, the resulting effect estimates may not be valid.

Baricitinib and tralokinumab were included as comparators in the NMAs, however, the use of baricitinib for AD is limited in Canada given the lack of a specific indication for AD, and the availability of more efficacious and tolerable JAK inhibitors (i.e., abrocitinib, upadacitinib). Tralokinumab, though indicated for AD, received a do not reimburse recommendation from CADTH and is not reimbursed in Canada. As such, comparative results versus these treatments were not included in this report.

Outcomes included in the NMA were relevant to the treatment of AD in Canada, though the clinical expert consulted by CADTH highlighted that EASI scores are generally not calculated in routine clinical practice. Additionally, outcomes of importance to this review, including harms and HRQoL, were not included in the NMA.

In all random effects analyses, results were associated with wide 95% CrIs, with most estimates crossing the 0 or 1 threshold, suggesting notable imprecision in the results, and precluding conclusions on which treatment is favoured. For some comparisons in the monotherapy [redacted] there was generally insufficient evidence to demonstrate a difference between treatments for most outcomes. Further, abrocitinib 200 mg daily, upadacitinib 15 mg daily, and upadacitinib 30 mg daily (± TCS) were favoured over lebrikizumab (± TCS) for most outcomes but were also associated with wide 95% CrIs. Overall, this imprecision limits the interpretability of the treatment effect of lebrikizumab relevant to other comparators. Furthermore, this NMA was primarily restricted to adults, thus, it is unclear whether the results may be generalized to adolescents with AD.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

The sponsor submitted 4 studies that provided additional data to cover gaps in the systematic review evidence:

- ADvantage, a phase 3, 52-week (16-week double-blind induction period followed by a 36-week open-label maintenance period), RCT to address uncertainty regarding the efficacy and safety of lebrikizumab specifically in patients whose AD is not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable (N = 331).

- ADopt-VA, a 16-week phase 3, randomized, double-blind, placebo controlled, parallel-group trial to address the uncertainty regarding the impact of lebrikizumab on vaccine immune responses. This trial also provides additional evidence of the efficacy and safety of lebrikizumab (N = 247).
- ADhere-J, a 68-week (16-week induction period plus a 52-week maintenance period), phase 3, randomized, double-blind, placebo-controlled, parallel-group study to address uncertainty regarding the efficacy and safety of lebrikizumab specifically in Japanese patients (N = 268).
- ADore, a 52-week, open-label, single arm study to address the uncertainty regarding the efficacy and safety of lebrikizumab specifically among adolescent patients (N = 206 received treatment, 172 completed the treatment period).

ADvantage

Results

A summary of efficacy results for patients randomized to lebrikizumab + TCS group relative to placebo +TCS at Week 16 is provided below:

- EASI 75 was 68.4% versus 40.8%, p<0.0001, [redacted]
- IGA 0/1 and ≥2-point improvement, was 42.0% versus 24.5%, [redacted]
- Pruritus NRS ≥4-point improvement, was 49.9% versus 29.7%, [redacted]
- POEM mean (SD) change from baseline, [redacted]
- DLQI mean (SD) change from baseline [redacted]
- CDLQI mean (SD) change from baseline[redacted]

In terms of safety, a summary of harms results for patients randomized to lebrikizumab + TCS group relative to placebo +TCS group at Week 16 is provided below:

- Proportion of patients with at least one AE were 61.8% versus 53.2%
- Proportion of patients with at least one SAE were [redacted]
- Proportion of patients with at least one AE leading to study drug discontinuation were 0.9% versus 1.8%
- Proportion of patients with conjunctivitis AE were [redacted]

Up to week 52, harm results for patients randomized to the lebrikizumab + TCS group were reported as [redacted] for patients with at least one AE, [redacted] for patients with at least one SAE, and [redacted] for patients with at least one AE leading to study drug discontinuation.

