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Reimbursement Recommendation

Nemolizumab (Nemluvio)

Indication: For the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older who are candidates for systemic therapy

Sponsor: Galderma Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Nemluvio?

Canada's Drug Agency (CDA-AMC) recommends that Nemluvio should be reimbursed by public drug plans for the treatment of patients aged 12 years and older with moderate to severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable if certain conditions are met.

Which Patients Are Eligible for Coverage?

Nemluvio should only be covered to treat patients aged 12 years and older with moderate to severe AD, provided that Nemluvio is covered in a similar way to other advanced systemic therapies (i.e., biologics and JAK inhibitors) currently reimbursed by public drug plans for the treatment of moderate to severe AD.

What Are the Conditions for Reimbursement?

In addition to following the pre-existing criteria for other advanced systemic therapies, Nemluvio should not be used in combination with other advanced systemic therapies. Nemluvio should only be reimbursed if the cost is reduced such that the total treatment cost of Nemluvio does not exceed the total treatment cost of the least costly advanced therapies reimbursed for moderate to severe AD.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials that enrolled patients aged 12 years and older with moderate to severe AD demonstrated that Nemluvio reduced AD severity and itching compared to placebo.
- Nemluvio may meet some important needs for patients including reducing AD severity and itch.
- Based on the CDA-AMC assessment of the health economic evidence, Nemluvio does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Nemluvio compared with advanced therapies reimbursed for the treatment of moderate to severe AD.
- Based on public list prices, Nemluvio is estimated to cost the public drug plans approximately $45 million over the next 3 years.

Summary

Additional Information

What Is AD?

AD is a condition that affects the skin, causing dry, red skin that is extremely itchy. Constant scratching causes the skin to split and bleed, which can lead to infections. Oozing and weeping sores occur in more severe forms. Severe AD can be physically incapacitating and cause anxiety or depression. Lifetime prevalence in Canada is estimated to be up to 15% in children and adolescents and 3.5% in adults in Canada.

Unmet Needs in AD

There is no cure for AD, and current treatment aims to provide symptom relief and control in the longer term. Although there are treatments for AD approved in Canada, some patients' symptoms may not be controlled with existing drugs, and other treatment options are needed.

How Much Does Nemluvio Cost?

Treatment with Nemluvio is expected to cost approximately $28,519 per patient in the first year of treatment and $19,534 in subsequent years.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that nemolizumab be reimbursed for the treatment of 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 only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 double-blind, phase III randomized controlled trials (RCTs) (ARCADIA 1 [N = 941] and ARCADIA 2 [N = 787]) in adults and adolescents (aged ≥ 12 years) with moderate to severe AD demonstrated that treatment with nemolizumab resulted in a statistically significant increase in the proportion of patients achieving treatment success, defined as an Investigator Global Assessment (IGA) score of clear (0) or almost clear (1) and a 2-point or greater reduction in the IGA scale from baseline (strata-adjusted difference = 11.5%; 97.5% confidence interval [CI], 4.7% to 18.3% and 12.2%; 97.5% CI, 4.6% to 19.8%, respectively), and the proportion of patients with a 75% improvement in the Eczema Area and Severity Index (EASI-75) from baseline (strata-adjusted difference = 14.9%; 97.5% CI, 7.8% to 22.0% and 12.5%; 97.5% CI, 4.6% to 20.3%, respectively) relative to placebo at 16 weeks. The evidence also demonstrated a statistically significant increase in the proportion of patients with an improvement of 4 or more points in the Peak Pruritus Numeric Rating Scale (PP-NRS) from baseline (strata-adjusted difference = 24.9%; 97.5% CI, 18.4% to 31.5% and 23.5%; 97.5% CI, 16.1% to 30.3%, respectively). Results from 1 additional double-blind, phase IIIb RCT (ARCADIA CYCLO [N = 276]) in adults (≥ 18 years) with chronic AD whose condition was not adequately controlled with cyclosporine, or in whom cyclosporine was unsuitable also demonstrated a statistically significant increase in the proportion of patients with EASI-75 (strata-adjusted difference = 12.2%; 95% CI, 0.7% to 23.6%), the proportion of patients with PP-NRS improvement of 4 or more points (strata-adjusted difference = 21.7%; 95% CI, 11.4% to 32.0%), but not for [redacted] relative to placebo at 16 weeks.

Despite the number of alternative therapies available, there is a lack of direct comparative evidence for nemolizumab and other advanced systemic therapies in AD (i.e., dupilumab, upadacitinib, abrocitinib). Indirect evidence submitted by the sponsor consisting of a network meta-analysis (NMA) suggested no difference between nemolizumab and other biologic therapies for the same indication, and results compared to JAK inhibitors were inconsistent, either favouring the JAK inhibitor(s), or suggesting no difference between treatments.

Patients and clinicians emphasized the need for new treatments that improve disease control as well as symptom and pain relief (e.g., itch, dryness, inflammation, blistering), convenience, and improved health-related quality of life. CDEC concluded that nemolizumab may meet some of the needs identified by patients, including providing an additional treatment option that may result in improvement in eczema activity and symptoms relative to placebo.

At the sponsor-submitted price for nemolizumab and publicly listed prices for the comparators, nemolizumab is expected to be more costly than dupilumab, upadacitinib, and abrocitinib in the first year of treatment. In subsequent years, nemolizumab is expected to be more costly than upadacitinib 15 mg and abrocitinib, but less costly than upadacitinib 30 mg and dupilumab. As nemolizumab is considered no more effective than comparators, the total drug cost of nemolizumab should not exceed the total drug cost of the lowest cost-advanced therapy reimbursed for the treatment of moderate to severe AD.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, and prescribing		
1. Eligibility for reimbursement of nemolizumab should be based on the criteria used by each of the public drug plans for initiation, renewal, discontinuation, and prescribing of other advanced systemic therapies (i.e., biologics and JAK inhibitors) currently reimbursed for the treatment of moderate to severe AD with the addition of condition 2 for prescribing.	There is no evidence that nemolizumab should be held to a different standard than other advanced systemic therapies used to treat moderate to severe AD (i.e., biologics and JAK inhibitors) currently reimbursed when considering initiation, renewal, and prescribing.	—
2. Nemolizumab should not be reimbursed for use in combination with other advanced systemic therapies (i.e., biologics or JAK inhibitors) for the treatment of moderate to severe AD.	No evidence was identified to demonstrate whether nemolizumab offers additional benefit when used in combination with other advanced systemic therapies used in AD.	—
Pricing		
3. Nemolizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly advanced therapy reimbursed for the treatment of moderate to severe AD.	Indirect evidence suggested no difference between nemolizumab and other biologic therapies, and results compared to JAK inhibitors either favoured the JAK inhibitors or suggested no difference between treatments. As such, there is insufficient evidence to justify a cost premium for nemolizumab over the least expensive advanced therapy reimbursed for moderate to severe AD.	—

AD = atopic dermatitis.

Discussion Points

- **Unmet needs:** CDEC noted the multiple unmet needs identified by patients and clinicians including the need for additional treatment options given that many patients (estimated 30% to 40%) will

not experience response to, or will have disease that becomes refractory to, current nonbiologic therapies. CDEC discussed that patients seek treatments which result in improved disease control, symptom and pain relief (e.g., itch, dryness, inflammation, blistering), convenience, and improved quality of life (QoL).

- **Place in therapy:** CDEC and the clinical experts discussed the reimbursement request, noting that the place in therapy for nemolizumab should be the same as other biologic therapies. CDEC noted that of the 3 trials submitted, only the ARCADIA CYCLO trial enrolled a patient population that were refractory to cyclosporine or for whom this therapy is not advisable. The inclusion criteria for the ARCADIA 1 and ARCADIA 2 trials required that patients experience an inadequate response to topical therapies in the past 6 months. Between 29.1% and 38.1% of patients in the ARCADIA 1 and ARCADIA 2 trials reported prior experience with immunosuppressive therapies, and between 5.4% and 7.5% reported experience with biologics, whereas [redacted] of patients in the ARCADIA CYCLO trial had previous immunosuppressant use ([redacted]. CDEC and the clinical experts noted that this generally aligns with the evidence submitted for other therapies currently reimbursed for AD.
- **Certainty of evidence:** CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of outcomes selected for the review of nemolizumab, highlighting with moderate to high certainty that nemolizumab resulted in increased proportions of patients with an IGA score of 0 or 1, increased proportions of patients with EASI-75 response, and increased proportions of patients with at least a 4-point improvement in the PP-NRS relative to placebo. CDEC noted the high placebo response rate in all 3 ARCADIA trials and was uncertain whether the results for EASI-75 and IGA were clinically meaningful, as the CIs for these outcomes included the possibility of no clinically meaningful benefit based on the threshold identified by the clinical experts. Additionally, CDEC noted that results were only available for the entire randomized population up to 16 weeks, and the maintenance period in the ARCADIA 1 and ARCADIA 2 trials consisted of an enriched population of patients who achieve a clinical response to nemolizumab, not the entire randomized study population.
- **Indirect evidence:** Given the available advanced systemic therapies in moderate to severe AD, CDEC discussed the relevant comparators for this review. The sponsor-submitted NMAs compared nemolizumab to relevant, reimbursed comparators — abrocitinib, upadacitinib, and dupilumab — in patients aged 12 years and older who were candidates for systemic therapy and were also experienced with cyclosporine. Results of the NMAs suggested that upadacitinib 30 mg was favoured over nemolizumab for EASI-75, PP-NRS improvement of 4 points or more, and IGA response, while abrocitinib was favoured over nemolizumab for IGA response. Across all outcomes, there was no difference detected between dupilumab and nemolizumab. CDEC noted the imprecision and uncertainty in the estimates given the wide 95% credible intervals (CrIs), and additional limitations of the indirect evidence including the lack of adolescent patients and lack of results beyond 16 weeks. CDEC was unable to draw firm conclusions on the comparative effectiveness of nemolizumab.