Critical Appraisal

Since few adolescents were enrolled in this study, generalizability to this age group is limited. No control for multiplicity was included for analyses of the secondary efficacy endpoints, therefore, the study is at risk of type I error (false positive results) for all endpoints except for EASI 75. Dosage of maintenance therapy was 250 mg every 2 weeks which is not consistent with Health Canada product monograph which recommends 250 mg every 4 weeks after 16 weeks. In the lebrikizumab group versus placebo group, [redacted] discontinued the study which might increase risk of bias due to missing outcomes data.

ADopt-VA

Results

The efficacy results reported in ADopt-VA that correspond to patients randomized to lebrikizumab compared to placebo at Week 16 are available below:

- EASI 75 was 58.0% versus 32.7%, p<0.001[redacted]
- IGA 0/1 and ≥2-point improvement, 40.6% versus 18.9%, [redacted]
- Pruritus NRS ≥4-point improvement was [redacted]

- POEM LS mean change from baseline (SE) was -9.4 (0.8) versus -6.6 (0.8), [redacted]

In terms of safety, a summary of the harms for patients randomized to lebrikizumab compared to placebo at Week 16 is available below:

- Proportion of patients with at least one AE were 38.4% versus 34.4%
- Proportion of patients with at least one SAE were 0.8% versus 0.8%
- Proportion of patients with at least one AE leading to study drug discontinuation were 2.4% versus 4.1%
- Proportion of patients with conjunctivitis AE were [redacted].

Critical Appraisal

There is an increased risk of type I error (false positive results) for all endpoints. The results of this study may not be generalizable to adolescent patients. The use of TCS was [redacted] in lebrikizumab group versus [redacted] in placebo group, and its effect on the results is not clear. The discontinuation rate was [redacted] in the placebo group vs [redacted] in the lebrikizumab group which might increase the risk of bias due to missing outcomes data.

ADhere-J

A total of [redacted] in ADhere-J completed the induction period, including patients receiving placebo, patients in the lebrikizumab every 4 weeks treatment group, and patients in the lebrikizumab every 2 weeks treatment group. The responders of the lebrikizumab every 4 weeks treatment group continued on treatment with 250 mg lebrikizumab every 4 weeks. The responders of the lebrikizumab every 2 weeks treatment group were randomly allocated to receive 250 mg lebrikizumab every 2 weeks or 250 mg lebrikizumab every 4 weeks. The non-responders or those who used rescue therapy in the induction period moved to the escape arm and received 250 mg lebrikizumab every 2 weeks. In the placebo group, the responders continued to receive placebo, while those who were non-responders or those who used rescue therapy in the induction period moved to the escape arm and received a loading dose of 500 mg lebrikizumab at Week 16 and Week 18.

Results

A summary of the efficacy results for the Induction Period corresponding to patients randomized to placebo + TCS relative to lebrikizumab every 2 weeks +TCS at Week 16 is available below:

- EASI 75 was 13.4% versus 51.2%, p <0.001
- IGA 0/1 and ≥2-point improvement was 6.1% versus 33.4%, p <0.001
- pruritis NRS ≥4-point improvement was 3.3% versus 32.7%, p <0.001
- [redacted]

Harm results for induction period in placebo versus lebrikizumab every 2 weeks +TCS:

- Proportion of patients with at least one AE was 63.4 versus 75.6%
- Proportion of patients with at least one SAEs was 2.4% versus 0.8%

[redacted]

Critical Appraisal

This study is limited to Japanese patients only, and generalizability to Canadian patients is uncertain. Not all patients in the induction phase received the HC recommended dose. High Potency TCS use was [redacted] in the placebo group, [redacted] in the lebrikizumab every 4 weeks group, and [redacted] in the lebrikizumab every 2 weeks group; the effect of this difference on the results is unclear. DLQI, CDLQI

and POEM were not included in multiplicity testing and are at risk of type 1 error. For the maintenance period, discontinuation was [redacted] in the placebo group versus [redacted] in the lebrikizumab every 2 weeks Responder/every 4 weeks+TCSgroup. The impact of missing data on the findings is unclear.