- **Harm profile:** Clinical experts noted that the tolerability profile of nemolizumab was consistent with other biologics used in the treatment of AD and there were fewer safety and monitoring concerns compared to JAK inhibitors. CDEC noted that the safety profile of nemolizumab in the ARCADIA long-term extension (LTE) study was consistent with that of the ARCADIA 1 and ARCADIA 2 trials, and no new safety signals were observed. Based on the sponsor-submitted NMA, there was no difference detected between nemolizumab and any other treatments for AEs, although the results were inconclusive due to the wide CrIs.
- **Trial eligibility and generalizability:** All ARCADIA trials excluded patients with uncontrolled asthma, and a history of bronchitis and/or chronic obstructive pulmonary disease (COPD). As such, CDEC noted that patients with type II inflammation (i.e., elevated eosinophils) may have been more likely to be excluded from these trials and emphasized the uncertainty in whether the observed benefit or lack of harm will be consistent in patients with these conditions. CDEC acknowledged that new or worsening asthma was an adverse event of special interest (AESI) in the ARCADIA trials, and the rates of new or worsening asthma were low (ranging from 1.6% to 5.2% across trials). CDEC also discussed the minimum Eczema Area and Severity Index (EASI) score thresholds required for enrolment into the trials (a minimum score of 16 in the ARCADIA 1 and ARCADIA 2 trials, and a minimum score of 20 for the ARCADIA CYCLO trial), which were in line with reimbursed therapies for moderate to severe AD. CDEC noted that the mean baseline EASI scores in the ARCADIA trials were higher than 27 points, which suggested a more severe population; however, the majority of patients had IGA scores of 3, which was indicative of a moderate population. CDEC noted that subgroup analyses were not conducted for patients with moderate EASI scores; therefore, it is unclear whether the results of these trials were generalizable to patients with more moderate disease per the EASI measure.
- **Other considerations:** CDEC discussed the dosing interval of nemolizumab. The results from the initial period were based on every 4-week dosing, while the maintenance results contained every 4-week and every 8-week schedules. CDEC noted that during the maintenance phase of the ARCADIA 1 and ARCADIA 2 trials, there was not a consistent dose-related benefit, and clinical experts noted that some patients may receive more benefit from every 4-week dosing versus every 8-week dosing. CDEC concluded that the evidence supporting 1 dosing regimen or the other was uncertain.

Background

AD is a chronic, relapsing, inflammatory, and noncontagious skin disease that is thought to involve a complex interplay of genetic, immune, and neuroimmune dysregulation; skin barrier dysfunction; microbial imbalance; and environmental factors. It occurs most frequently in early childhood, and it is estimated that the prevalence of eczema in Canada is 15% in children and adolescents (aged 0.5 years to 17 years), and 3.5% in adults. AD can be mild, moderate, or severe, depending on the extent and the severity of symptoms. The management of AD involves a multipronged approach including patient education, skin hydration, restoration

of the skin, elimination of exacerbating factors, and pharmacologic treatment of skin inflammation. Topical drugs may be used concurrently with phototherapy or systemic drugs for the maintenance of response, rescue treatment, or control of flares. Patients with persistent, moderate to severe AD despite optimized topical therapy require systemic treatment to achieve disease control. The clinical experts consulted for this review noted that a typical progression would be for patients to trial conventional systemic therapies (e.g., methotrexate, mycophenolate mofetil, and cyclosporine) for a period of 3 months and if well-controlled, they would continue to receive that therapy, but if they do not experience response, then they may switch to another conventional systemic therapy or the advanced therapies (dupilumab, abrocitinib, and upadacitinib are recommended by CDA-AMC for reimbursement in moderate to severe AD). They noted a trial of 3 to 6 months is usually used to determine response. If the patient's skin is not completely clear, they may add a topical therapy. Occasionally, the experts noted that a combination of systemic therapies may be used.

Nemolizumab has received approval by Health Canada for the treatment of moderate to severe AD in patients aged 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Nemolizumab is a humanized monoclonal antibody of the IgG2 subclass. It is available as a subcutaneous injection, and the dosage recommended in the product monograph is an initial dose of 60 mg (two 30 mg injections) followed by 30 mg given every 4 weeks. After 16 weeks of treatment, for patients who achieve a clinical response, the recommended maintenance dose of nemolizumab is 30 mg every 8 weeks.

Sources of Information Used by the Committee

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

- a review of 3 RCTs, 2 in patients aged 12 years or older with moderate to severe AD and 1 in patients aged 18 years or older with moderate to severe AD who had a documented history of inadequate response, intolerance or unacceptable toxicity to cyclosporine, or had cyclosporine be medically inadvisable; 1 LTE study; and 1 indirect treatment comparison
- patients' perspectives gathered by 1 patient group, the Eczema Society of Canada (ESC)
- input from public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with moderate to severe AD
- input from 2 clinician groups, the Dermatology Association of Ontario (DAO) and the Atlantic Dermatology Group
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

One patient group submitted input for this review, the ESC, a registered charity in Canada aiming to improve the lives of people living in Canada with eczema through support, education, awareness, and research. Information was gathered for this submission through questionnaires, patient interviews, review of published literature, and data from multiple surveys with a combined total of more than 3,000 survey respondents living in Canada.

Patients with AD described significant physical and emotional burdens, including painful, itchy skin lesions that crack, bleed, and lead to scarring, pigment changes, and infection risk. Persistent itching disrupts sleep, school and/or work, and daily life, with some patients experiencing chronic pain and no relief. Emotionally, patients reported isolation, frustration, anxiety, depression, and difficulties with social and intimate relationships due to low self-esteem and treatment failures. Historically, systemic options were limited to phototherapy, off-label immunosuppressants, and steroids, which many fear using long-term. While newer systemic therapies have helped some, access and response remain inconsistent. Patients expressed frustration with the trial and error nature of treatment and emphasized that due to the heterogeneous nature of AD, no single therapy works for all.

ESC highlighted the urgency for innovative therapies that can offer long-term relief and improve QoL. Outcomes of treatment identified as most important to patients with AD include improved disease control, symptom and pain relief (e.g., itch, dryness, inflammation, blistering), convenience, and improved QoL. ESC described general patient experiences with nemolizumab, although the source of these experiences (e.g., patient interviews, survey responses, general trial observations) was not specified. Patients treated with nemolizumab reported substantial reductions in itch, with noticeable improvements in skin clearance from rashes, lesion, sores, and open wounds, which provided further benefit in improving sleep, productivity, self-esteem, and mental health. ESC noted that many patients who were previously unsuccessful with approved and off-label medications reported success with nemolizumab.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts noted that pruritus (itch) is a very debilitating and unpredictable aspect of AD, and better treatments are needed to target this symptom. In addition, approximately 30% to 40% of patients will either not experience response, or will have disease that becomes refractory to, currently available nonbiologic treatments (1 expert noted this would be about 20% if biologics were also considered); therefore, new treatments are needed. Moderate to severe AD often comes with a high burden of disease, which also impacts patient health-related QoL and their ability to carry out activities due to symptoms, or due to a feeling of self-consciousness. The currently available treatments (e.g., JAK inhibitors) are not always well tolerated and have contraindications or black box warnings, further reinforcing the need for new treatment options.

The clinical experts noted that nemolizumab is the only treatment with a mechanism of action targeting IL-31, which is involved in the sensation of pruritus. It could be used as monotherapy or in combination with topical therapies, phototherapy, and other conventional immunosuppressing systemic drugs. They noted that nemolizumab should be considered a first-line systemic therapy after topical therapies, and considered alongside the other biologics such as dupilumab, tralokinumab, or lebrikizumab. The clinical experts noted that the reimbursement criteria for dupilumab could also be considered appropriate for nemolizumab (e.g., having failed 1 conventional systemic therapy trial); however, the choice to use a conventional treatment or advanced systemic drug would be partially determined by the drug coverage.

The experts noted that nemolizumab would be suitable for all patients with moderate to severe AD, and 1 expert noted it would also be appropriate for patients who do not tolerate, experience response to, or cannot access phototherapy, as well as those who have been unsuccessful or have had a relative contraindication to alternate systemic therapies. The experts further noted that patients who were significantly impacted by pruritus, who have had significant flares of AD, whose current therapy had stopped working, or whose AD had a significant impact on their lives would be those most in need of additional interventions and most likely to benefit. There are no specific criteria or laboratory tests required for diagnosis, as AD is typically diagnosed clinically and is a common disease. The experts noted that there are no biomarkers or tests that would indicate a patient's likelihood of response to nemolizumab.

Measures used in the pivotal trials are also used in clinical practice to assess response, including patient global assessment improvement, EASI reduction, numeric rating scale (NRS) for itch, and Dermatology Life Quality Index (DLQI). The clinical experts also noted that other subjective changes reported by patients in clinical practice may include changes to sleep, daily activities, work productivity, improvement in mental health, and reduction of scratching or itching. They commented that the measures used in clinical practice vary and may be chosen according to the reimbursement criteria set by payers to obtain coverage for a treatment (e.g., change in EASI score at 6 months). Patients are often assessed every 3 months initially and when patients are improved and stable, they are typically assessed every 6 months.

Treatment should be discontinued if there has been no meaningful response after 6 months of therapy, if the patient experiences an allergy or hypersensitivity, or if they experience intolerable adverse events (AEs). The experts noted that definition of a meaningful response could vary and the decision to discontinue is often shared between the clinician and the patient. One expert shared an example that patients with minimal disease response according to a tool such as EASI may still wish to continue treatment if their pruritus is controlled. If there is a partial response, the experts noted that the addition of a new therapy should be considered first, rather than discontinuing the current treatment.

According to the experts, patients should receive a proper diagnosis of AD by a dermatologist before nemolizumab is prescribed. Patients can be managed and monitored by dermatologists in any outpatient clinic (community or hospital). After 6 months of treatment and confirmation of clinical efficacy, primary care providers could also manage the prescribing until reinvolvement of the dermatologist is necessary.

Clinician Group Input

One joint input was submitted for this review by the DAO and the Atlantic Dermatology Group. DAO provides broad representation for more than one-half of registered dermatologists in Canada. The Atlantic Dermatology Group is a group of hospital-based and academic-based dermatologists practising in the Atlantic provinces. Information for this submission was gathered through a review of published literature, clinical trial data, and those with experience with nemolizumab clinical trials.

The input from clinician groups was generally consistent with the clinical experts consulted for this review, emphasizing the ongoing unmet need for treatments that provide rapid and sustained relief from pruritus, as well as improvements in sleep and QoL for patients with moderate to severe AD. Like the experts, the clinician groups highlighted the limitations of current therapies, including slow onset of action with biologics and safety concerns or monitoring requirements with JAK inhibitors. Aligning with expert input, the clinician groups considered nemolizumab a suitable first-line systemic option, to be positioned alongside existing biologics, particularly for patients with an inadequate response to topicals or systemic therapies, or who require more rapid symptom relief. Both also highlighted the novel mechanism and monthly dosing schedule as factors that could improve adherence and convenience. The clinician groups provided additional details on patient selection, noting that nemolizumab may be particularly appropriate for patients with contraindications to JAK inhibitors (e.g., cardiovascular disease, immunosuppression concerns, thromboembolism). They also noted that patients with mild AD that can be managed effectively by topicals alone are less appropriate candidates.

Consistent with expert input, the clinician groups noted a range of clinical and patient-reported tools (e.g., IGA, EASI, PP-NRS, sleep scores) that could be used to assess treatment response, and support reassessment intervals from 4 to 12 months. However, they provided more specific discontinuation criteria, such as not achieving a 4-point or more reduction in PP-NRS or sleep NRS or less than 50% improvement in EASI by week 16, while the experts emphasized a flexible, shared decision-making approach. Both clinical experts and clinician groups agreed that initiation should be done by dermatologists in an outpatient setting, but the clinician groups added that allergists could also initiate therapy, and that self-injection could be possible after training. The clinician group noted that because misdiagnosis of AD can occur, particularly in adult-onset cases, clinical expertise in differentiating AD from other eczematous conditions (e.g., contact dermatitis, seborrheic dermatitis, cutaneous T-cell lymphoma) is essential to ensure appropriate patient selection.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
There are comparator treatments funded by jurisdictions, but the studies provided by the sponsor compare nemolizumab to placebo. Would the anticipated place in therapy for nemolizumab be the same as the comparators (i.e., abrocitinib, dupilumab, upadacitinib)?	The clinical experts and CDEC noted that nemolizumab could be listed alongside the specific comparators.
Considerations for initiation of therapy	
The primary and key secondary end points in the ARCADIA 1 and ARCADIA 2 trials were IGA success (defined as a score of 0 [clear skin] or 1 [almost clear skin], representing a ≥ 2 point improvement from baseline) and EASI-75 response (≥ 75% improvement in EASI from baseline) at week 16. Previous CDEC recommendations have provided a reimbursement condition that both an EASI score and IGA score be provided at initiation; however, only EASI-75 is a required renewal condition. Is there merit to requiring both EASI and IGA scores at baseline, rather than just an EASI score, considering IGA is not required again at renewal for comparator treatments (i.e., are there situations where an individual would not be considered to have moderate to severe AD per their IGA score [score of 3 or 4] but not per EASI [score of 16 or greater])?	CDEC agreed with the clinical experts that there is some ambiguity around the definitions of AD severity when using IGA and EASI scores. An IGA score of 3 is considered moderate AD and 4 is severe. However, an EASI score of 16 would be considered more severe AD and an EASI score as low as 7 would be considered moderate AD. Therefore, a patient with an EASI score of less than 16 could also have moderate AD.
The requested reimbursement criteria is aligned with the key inclusion criteria in the ARCADIA studies (e.g., adult and adolescents aged ≥ 12 years with moderate to severe AD); however, the studies also required individuals to have pruritus associated with their AD (PP-NRS score of ≥ 4). Is the PP-NRS used in clinical practice? If so, should a PP-NRS be obtained at the initiation of therapy? Should patients be required to have a PP-NRS score of 4 or greater to initiate the use of nemolizumab?	The clinical experts noted that PP-NRS has not been used as a criterion for any other advanced systemics, and its use in clinical practice is variable; but may be used in private reimbursement for other disease indications. It should not be mandatory in addition to other reimbursement criteria, but it would have a role as a marker of application and for reimbursement because nemolizumab has a potential mechanism to address pruritus in AD. The clinical experts suggested that it could replace either IGA or EASI. CDEC agreed with the clinical experts.
Reviews by CDEC for comparators (i.e., abrocitinib, dupilumab, and upadacitinib) have resulted in a reimbursement recommendation that therapy be initiated in individuals with refractory disease, are intolerant to, or are ineligible for: • maximally tolerated topical therapies with phototherapy (where available) • maximally tolerated topical therapies combined with at least 1 of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine). Although individuals in the ARCADIA 1 and ARCADIA 2 trials were not required to have had a prior trial of phototherapy, should individuals be required to be refractory to maximally tolerated topical therapies with phototherapy (where available) before becoming eligible to receive nemolizumab? Although individuals in the ARCADIA 1 and ARCADIA 2	A trial of phototherapy should not be required as only a small proportion of patients can access it. For example, in psoriasis, phototherapy is considered an immunomodulator by some jurisdictions for reimbursement purposes, and therefore patients who are refractory to phototherapy do not have to subsequently trial a systemic immunomodulator before trying advanced systemic drugs. Ideally, patients should not have had to trial a systemic immunomodulator before becoming eligible to receive nemolizumab or other advanced systemic drugs for this indication. Several private drug plans do not require this, but they acknowledged that the public plan reimbursement criteria for other advanced systemic drugs currently do. CDEC agreed with the clinical experts.

Implementation issues	Response
trials were not required to have had a prior trial of a systemic immunomodulator, should individuals be required to be refractory to maximally tolerated topical therapies with a systemic immunomodulator before becoming eligible to receive nemolizumab?	
Would it be appropriate to initiate the use of nemolizumab in patients whose AD has not responded to previous treatment with a biologic drug or JAK inhibitor?	It is variable whether a patient's AD will respond to 1 class of systemic drugs vs. another, and therefore it would be appropriate to initiate the use of nemolizumab in these patients. However, CDEC noted that there is no evidence supporting the use of nemolizumab in those who are refractory to advanced therapies given the limited representation in the available evidence.
Consider alignment with criteria recommendation for comparators (i.e., abrocitinib, dupilumab, and upadacitinib).	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
Considering the key secondary end point related to PP-NRS (as previously described), could there be a situation where individuals do not achieve EASI-75 but may continue to benefit from nemolizumab based on improvements in PP-NRS?	Given the potential of nemolizumab to address itch, patients who have not yet achieved EASI-75 but have achieved substantial itch reduction may still derive benefit from nemolizumab. CDEC agreed with the clinical experts.
If consideration for renewal should be given to individuals with improvement in PP-NRS, is there a minimum improvement which should be required?	CDEC and the clinical experts agreed that a change of 4 points or higher — similar to the pivotal trial — would be reasonable, although the timing of the assessment would also be important (e.g., 6 months similar to other assessments).
Consider alignment with criteria recommendation for comparators (i.e., abrocitinib, dupilumab, and upadacitinib).	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
Following the initial 16 weeks of ARCADIA 1 and ARCADIA 2 trials, patients who achieve a clinical response to receiving nemolizumab were rerandomized 1:1:1 to nemolizumab 30 mg every 4 weeks, nemolizumab 30 mg every 8 weeks (with placebo every 8 weeks to obtain an every 4-week injection interval), or placebo every 4 weeks. The monograph dosing for nemolizumab is 60 mg initially, followed by 30 mg every 4 weeks. After 16 weeks of treatment, patients who achieve a clinical response are recommended to continue therapy at a maintenance dose of nemolizumab 30 mg every 8 weeks. The rerandomized results showed the percent of individuals maintaining their EASI-75 improvement in the nemolizumab every 4 weeks group, the nemolizumab every 8 weeks group, and the placebo every 4 weeks group was: • 85.9%, 90.8%, and 84.7% at week 20 • 74.8%, 76.7%, and 66.9% at week 28 • 62.6%, 63.8%, and 47.8% at week 40 • 55.8%, 58.9%, and 44.6% at week 48. Should nemolizumab be funded at a maximum of 30 mg every	The clinical experts noted that having the option to dose nemolizumab every 8 weeks would be good; however, some patients might achieve more benefit from receiving nemolizumab every 4 weeks, and therefore having the option of every 4 weeks would also be helpful. CDEC noted that during the maintenance phase, there is not a consistent dose-related benefit, and results were less certain as this consisted of an enriched population but noted that the Health Canada indication specifies that nemolizumab would be used every 8 weeks after 16 weeks.

Implementation issues	Response
8 weeks during the maintenance phase (i.e., after 16 weeks of treatment)? Or are there individuals who may benefit from ongoing nemolizumab 30 mg every 4 weeks?	
Can nemolizumab be used in combination with other therapies for AD, such as immunosuppressants, phototherapy, biologics, or JAK inhibitors?	The clinical experts stated that nemolizumab could be combined with other therapies for AD. However, CDEC noted that there is no evidence supporting the use of nemolizumab in combination with other advanced therapies (i.e., biologics or JAK inhibitors) as these patients were excluded from the ARCADIA trials.
System and economic issues	
The cost of nemolizumab is higher in year 1 than comparators due to loading and the need for an initial every 4-week dosing. In subsequent years, the cost is lower than dupilumab since individuals who experience response to nemolizumab can reduce frequency to every 8-week dosing. If individuals remain on nemolizumab every 4 weeks long-term, that could significantly change the annual cost of nemolizumab. A scenario analysis is included to explore the impact of every 4-week dosing.	This is a comment from the drug programs to inform CDEC deliberations.
All 3 of the comparators (abrocitinib, dupilumab, and upadacitinib) have confidential pricing in place for AD.	This is a comment from the drug programs to inform CDEC deliberations.

AD = atopic dermatitis; CDEC = Canadian Drug Expert Committee; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-75 = a 75% improvement in the Eczema Area and Severity Index; IGA = Investigator Global Assessment Scale; PP-NRS = Peak Pruritus Numeric Rating Scale; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

Three studies (ARCADIA 1, ARCADIA 2, and ARCADIA CYCLO) were included in the systematic review.