ADore

Results

The efficacy results reported in the ADore study at Week 52 have been summarized:

- EASI 75 (MCMC-MI analysis) was 81.9%;
- IGA 0/1 and ≥2-point improvement (MCMC-MI analysis) was 62.6%;
- DLQI mean (SE) change from baseline (MCMC-MI) was -8.9 (0.9) N = 35;
- CDLQI mean (SE) change from baseline (MCMC-MI)was -6.5 (0.5), N = 168.

The harms results reported in the ADore study at Week 52 have been summarized:

- Proportion of patients with at least one AE was 65%;
- Proportion of patients with at least one SAEs was 2.4%;
- Proportion of patients with at least one AE leading to study treatment discontinuation was 2.4%; patients with conjunctivitis AE was 6.8%.
- one death (0.5%), which was reported as due to cardiac arrest.

Critical Appraisal

There is risk of bias in the measurement of the outcomes due to the open label design and subjectivity of the outcomes. There is no comparator, which limits causal inferences. Maintenance therapy dose was not consistent with Health Canada product monograph. There is a [redacted] which might contribute to risk of bias due to missing outcome data.

Key Takeaways for Studies Addressing Gaps in the Evidence

In patients with moderate to severe AD who received induction therapy with lebrikizumab 250 mg every 2 weeks (with or without TCS), the results of the supplementary trials (ADvantage, ADhere-J, and ADopt-VA) were generally consistent with the findings of the pivotal trials. The efficacy findings favoured lebrikizumab when compared to placebo for EASI 75, IGA 0/1 and pruritus NRS≥ 4 points at 16 weeks in the RCTs addressing gaps in the evidence (ADvantage, ADhere-J, and ADopt-VA).

In terms of harms results at week 16, in the ADvantage study a higher proportion of patients in the lebrikizumab group compared with the placebo group reported TEAEs and serious TEAEs. In ADopt-VA, the proportion of patients with TEAEs and the proportion of patients with at least one AE leading to study drug discontinuation were higher in lebrikizumab group compared to placebo group. In ADhere-J, the proportion of patients who reported TEAEs, and patients with 1 or more AEs leading to study drug discontinuation were higher in every 2 weeks group versus placebo group. In the open label ADore study, 2.4% of patients reported at least 1 AE leading to permanent discontinuation from the study treatment including 1 death.