ARCADIA 1 and ARCADIA 2 Trials

The study designs for the ARCADIA 1 and ARCADIA 2 trials were identical; both were phase III, double-blind, placebo-controlled, multicentre RCTs evaluating the efficacy and safety of nemolizumab in adults and adolescents (aged ≥ 12 years) with moderate to severe AD. The coprimary end point of the ARCADIA 1 and ARCADIA 2 studies was the proportion of patients with IGA success, and the proportion of patients with EASI-75 at week 16. Key secondary end points also evaluated changes in PP-NRS across the study period. Patients were randomized via interactive response technology 2:1 to receive nemolizumab (ARCADIA 1: N = 620; ARCADIA 2: N = 522) or placebo (ARCADIA 1: N = 321; ARCADIA 2: N = 265) for 16 weeks. After the 16-week initial treatment period, patients in the treatment arm who achieved a clinical response to treatment (defined as an IGA of 0 [clear] or 1 [almost clear] or EASI-75 at week 16) were rerandomized 1:1:1 to receive either nemolizumab every 4 weeks (N = 169), nemolizumab every 8 weeks (N = 169), or placebo (N = 169) for the maintenance period.

ARCADIA CYCLO Trial

ARCADIA CYCLO was a phase IIIb, double-blinded, placebo-controlled, multicentre RCT evaluating the efficacy and safety of nemolizumab in adult patients aged 18 years or older with chronic AD who had a documented history of inadequate response, intolerance or unacceptable toxicity to cyclosporine, or had cyclosporine be medically inadvisable. Patients were randomized 1:1 to receive nemolizumab (N = 138) or placebo (N = 138). The primary end point of the ARCADIA CYCLO trial was the proportion of patients with EASI-75, and proportion of patients with an improvement of PP-NRS of 4 or more from baseline at week 16.

Efficacy Results

ARCADIA 1 and ARCADIA 2 Trials: Initial Period

Proportion of Patients With IGA Success at Week 16

For patients in ARCADIA 1, at week 16 35.6% of patients in the nemolizumab arm and 24.6% of patients in the placebo arm attained IGA success (defined as IGA 0 or 1 and a ≥ 2-point reduction from baseline). The strata-adjusted difference between arms was 11.5% (97.5% CI, 4.7% to 18.3%, P = 0.0003). For patients in ARCADIA 2, at week 16, 37.7% of patients in the nemolizumab arm and 26.0% of patients in the placebo arm attained IGA success. The strata-adjusted difference between arms was 12.2% (97.5% CI, 4.6% to 19.8%, P = 0.0006).

Proportion of Patients Who Attained EASI-75 at Week 16

For patients in the ARCADIA 1 trial at week 16, 43.5% of patients in the nemolizumab arm and 29.0% of patients in the placebo arm attained EASI-75. The strata-adjusted difference between arms was 14.9% (97.5% CI, 7.8% to 22.0%; P = < 0.0001). For patients in the ARCADIA 2 trial at week 16, 42.1% of patients in the nemolizumab arm and 30.2% of patients in the placebo arm attained EASI-75. The strata-adjusted difference between arms was 12.5% (97.5% CI, 4.6% to 20.3%; P = 0.0006).

Change From Baseline to Week 16 in Total EASI Scores

For patients in the ARCADIA 1 trial, the least squares (LS) mean change from baseline in total EASI score was –12.36 (95% CI, –13.96 to –10.76) in the nemolizumab arm, and –8.68 (95% CI, –10.77 to –6.58) in the placebo arm. The LS mean difference was –3.68 (95% CI, –6.08 to –1.28; P = 0.0026). For patients in the ARCADIA 2 trial, the LS mean change from baseline in total EASI score was –13.15 (95% CI, –14.57 to –11.73) in the nemolizumab arm and –9.02 (95% CI, –10.97 to –7.08) in the placebo arm. The LS mean difference between study arms was –4.13 (95% CI, –6.36 to –1.89; P = 0.0003).

Proportion of Patients With an Improvement of PP-NRS Scores of 4 or More at Week 16

For patients in the ARCADIA 1 trial at week 16, 42.7% of patients in the nemolizumab arm and 17.8% of patients in the placebo arm reported a reduction in PP-NRS scores of 4 points or more. The strata-adjusted LS mean difference between arms was 24.9% (97.5% CI, 18.4% to 31.5%; P < 0.0001). For patients in the ARCADIA 2 trial at week 16, 41.0% of patients in the nemolizumab arm and 18.1% of patients in the placebo arm reported a reduction in PP-NRS scores of 4 points or more. The strata-adjusted LS mean difference between arms was 23.2% (97.5% CI, 16.1% to 30.3%; P < 0.0001).

Proportion of Patients With PP-NRS Scores of 2 Points or Less at Week 16

For patients in the ARCADIA 1 trial, at week 16, 30.6% of patients in the nemolizumab arm and 11.2% of patients in the placebo arm reported a PP-NRS score of 2 points or less. The strata-adjusted LS mean difference between arms was 19.5% (97.5% CI, 13.7% to 25.2%; P = < 0.0001). For patients in the ARCADIA 2 trial at week 16, 28.4% of patients in the nemolizumab arm and 11.3% of patients in the placebo arm reported a PP-NRS score of 2 points or less. The strata-adjusted LS mean difference between arms was 17.1% (97.5% CI, 10.9% to 23.3%; P = < 0.0001).

Change From Baseline to Week 16 in PP-NRS Scores

For patients in the ARCADIA 1 trial, the LS mean change from baseline in PP-NRS score was –3.77 (95% CI, –4.02 to –3.53) in the nemolizumab arm, and –1.94 (95% CI, –2.26 to –1.61) in the placebo arm. The LS mean difference was –1.84 (95% CI, –2.21 to –1.47; P = < 0.0001). For patients in the ARCADIA 2 trial, the LS mean change from baseline in PP-NRS score was –3.71 (95% CI, –3.94 to –3.47) in the nemolizumab arm and –1.95 (95% CI, –2.27 to –1.63) in the placebo arm. The LS mean difference between study arms was –1.76 (95% CI, –2.13 to –1.39; P = < 0.0001).

Change From Baseline to Week 16 in DLQI Total Scores

For adult patients in the ARCADIA 1 trial, the LS mean change from baseline in DLQI total score was –7.76 (95% CI, –8.49 to –7.03) in the nemolizumab arm, and –5.26 (95% CI, –6.23 to –4.29) in the placebo arm. The LS mean difference was –2.50 (95% CI, –3.63 to –1.37; P = < 0.0001). For adult patients in the ARCADIA 2 trial, the LS mean change from baseline in DLQI total score was –6.96 (95% CI, –7.67 to –6.25) in the nemolizumab arm and –4.52 (95% CI, –5.48 to –3.56) in the placebo arm. The LS mean difference between study arms was –2.44 (95% CI, –3.58 to –1.30; P = < 0.0001).

Change From Baseline to Week 16 in Children’s Dermatology Quality of Life Total Scores

For adolescent patients in the ARCADIA 1 trial, the LS mean change from baseline in the Children’s DLQI (CDLQI) total score was –6.92 (95% CI, –9.26 to –4.58) in the nemolizumab arm, and –5.10 (95 CI, –7.71 to –2.50) in the placebo arm. The LS mean difference was –1.82 (95% CI, –4.88 to 1.25; P = 0.2454). For adolescent patients in the ARCADIA 2 trial, the LS mean change from baseline in the CDLQI total score was –7.40 (95% CI, –8.97 to –5.82) in the nemolizumab arm and –5.02 (95% CI, –7.48 to –2.56) in the placebo arm. The LS mean difference between study arms was –2.38 (95% CI, –5.03 to 0.27; P = 0.0788).

Incidence of Rescue Therapy Use

In the ARCADIA 1 trial, during the initial period a total of 3.4% of patients in the nemolizumab arm and 4.0% of patients in the placebo arm reported using rescue therapy. In the ARCADIA 2 trial, during the initial period a total of 2.1% of patients in the nemolizumab arm and 4.2% of patients in the placebo arm reported using rescue therapy.

ARCADIA 1 and ARCADIA 2 Trials: Pooled Maintenance Period

The ARCADIA 1 and ARCADIA 2 trials were noted by the sponsor to be replicate studies, having identical inclusion and exclusion criteria, study design, and analysis methods. In addition, a similar proportion of patients in each study who achieved a clinical response continued on to the maintenance period, and study

discontinuations or losses to follow-up were broadly similar. Therefore, the pooled maintenance period results were appraised in the report. Of the intent-to-treat population initially randomized in the initial period, 169 patients were rerandomized to the nemolizumab every 4 weeks arm, 169 to the nemolizumab every 8 weeks arm, and 169 to the placebo arm.

Proportion of Patients Maintaining IGA Success Until Week 48 From the Subset With IGA Success at Week 16

At week 48, 31.7% of patients in the nemolizumab every 4 weeks arm (N = 142), 37.3% of patients in the nemolizumab every 8 weeks arm (N = 142), and 31.3% of patients in the placebo arm (N = 131) reported maintaining IGA success at all study visits until week 48. The strata-adjusted LS mean difference between nemolizumab every 4 weeks and placebo was 0.5% (95% CI, –10.5% to 11.6%). The strata-adjusted LS mean difference between nemolizumab every 8 weeks and placebo was 6.0% (95% CI, –5.2% to 17.1%).

At week 48, 63.4% of patients in the nemolizumab every 4 weeks arm (N = 142), 64.1% of patients in the nemolizumab every 8 weeks arm (N = 142), and 55.0% of patients in the rerandomized placebo arm (N = 131) reported IGA success. The strata-adjusted LS mean difference between nemolizumab every 4 weeks and placebo was 8.5% (95% CI, –3.0% to 20.2%). The strata-adjusted LS mean difference between nemolizumab every 8 weeks and placebo was 9.1% (95% CI, –2.5% to 20.6%).

Proportion of Patients Maintaining EASI–75 Until Week 48 From the Subset With EASI-75 at Week 16

At week 48, 55.8% of patients in the nemolizumab every 4 weeks arm (N = 163), 58.9% of patients in the nemolizumab every 8 weeks arm (N = 163), and 44.6% of patients in the placebo arm (N = 163) reported maintaining EASI-75 at all study visits until week 48. The strata-adjusted LS mean difference between nemolizumab every 4 weeks and placebo was 11.2% (95% CI, 0.3% to 22.1%). The strata-adjusted LS mean difference between nemolizumab every 8 weeks and placebo was 14.1% (95% CI, 3.3% to 24.9%).

At week 48, 76.3% of patients in the nemolizumab every 4 weeks arm (N = 169), 75.7% of patients in the nemolizumab every 8 weeks arm (N = 169), and 63.9% of patients in the rerandomized placebo arm (N = 169) reported attaining EASI-75. The strata-adjusted LS mean difference between nemolizumab every 4 weeks and placebo was 12.4% (95% CI, 2.7% to 22.0%). The strata-adjusted LS mean difference between nemolizumab every 8 weeks and placebo was 11.8% (95% CI, 2.1% to 21.5%).

Change From Week 16 to Week 48 in EASI Scores

The LS mean change from baseline in EASI scores was 2.01 (95% CI, –0.16 to 4.19; N = 169) in the nemolizumab every 4 weeks arm; 2.98 (95% CI, 0.80 to 5.17; N = 169) in the nemolizumab every 8 weeks arm; and 6.79 (95% CI, 4.62 to 8.96; N = 169) in the placebo arm. The LS mean difference from placebo was –4.78 (95% CI, –7.85 to –1.70) in the nemolizumab every 4 weeks arm and –3.80 (95% CI, –6.89 to –0.72) in the nemolizumab every 8 weeks arm.

Proportion of Patients With PP-NRS Improvement of 4 or More From Initial Baseline to Week 48 From the Subset With PP-NRS of 4 or More at Week 16

At week 48, out of the subset of patients who had a PP-NRS score improvement of 4 points or more at week 16, 46.9% of patients in the nemolizumab every 4 weeks arm (N = 98), 40.4% of patients in the nemolizimab every 8 weeks arm (N = 94), and 31.3% of patients in the placebo arm (N = 83) reported an improvement in PP-NRS scores of 4 points or more from the initial period baseline. The strata-adjusted proportion difference versus placebo was 15.4% (95% CI, 1.3% to 29.4%) in the nemolizumab every 4 weeks arm and 9.1% (95% CI, –5.0% to 23.2%) in the nemolizumab every 8 weeks arm.

At week 48 of the entire maintenance period population, 36.7% of patients in the nemolizumab every 4 weeks arm (N = 169), 29.0% of patients in the nemolizimab every 8 weeks arm (N = 169), and 21.3% of patients in the placebo arm (N = 169) reported an improvement in PP-NRS scores of 4 points or more from the initial period baseline. The strata-adjusted proportion difference versus placebo was 15.4% (95% CI, 5.8% to 24.9%) in the nemolizumab every 4 weeks arm and 7.7% (95% CI, –1.5% to 16.9%) in the nemolizumab every 8 weeks arm.

Proportion of Patients With PP-NRS of 2 or Less at Week 48 From the Subset With PP-NRS of 2 or Less at Week 16

At week 48, 39.7% of patients in the nemolizumab every 4 weeks arm (N = 169), 43.0% of patients in the nemolizimab every 8 weeks arm (N = 169), and 34.4% of patients in the placebo arm (N = 169) reported a PP-NRS score of 2 points or less. The strata-adjusted proportion difference versus placebo was 5.9% (95% CI, –10.1% to 21.8%) in the nemolizumab every 4 weeks arm and 8.6% (95% CI, –7.4% to 24.6%) in the nemolizumab every 8 weeks arm.

At week 48, out of the entire maintenance period population, 30.2% of patients in the nemolizumab every 4 weeks arm (N = 169), 27.8% of patients in the nemolizimab every 8 weeks arm (N = 169), and 18.9% of patients in the placebo arm (N = 169) reported a PP-NRS score of 2 points or less. The strata-adjusted proportion difference versus placebo was 11.2% (95% CI, 2.1% to 20.3%) in the nemolizumab every 4 weeks arm and 8.9% (95% CI, –0.1% to 17.8%) in the nemolizumab every 8 weeks arm.

Change From Week 16 to Week 48 in PP-NRS

The LS mean change from baseline in PP-NRS score was –0.46 (95% CI, 0.88 to –0.05; N = 143) in the nemolizumab every 4 weeks arm, 0.10 (95% CI, –0.29 to 0.48; N = 155) in the nemolizumab every 8 weeks arm, and 1.35 (95% CI, 0.95 to 1.74; N = 152) in the placebo arm. The LS mean difference from placebo was –1.81 (95% CI, –2.39 to –1.23) in the nemolizumab every 4 weeks arm and –1.25 (95% CI, –1.79 to –0.71) in the nemolizumab every 8 weeks arm.

Change From Week 16 to Week 48 in DLQI Total Score

The LS mean change from baseline in DLQI score was –0.43 (95% CI, –1.11 to 0.24; N = 119) in the nemolizumab every 4 weeks arm, 0.14 (95% CI, –0.50 to 0.79; N = 130) in the nemolizumab every 8 weeks arm, and 0.70 (95% CI, 0.00 to 1.40; N = 110) in the placebo arm. The LS mean difference from placebo was

–1.14 (95% CI, –2.11 to –0.16) in the nemolizumab every 4 weeks arm and –0.56 (95% CI, –1.52 to 0.40) in the nemolizumab every 8 weeks arm.

Change From Week 16 to Week 48 in CDLQI Total Score

The LS mean change from baseline in CDLQI score was –0.54 (95% CI, –1.45, 0.36; N = 29) in the nemolizumab every 4 weeks arm, –1.27 (95% CI, –2.30 to –0.23; N = 22) in the nemolizumab every 8 weeks arm, and 0.34 (95% CI, –0.71 to 1.38; N = 22) in the placebo arm. The LS mean difference from placebo was –0.88 (95% CI, –2.27 to 0.51) in the nemolizumab every 4 weeks arm and –1.60 (95% CI, –3.08 to –0.12) in the nemolizumab every 8 weeks arm.

Incidence of Rescue Therapy Use

In the maintenance period, a total of 1.2% of patients in the nemolizumab every 4 weeks arm, 2.4% in the nemolizumab every 8 weeks arm, and 5.3% of patients in the placebo arm reported using rescue therapy.

ARCADIA CYCLO Trial

Proportion of Patients With EASI-75

At week 16, 47.1% of patients in the nemolizumab arm and 34.8% of patients in the placebo arm reported EASI-75. The strata-adjusted difference between the study arms was 12.2% (95% CI, 0.7% to 23.6%; P = 0.040).

Proportion of Patients With Prior Cyclosporine Use With EASI-75

Percent Change From Baseline in EASI

Proportion of Patients With an Improvement of PP-NRS of 4 or More From Baseline to Week 16

At week 16, 39.1% of patients in the nemolizumab arm and 17.4% of patients in the placebo arm reported an improvement in PP-NRS scores of 4 points or more. The strata-adjusted difference versus placebo was 21.7% (95% CI, 11.4% to 32.0%; P < 0.001).

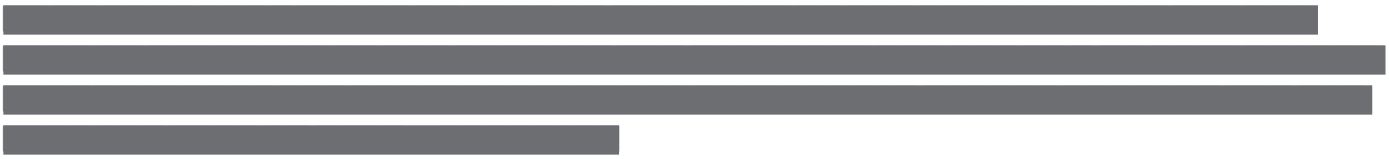
Proportion of Patients With PP-NRS Less Than 2 at Week 16

Percent Change From Baseline to Week 16 in PP-NRS

Proportion of Patients With IGA Success

Change From Baseline to Week 16 in DLQI Total Score

Incidence of Resue Treatment Use



Harms Results

Adverse Events

ARCADIA 1 Trial

During the initial period of the ARCADIA 1 trial, 49.7% of patients in the nemolizumab arm and 45.5% of patients in the placebo arm reported at least 1 AE. The most commonly reported AEs during this period were infections and infestations (18.3% nemolizumab arm, 20.3% placebo arm); skin and subcutaneous tissue disorders (18.3% nemolizumab arm, 14.0% placebo arm); and respiratory, thoracic, or mediastinal disorders (9.4% nemolizumab arm, 8.7% placebo arm).

During the maintenance period of the ARCADIA 1 trial, 58.2% of patients in the nemolizumab every 4 weeks arm, 55.6% in the nemolizumab every 8 weeks arm, 58.2% in the rerandomized placebo arm and 55.0% in the carry-over placebo arm reported AEs. The most common AEs were infections and infestation (34.1% nemolizumab every 4 weeks, 34.4% nemolizumab every 8 weeks, 34.1% rerandomized placebo, 34.0% nonrandomized placebo arms); skin and subcutaneous issues (12.1% nemolizumab every 4 weeks, 11.1% nemolizumab every 8 weeks, 14.3% rerandomized placebo, 14.0% nonrandomized placebo); and respiratory, thoracic, and mediastinal disorders (12.1% nemolizumab every 4 weeks, 11.1% nemolizumab every 8 weeks, 13.2% rerandomized placebo, 7.0% nonrandomized placebo arm). There was a numerically higher proportion of patients reporting infections and infestations in the maintenance period relative to the

initial period, and a numerically higher number of patients in the nemolizumab every 4 weeks arm who reported gastrointestinal disorders (12.1%) relative to the other arms in the maintenance period (ranging from 5.6% to 7.7% of patients).

ARCADIA 2 Trial

During the initial period of the ARCADIA 2 trial, 41.4% of patients in the nemolizumab arm and 44.5% of patients in the placebo arm reported at least 1 AE. The most commonly reported AEs during this period were infections and infestations (17.0% nemolizumab arm, 20.2% placebo arm); skin and subcutaneous tissue disorders (12.1% nemolizumab arm, 9.9% placebo arm); and respiratory, thoracic, or mediastinal disorders (5.6% nemolizumab arm, 5.3% placebo arm).