Some of the limitations in the ADvantage study included uncertain generalizability to adolescent patients, dosage inconsistency with the Health Canada recommended dose, lack of control for multiplicity for secondary efficacy endpoints (thus increased risk of type I errors), and risk of bias due to missing outcomes data. In ADopt-VA, there is increased risk of type I error, uncertain generalizability to adolescent patients, between group differences in the use of TCS, and risk of bias due to missing outcome data. In ADhere-J, there was uncertain generalizability to Canadian patients, the dosage was inconsistent with the Health Canada recommended dose for the induction period, there were between group differences in the use of high potency TCS, there was an increased risk of type I error for DLQI, CDLQI and POEM, and there were between group differences in discontinuations during the maintenance period.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with moderate-to-severe AD
Treatment	Lebrikizumab plus TCS
Dose regimen	The recommended dosage is an initial dose of 500 mg injected subcutaneously at week 0 and week 2, followed by 250 mg every two weeks until week 16, at which time clinical response is assessed. Upon clinical response, a maintenance dose of 250 mg every 4 may be used.
Submitted price	Lebrikizumab, 250 mg/2 mL single-dose prefilled pen: $1,876.71 Lebrikizumab, 250 mg/2 mL single-dose prefilled syringe with needle shield: $1,876.71
Submitted treatment cost	First year: $35,657 Subsequent years: $24,397
Comparators	Abrocitinib 100 mg plus TCS Abrocitinib 200 mg plus TCS Dupilumab plus TCS Upadacitinib 15 mg plus TCS Upadacitinib 30 mg plus TCS BSC, assumed to be equivalent to placebo
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (70 years)
Key data source	Clinical efficacy data were informed by sponsor-submitted NMAs
Key limitations	• The comparative efficacy of lebrikizumab plus TCS relative to other biologics and JAK inhibitors used to treat AD in Canada is uncertain owing to a lack of head-to-head trials and limitations with the sponsor's NMA. Indirect evidence submitted by the sponsor suggests that, when used in combination with TCS, there is insufficient evidence to show a difference in the efficacy in terms of EASI response for lebrikizumab compared with dupilumab, abrocitinib 100 mg and upadacitinib 15 mg. Further, indirect evidence submitted by the sponsor suggests that abrocitinib 200 mg and upadacitinib 30 mg (all used in combination with TCS) may result in a greater proportion of patients achieving EASI response compared with lebrikizumab plus TCS. • The comparative safety of lebrikizumab plus TCS relative to other biologics and JAK inhibitors used to treat AD in Canada is unknown owing to a lack of direct and indirect evidence. • The relevance of BSC as a comparator is uncertain. In the sponsor submission, BSC was not defined. Clinical expert feedback consulted by CADTH expressed that BSC in clinical practice consists of various over the counter emollients and anti-inflammatory treatments such as TCS and calcineurin inhibitors. Based on clinical expert feedback received by CADTH which indicated that the proportion of patients who are currently receiving BSC is very low given the availability of existing biologics and JAK inhibitors to treat moderate to severe AD in Canada and that the proportion of patients who would switch from BSC to lebrikizumab should it become available would be negligible. • The sponsor inappropriately applied treatment-specific health state utility values in the maintenance health state, which is contradictory to CADTH recommendations.
CADTH reanalysis results	• The CADTH reanalysis: corrected comparator pricing; removed BSC as a comparator from the analysis; and, removed treatment specific utilities from the maintenance health state. CADTH was unable to address limitations related to the lack of robust comparative clinical efficacy or safety data. • In the CADTH base case, similar to the sponsor's results, lebrikizumab plus TCS yielded the fewest total QALYs compared with other biologics and JAK inhibitors and was more costly than abrocitinib 100 mg plus TCS, abrocitinib 200 mg plus TCS and upadacitinib 15 mg plus TCS. • Based on the comparative clinical information submitted by the sponsor, there is insufficient evidence to show a difference in efficacy for lebrikizumab plus TCS compared with dupilumab

Component	Description
	plus TCS, abrocitinib 100 mg plus TCS and upadacitinib 15 mg plus TCS; further, lebrikizumab plus TCS may result in less favourable clinical outcomes compared with abrocitinib 200 mg plus TCS and upadacitinib 30 mg plus TCS. As such, there is no clinical evidence to support a price premium for lebrikizumab over existing biologic and JAK inhibitor treatments used to treat AD in Canada.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: The proportion of patients eligible to receive therapy is uncertain; The market share estimates in the reference scenario for all comparators are highly uncertain; Total treatment costs are uncertain due to use of blended cost methods when determining annual drug acquisition costs.

CADTH reanalyses included changes to update the proportion of adult and adolescent patients whose AD cannot be adequately controlled with topical prescription therapies and increase the market shares of upadacitinib. In the CADTH base case the budget impact of reimbursing lebrikizumab for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable is expected to be $65,018,149 over three years (year 1: $12,449,072; year 2: $21,089,890; year 3: $31,419,187).

The budget impact was sensitive to assumptions regarding the proportion of patients eligible for systemic therapies.

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. Edward Xie, and Dr. Peter Zed.

Meeting date: March 28, 2024

Regrets:

1 expert committee member did not attend.

Conflicts of interest:

None