During the maintenance period of the ARCADIA 1 trial, 48.1% of patients in the nemolizumab every 4 weeks arm, 51.9% in the nemolizumab every 8 weeks arm, 58.4% in the rerandomized placebo arm, and 44.0% in the carry-over placebo arm reported AEs. The most common AEs were infections and infestation (27.8% nemolizumab every 4 weeks, 22.1% nemolizumab every 8 weeks, 31.2% rerandomized placebo, 28.6% nonrandomized placebo arms); skin and subcutaneous issues (13.9% nemolizumab every 4 weeks, 10.4% nemolizumab every 8 weeks, 13.0% rerandomized placebo, 9.5% nonrandomized placebo); and respiratory, thoracic, and mediastinal disorders (10.1% nemolizumab every 4 weeks, 6.5% nemolizumab every 8 weeks, 11.7% rerandomized placebo, 2.4% nonrandomized placebo arm). A numerically higher proportion of patients in the rerandomized placebo arm reported COVID-19 (16.9%) relative to other study arms (ranging from 3.8% to 7.1%).

ARCADIA CYCLO Trial

Serious Adverse Events

ARCADIA 1 Trial

During the initial period of the ARCADIA 1 trial, 1.0% of patients in the nemolizumab arm and 1.2% of patients in the placebo arm reported any serious adverse event (SAE). AD SAEs were reported by 2 patients in the nemolizumab arm, and 3 patients in the placebo arm. The remaining SAEs by preferred term were reported in fewer than 2 patients.

During the maintenance phase of the ARCADIA 1 trial, 4.4% of patients in the nemolizumab every 4 weeks arm, 3.3% in the nemolizumab every 8 weeks arm, 2.2% in the rerandomized placebo arm, and 1.0% in the

nonrandomized placebo arm reported any SAEs. The SAEs by preferred term were reported in fewer than 2 patients.

ARCADIA 2 Trial

During the initial period of the ARCADIA 2 trial, 2.5% of patients in the nemolizumab arm and 1.1% of patients in the placebo arm reported any SAE. SAEs reported in more than 2 patients in the nemolizumab arm included 3 patients reporting infections and infestations, 3 patients reporting musculoskeletal and connective tissue disorders, 3 patients reporting skin and subcutaneous tissue disorders, and 2 patients reporting gastrointestinal disorders.

During the maintenance phase of the ARCADIA 2 trial, 7.6% of patients in the nemolizumab every 4 weeks arm, 0 in the nemolizumab every 8 weeks arm, 2.6% in the rerandomized placebo arm, and 1.2% in the nonrandomized placebo arm reported any SAEs. There were no SAEs reported in more than 2 patients.

ARCADIA CYCLO Trial

During the ARCADIA CYCLO trial, 2.2% of patients in the nemolizumab arm and 1.5% of patients in the placebo arm reported SAEs. In the nemolizumab arm, SAEs were reported in 2 patients in the category of infections and infestations. In the placebo arm, SAEs by preferred term were reported in fewer than 2 patients.

Withdrawals Due to Adverse Events

ARCADIA 1 Trial

During the initial period, 1.8% of patients in the nemolizumab arm and 4.0% of patients in the placebo arm discontinued study drug treatment due to AEs. In the maintenance period, 1.1% of patients in the nemolizumab every 4 weeks arm, 3.3% in the nemolizumab every 8 weeks arm, 2.2% in the rerandomized placebo arm, and 2.0% in the carry-over placebo arm discontinued due to AEs. In both the initial and maintenance periods, AD was the most common reason for discontinuation (initial period: 1.6% of patients in the nemolizumab arm, 4.0% of patients in the placebo arm; maintenance period: 0% nemolizumab every 4 weeks arm, 2.2% nemolizumab every 8 weeks arm, 1.1% rerandomized placebo arm, 2.0% carry-over placebo arm).

ARCADIA 2 Trial

During the initial period, 3.5% of patients in the nemolizumab arm and 1.1% of patients in the placebo arm reported discontinuing due to AEs. In the maintenance period, 3.8% of patients in the nemolizumab every 4 weeks arm, 2.6% in the nemolizumab every 8 weeks arm, 3.9% in the rerandomized placebo arm, and 2.4% in the nonrandomized placebo arm withdrew due to AEs. In both the initial and maintenance periods, the most common reason for withdrawal of the study drug was AD (initial period: 1.5% of patients in the nemolizumab arm, 0.8% placebo arm; maintenance period: 2.5% nemolizumab every 4 weeks arm, 2.6% nemolizumab every 8 weeks arm, 2.6% rerandomized placebo arm, 2.4% carry-over placebo arm).

ARCADIA CYCLO Trial

Mortality

There were no deaths reported in the ARCADIA 1, ARCADIA 2, or ARCADIA CYCLO trials.

Notable Harms

The adverse events of special interest (AESIs) identified in the submission for the ARCADIA 1 and ARCADIA 2 trials were injection site reactions, newly diagnosed or worsening asthma, infections, peripheral edema, and elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × upper limit of normal) in combination with elevated bilirubin (> 2 × upper limit of normal). The AESIs identified in the submission for the ARCADIA CYCLO trial were injection-related reactions, drug hypersensitivity, infections, COVID-19, asthma, peak expiratory flow rate decrease, and peripheral edema. The submission did not contain details on whether these AESIs were prespecified or identified during the conduct of the studies.

ARCADIA 1 Trial

During the initial period, injection-related reactions were reported in 0.2% of patients in the nemolizumab arm, and 0 patients in the placebo arm; 0 patients reported injection-related reactions in the maintenance period. Newly diagnosed or worsening asthma were reported in 5.2% of patients in the nemolizumab arm and 3.4% of patients in the placebo arm during the initial period; 3.3% nemolizumab every 4 weeks arm, 6.7% nemolizumab every 8 weeks arm, 2.2% rerandomized placebo arm, and 5.0% carry-over placebo arm in the maintenance period. Infections were reported in 3.2% in the nemolizumab arm, 3.1% in the placebo arm during the initial period; 13.2% nemolizumab every 4 weeks, 12.2% nemolizumab every 8 weeks, 13.2% rerandomized placebo, and 12.0% carry-over placebo arm during the maintenance period. Peripheral edema was reported in 1.1% nemolizumab arm and 0.3% placebo arm during the initial period; 1.1% nemolizumab every 4 weeks, 2.2% nemolizumab every 8 weeks, 1.1% rerandomized placebo, and 0 patients in the carry-over placebo arm during the maintenance period. Elevated ALT or AST in combination with elevated bilirubin was not reported during the trial.

ARCADIA 2 Trial

During the initial period and maintenance periods, no injection-related reactions were reported. Newly diagnosed or worsening asthma was reported in 2.9% of patients in the nemolizumab arm and 3.0% of patients in the placebo arm during the initial period; 5.1% nemolizumab every 4 weeks arm, 0% nemolizumab every 8 weeks arm, 2.6% rerandomized placebo arm, and 0% carry-over placebo arm in the maintenance period. Infections were reported in 3.9% nemolizumab arm, 4.6% placebo arm during the initial period; 5.1% nemolizumab every 4 weeks, 7.8% nemolizumab every 8 weeks, 16.9% rerandomized placebo, and 10.7% carry-over placebo arm during the maintenance period. Peripheral edema was reported

in 2.3% nemolizumab arm, 0.4% placebo arm during the initial period; 0% nemolizumab every 4 weeks, 0% nemolizumab every 8 weeks, 2.6% rerandomized placebo, and 0% patients in the carry-over placebo arm during the maintenance period. Elevated ALT or AST in combination with elevated bilirubin was not reported during the trial.

ARCADIA CYCLO Trial

Critical Appraisal

Internal Validity

In all ARCADIA studies (ARCADIA 1, ARCADIA 2, and ARCADIA CYCLO), the procedures for randomization, treatment allocation, blinding, and study drug administration were all described and likely at low risk of bias; however, the study design is subject to some limitations. In the ARCADIA 1 and ARCADIA 2 trials, only patients who achieved a clinical response (defined by an IGA score of 0 [clear] or 1 [almost clear], or a ≥ 75% improvement in EASI from baseline) continued from the initial period on to the maintenance period. This imparts a response bias for the maintenance phase as the patients included in the maintenance phase are an enriched population of patients who have already experienced response to treatment by 16 weeks. It is not known whether those who did not experience response to treatment had specific common characteristics that would have impacted their likelihood of experiencing response to treatment. The duration of the initial treatment period, while generally consistent with studies for other treatments reimbursed for moderate to severe AD, may not be long enough to obtain complete treatment response, as the clinical experts consulted for this review noted that a trial of up to 6 months is used in clinical practice, which is a relevant consideration for all ARCADIA trials. There was no run-in period for the ARCADIA CYCLO trial, while patients' background treatment was standardized in the ARCADIA 1 and ARCADIA 2 trial. As patients in the ARCADIA CYCLO trial have more severe disease, this may impact the certainty in the results as patients' background therapies in the ARCADIA CYCLO trial could have differed in efficacy and type of product.

With regards to the statistical analysis across trials, the assessment of outcomes for the coprimary and key secondary outcomes in the initial period is likely at lower risk of bias due to being controlled for multiplicity; however, the order of hypothesis testing for the outcomes is unknown and therefore the alpha spending among the list of outcomes, or when testing might have ended, is also unknown. In the ARCADIA 1 and ARCADIA 2 trials, the results of the sensitivity analyses testing different methods of classifying missing data for patients whose disease responded to treatment and those whose disease did not respond to treatment were also consistent with the main analysis, which suggests the results are reasonably robust. However, the statistical analysis methods are subject to some limitations that impact internal validity, and which

increase the uncertainty in the results. In the ARCADIA 1 and ARCADIA 2 trials, there were several protocol amendments, although it is unclear how many patients were impacted by the modification, or what impact this may have had on the results. Per the individual statistical analysis plan for the ARCADIA 1 and ARCADIA 2 trials, no hypothesis testing was conducted on outcomes in the maintenance phase; however, the pooled Clinical Study Report described statistical tests comparing nemolizumab arms to the rerandomized placebo group. In addition, there was no control of multiplicity for the secondary outcomes in the initial period (change from baseline in PP-NRS, EASI, DLQI, and CDLQI) and maintenance period (all outcomes); therefore, there is a risk of increased type I error for these outcomes. The study populations of the ARCADIA 1 and ARCADIA 2 trials appeared broadly similar in terms of disposition, and the studies employed identical designs, inclusion and exclusion criteria, as well as analysis methods. However, the statistical limitations mean that results from the maintenance period should only be considered supportive evidence of the impact of nemolizumab.

External Validity

Patients enrolled in the ARCADIA 1 and ARCADIA 2 studies were required to have an EASI score of 16 or more (20 or more in the ARCADIA CYCLO trial), and an IGA score of 3 or more in both studies. An EASI score of 7.1 to 21.0 is considered moderate AD, and severe AD ranges from 21.1 to 50.0. An IGA score of 3 is considered moderate AD. As such, patients enrolled in the ARCADIA trials may have more severe disease, and therefore the results may not be generalizable to all patients with moderate AD, depending on the disease severity criteria used. However, it is worth noting that an EASI score of 16 and an IGA score of 3 are consistent with other drugs evaluated for moderate to severe AD.

All the ARCADIA studies excluded patients with asthma, COPD, and certain medications which cause sedative effects. Patients who had not improved after 16 weeks of treatment with dupilumab were also excluded from the ARCADIA 1 and ARCADIA 2 trials. The reimbursement request includes patients who are refractory to systemic immunosuppressant therapies, which could include dupilumab; therefore, results from the trials will not be generalizable to patients with a history of dupilumab exposure. The clinical experts consulted for this review noted that these patients could be considered candidates for treatment with nemolizumab in clinical practice. In addition, the fact that only patients who achieved a clinical response were kept in the maintenance phase of the ARCADIA 1 and ARCADIA 2 trials means any results after 16 weeks may not include all the patients represented in the study enrolment criteria.

The ARCADIA trials were all placebo-controlled trials, which allows for adequate evaluation of the treatment effect of nemolizumab; however, it may overestimate the treatment effects. Patients in the ARCADIA 1 and ARCADIA 2 trials had their background therapy stabilized during the run-in period before randomization. There was a high placebo response observed in the ARCADIA trials, although it is unclear whether this is due to the background therapy received by all patients. If so, this also impacts patients receiving nemolizumab. Nemolizumab monotherapy was not evaluated in the evidence submitted, and therefore delineating the true impact of nemolizumab on the disease remains unknown and may overestimate the results of the ARCADIA studies, although, it is worth noting that patients in the real world would continue to receive their background therapies, as was done in the ARCADIA studies. Across all 3 trials, treatment

adherence was reported to be high [redacted] the levels of adherence observed may not be representative of clinical practice settings.

Most patients in the ARCADIA 1 and ARCADIA 2 studies were older than 18 years, while only 13.7% to 17.4% of patients were between the ages of 12 and 17 years. Outcomes specific to this population (i.e., the CDLQI) were highly uncertain because they come from a small proportion of patients in the study. Additionally, other results may not be generalized to this population; however, subgroup analysis by age group were generally consistent with the primary analysis.

In addition to the study design, the treatment history described in the inclusion and exclusion criteria does not exactly match the requested reimbursement criteria; the ARCADIA 1 and ARCADIA 2 trials did not require patients to have previous exposure to immunomodulatory therapies, and the ARCADIA CYCLO trial only required exposure or inadvisability for cyclosporine. In the ARCADIA 1 and ARCADIA 2 trials, less than 40% of patients had prior exposure to immunomodulatory treatment, less than 15% had exposure to cyclosporine, and approximately 5% had had exposure to dupilumab. Therefore, it is uncertain how applicable the overall results will be to patients with these treatment histories versus patients who are naive to systemic therapies, or who have been treated with other advanced systemic therapies. Subgroup analyses conducted in the ARCADIA 1 and ARCADIA 2 trials on prior use of systemic therapy, biologic therapy, or dupilumab did not show consistent trends between the 2 studies and some subgroups had small sample sizes, thus, firm conclusions could not be drawn. In addition, according to the clinical experts, the criteria for refractoriness to cyclosporine in the ARCADIA CYCLO trial were subjective and therefore might not be representative of all patients who might be unsuccessful in taking cyclosporine.

GRADE Summary of Findings and Certainty of the Evidence

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:

ARCADIA 1 and ARCADIA 2 trials:

- Proportion of patients with IGA success at week 16
- Proportion of patients with EASI-75 at week 16
- Proportion of patients with PP-NRS score improvement of 4 or more at week 16
- Proportion of patients with PP-NRS score of less than 2 at week 16
- Change from baseline to week 16 in DLQI
- Change from baseline to week 16 in CDLQI
- Harms (injection site reactions, newly diagnosed or worsening asthma)

ARCADIA CYCLO trial:

- Proportion of patients with EASI-75 at week 16
- Proportion of patients with PP-NRS score improvement of 4 points or more at week 16
- Proportion of patients with PP-NRS score of 2 or more at week 16

- Proportion of patients with IGA success at week 16
- Change from baseline in DLQI score at week 16
- Harms (injection site reactions, newly diagnosed or worsening asthma)

Table 3: Summary of Findings for Nemolizumab vs. Placebo for Patients Aged 12 Years and Older With Moderate to Severe AD

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Disease Activity Scores				
Proportion of patients with IGA success[a] Follow-up: 16 weeks	1,728 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: 356 per 1,000 (NR) • Placebo: 246 per 1,000 (NR) • Strata-adjusted difference: 115 per 1,000 (97.5% CI, 47 per 1,000 to 183 per 1,000) **ARCADIA 2 trial** • Nemolizumab: 377 per 1,000 (NR) • Placebo: 260 per 1,000 (NR) • Strata-adjusted difference: 122 per 1,000 (97.5% CI, 46 per 1,000 to 198 per 1,000)	Moderate[b]	Nemolizumab likely results in an increase in the proportion of patients with IGA success at week 16 when compared with placebo.
Proportion of patients with EASI-75[c] Follow-up: 16 weeks	1,728 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: 435 per 1,000 (NR) • Placebo: 290 per 1,000 (NR) • Strata-adjusted difference: 149 per 1,000 (97.5% CI, 78 per 1,000 to 220 per 1,000) **ARCADIA 2 trial** • Nemolizumab: 421 per 1,000 (NR) • Placebo: 302 per 1,000 (NR) • Strata-adjusted difference: 125 per 1,000 (97.5% CI, 46 per 1,000 to 203 per 1,000)	Moderate[b]	Nemolizumab likely results in an increase in the proportion of patients with EASI-75 at week 16 when compared with placebo.
Proportion of patients with PP-NRS improvement ≥ 4[d] Follow-up: 16 weeks	1,728 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: 427 per 1,000 (NR) • Placebo: 178 per 1,000 (NR) • Strata-adjusted difference: 249 per 1,000 (97.5% CI, 184 per 1,000 to 315 per 1,000) **ARCADIA 2 trial** • Nemolizumab: 410 per 1,000 (NR) • Placebo: 181 per 1,000 (NR) • Strata-adjusted difference: 232 per 1,000 (97.5% CI, 161 per 1,000 to 303 per 1,000)	High	Nemolizumab results in an increase in the proportion of patients with a PP-NRS score improvement of 4 points or more at week 16 when compared with placebo.
Proportion of patients with PP-NRS < 2[d] Follow-up: 16 weeks	1,728 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: 306 per 1,000 (NR) • Placebo: 112 per 1,000 (NR)	High	Nemolizumab results in an increase in the proportion of patients with a PP-NRS score of less than 2 at week

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Strata-adjusted difference: 195 per 1,000 (97.5% CI, 137 per 1,000 to 252 per 1,000) **ARCADIA 2 trial** • Nemolizumab: 284 per 1,000 (NR) • Placebo: 113 per 1,000 (NR) • Strata-adjusted difference: 171 per 1,000 (97.5% CI, 109 per 1,000 to 233 per 1,000)		16 when compared with placebo.
HRQoL				
DLQI or CDLQI: 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life)				
LS mean change from baseline in DLQI total score[e] Follow-up: 16 weeks	1,728 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: –7.76 (95% CI, –8.49 to –7.03) • Placebo: –5.26 (95% CI, –6.23 to –4.29) • LS mean difference: –2.50 (95% CI, –3.63 to –1.37) **ARCADIA 2 trial** • Nemolizumab: –6.96 (95% CI, –7.67 to –6.25) • Placebo: –4.52 (95% CI, –5.48 to –3.56) • LS mean difference: –2.44 (95% CI, –3.58 to –1.30)	Moderate[f]	Nemolizumab may result in a reduction in the change in DLQI total score from baseline to week 16 when compared to placebo.
LS mean change from baseline in CDLQI total score[e] Follow-up: 16 weeks	266 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: –6.92 (95% CI, –9.26 to –4.58) • Placebo: –5.10 (95% CI, –7.71 to –2.50) • LS mean difference: –1.82 (95% CI, –4.88 to 1.25) **ARCADIA 2 trial** • Nemolizumab: –6.96 (95% CI, –7.67 to –6.25) • Placebo: –4.52 (95% CI, –5.48 to –3.56) • LS mean difference: –2.44 (95% CI, –3.58 to –1.30)	Moderate[f]	Nemolizumab may result in a reduction in the change in CDLQI total score from baseline to week 16 when compared to placebo.
Harms				
Proportion of patients with injection-related reactions Follow-up: 16 weeks	937 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: 2 per 1,000 (NR) • Placebo: 0 per 1,000 (NR) • Difference: NR **ARCADIA 2 trial** • Nemolizumab: 0 per 1,000 (NR) • Placebo: 0 per 1,000 (NR) • Difference: NR	Moderate[g]	Nemolizumab likely results in little to no difference in the proportion of patients with injection-related reactions when compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Proportion of patients with newly diagnosed or worsening asthma Follow-up: 16 weeks	937 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: 52 per 1,000 (NR) • Placebo: 30 per 1,000 (NR) • Difference: NR **ARCADIA 2 trial** • Nemolizumab: 29 per 1,000 (NR) • Placebo: 30 per 1,000 (NR) • Difference: NR	Low[g,h]	The evidence is very uncertain about the effect of nemolizumab on the proportion of patients with newly diagnosed or worsening asthma when compared to placebo.
Proportion of patients with 1 or more SAEs, n (%) Follow-up: 16 weeks	937 (2 RCTs)	**ARCADIA 1 trial** • Nemolizumab: 10 per 1,000 (NR) • Placebo: 12 per 1,000 (NR) **ARCADIA 2 trial** • Nemolizumab: 40 per 1,000 (NR) • Placebo: 27 per 1,000 (NR)	Low[g,h]	The evidence is very uncertain about the effect of nemolizumab on the proportion of patients with 1 or more SAEs.

AD = atopic dermatitis; CI = confidence interval; CDLQI = ; Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-75 = a 75% improvement in the Eczema Area and Severity Index; HRQoL = health-related quality of life; IGA = Investigator Global Assessment Scale; LS = least square; NR = not reported; PP-NRS = Peak Pruritus Numeric Rating Scale; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus.

Notes: 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). IGA success was defined as an IGA score of 0 or 1 and at least a 2-point reduction from baseline.

[b]Rated down 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 provided by the clinical experts consulted for this review).

[c]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.

[d]The PP-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 previous 24 hours, with 0 indicating no itch and 10 indicating the worst itch imaginable.

[e]The DLQI (for patients aged 16 years and older) and the CDLQI (for those aged younger than 16 years) are patient-reported, 10-item, HRQoL questionnaires that cover 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) over the previous week. The total score ranges from 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life).

[f]Rated down 1 level for serious imprecision. The CI for differences between groups includes the potential for little to no difference (based on the threshold for clinically important between-group difference of 5 points provided by the clinical experts consulted for this review).

[g]Rated down 1 level for serious imprecision due to the low number of events and lack of 95% CIs. The lack of CIs means it cannot be determined whether there is the possibility of benefit, no benefit, or harm in the assessment of this outcome.

[h]Rated down 1 levels for very serious indirectness. The duration of follow-up was limited to 16 weeks, which is an insufficient duration of time to detect all occurrences of this harm.

Sources: Details included in the table are from the sponsor's Summary of Clinical Evidence, ARCADIA 1 Clinical Study Report, and ARCADIA 2 Clinical Study Report.

Table 4: Summary of Findings for Nemolizumab vs. Placebo for Patients Aged 12 Years and Older With Moderate to Severe AD Previously Exposed to Cyclosporine or for Whom Cyclosporine is Medically Inadvisable

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		Placebo	Nemolizumab	Difference		
Disease activity measures						
Proportion of patients with EASI-75[a] Follow-up: 16 weeks	276 (1 RCT)	348 per 1,000	471 per 1,000	122 per 1,000 (7 to 236 per 1,000)	Moderate[b]	Nemolizumab likely results in an increase in the proportion of patients with EASI-75 at week 16 when compared with placebo.
Proportion of patients with PP-NRS improvement ≥ 4[c] Follow-up: 16 weeks	276 (1 RCT)	174 per 1,000	391 per 1,000	217 per 1,000 (114 to 320 per 1,000)	High	Nemolizumab results in an increase in the proportion of patients with a PP-NRS score improvement of 4 points or more at week 16 when compared with placebo.
Proportion of patients with PP-NRS < 2[c] Follow-up: 16 weeks					Moderate[b]	Nemolizumab likely results in an increase in the proportion of patients with a PP-NRS score of less than 2 at week 16 when compared with placebo.
Proportion of patients with IGA success[d] Follow-up: 16 weeks					Moderate[b]	Nemolizumab likely results in little to no difference in the proportion of patients with IGA success at week 16 when compared with placebo.
HRQoL						
DLQI or CDLQI: 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life)						
LS mean change from baseline in DLQI total score[e] Follow-up: 16 weeks					Moderate[f]	Nemolizumab likely results in a reduction in the change in DLQI total score from baseline to week 16 when compared to placebo.
Harms						
Proportion of patients with injection-related reactions Follow-up: 16 weeks					Moderate[g]	Nemolizumab likely results in little to no difference in the proportion of patients with injection-related reactions when compared to placebo.

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		Placebo	Nemolizumab	Difference		
Proportion of patients with asthma Follow-up: 16 weeks	[redacted]	[redacted]	[redacted]	[redacted]	Low[g,h]	Nemolizumab may result in little to no difference in the proportion of patients with asthma when compared to placebo.
Proportion of patients with 1 or more SAEs	274 (1 RCT)	22 per 1,000 (NR)	15 per 1,000 (NR)	NR	Low[g,h]	Nemolizumab may result in little to no difference in the proportion of patients with 1 or more SAEs.

AD = atopic dermatitis; CI = confidence interval; CDLQI = ; Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-75 = a 75% improvement in the Eczema Area and Severity Index; HRQoL = health-related quality of life; IGA = Investigator Global Assessment Scale; NR = not reported; PP-NRS = Peak Pruritus Numeric Rating Scale; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus.

Notes: Study limitations (which refer 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 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.

[b]Rated down 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 provided by the clinical experts consulted for this review).

[c]The PP-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 previous 24 hours, with 0 indicating no itch and 10 indicating the worst itch imaginable.

[d]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). IGA success was defined as an IGA score of 0 or 1 and at least a 2-point reduction from baseline.

[e]The DLQI (for patients aged 16 years and older) and the CDLQI (for those aged younger than 16 years) are patient-reported, 10-item, HRQoL questionnaires that cover 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) over the previous week. The total score ranges from 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life).

[f]Rated down 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 5 points provided by the clinical experts consulted for this review).

[g]Rated down 1 level for serious imprecision due to the low number of events and lack of 95% CIs. The lack of CIs means it cannot be determined whether there is the possibility of benefit, no benefit, or harm in the assessment of this outcome.

[h]Rated down 1 level for serious indirectness. The duration of follow-up was limited to 16 weeks, which is insufficient evidence to detect all occurrences of this harm.

Sources: Details included in the table are from the sponsor's Summary of Clinical Evidence and ARCADIA CYCLO Clinical Study Report.

LTE Studies

Description of Studies

The ARCADIA LTE (NCT03989206*;* N = 1,751) is an ongoing phase III, single-arm, multicentre, prospective study to evaluate the long-term safety and efficacy of nemolizumab in adult and adolescent patients with moderate to severe AD, when administered with background topical corticosteroids, with or without topical calcineurin inhibitors. The ARCADIA LTE study design consisted of a 4-week screening period, a 200-week treatment period, and an 8-week follow-up period. Participants received nemolizumab (30 mg) every 4 weeks via subcutaneous injection in the treatment period. Results were from 1 interim analysis (cut-off date: September 30, 2022) up to 56 weeks of treatment, as the sponsor noted that sample sizes beyond this time point were too small to draw meaningful conclusions. The study is estimated to be completed in August 2026.

The primary outcomes in the ARCADIA LTE study were the incidence and severity of AEs throughout the study, the incidence of SAEs throughout the study, and the incidence and severity of AESIs throughout the study. Secondary outcomes aligned with outcomes assessed in the ARCADIA 1 and ARCADIA 2 trials that were identified as important to this review, and included the IGA, the EASI, and the DLQI-CDLQI.

The study population included patients from prior nemolizumab AD studies, including the ARCADIA 1, ARCADIA 2, and ARCADIA CYCLO trials, and adolescents from selected international sites who had not previously participated in a nemolizumab study. Inclusion criteria for the ARCADIA LTE study were consistent with that of the lead-in studies. Patients were excluded if they had a history of COPD and/or chronic bronchitis, body weight under 30 kg, uncontrolled asthma in the preceding 3 months, asthma exacerbation requiring hospitalization in the preceding 12 months, had experienced an AE in a previous nemolizumab study, or had received restricted prior treatments.

Efficacy Results

Proportion of Patients With IGA Success

At LTE baseline, 23.9% of all patients experienced IGA success (defined as an IGA score between 0 to 1). By treatment before the LTE, 28.5% of patients previously treated with nemolizumab and 17.7% of patients naive to nemolizumab experienced an IGA score of 0 to 1. At week 20, 42.5% of all patients in the LTE experienced IGA success. By prior treatment, 45.6% of patients previously treated with nemolizumab and 36.7% of patients naive to nemolizumab experienced an IGA score of 0 to 1. At week 56, 48.9% of all patients in the LTE experienced IGA success. By prior treatment, 47.1% of patients previously treated with nemolizumab and 49.0% of patients naive to nemolizumab experienced an IGA score of 0 to 1.

Proportion of Patients With Achieved EASI-75

At LTE baseline, 33.7% of all patients achieved EASI-75 improvement from lead-in study baseline. By prior treatment, 38.1% of patients previously treated with nemolizumab and 24.0% of patients naive to nemolizumab achieved EASI-75 improvement from lead-in baseline. At week 20, 66.3% of patients achieved EASI-75 improvement from lead-in baseline and 34% achieved EASI-75 improvement from LTE baseline. By prior treatment, the proportion of patients achieving EASI-75 from lead-in and LTE baseline, respectively, were 69.3% and 32.6% for those previously treated with nemolizumab and 61.5% and 36.2% for patients naive to nemolizumab. At week 56, 75.6% of patients achieved EASI-75 improvement from lead-in baseline and 57.4% achieved EASI-75 improvement from LTE baseline. By prior treatment, the proportion of patients achieving EASI-75 from lead-in and LTE baseline, respectively, were 73.0% and 52.5% for those previously treated with nemolizumab and 78.7% and 62.3% for patients naive to nemolizumab.

Change From Baseline in DLQI Total Score

At LTE baseline, the mean DLQI was 7.6 (standard deviation [SD] = 6.92) across all patients in the LTE, 6.6 (SD = 6.57) for patients previously treated with nemolizumab and 9.1 (7.25) for patients in the naive to nemolizumab group.

At week 20, the mean DLQI score was 4.7 (SD = 5.77) across all patients in the LTE. Patients previously treated with nemolizumab had a mean DLQI score of 4.6 (SD = 5.84), with a mean change from lead-in

baseline and LTE baseline of −10.4 (SD = 7.52) and −2.0 (SD = 5.54), respectively. Patients naive to nemolizumab had a mean DLQI score of 5.0 (SD = 5.55), with a mean change from lead-in baseline and LTE baseline of −10.2 (SD = 7.06) and −3.9 (SD = 6.02), respectively.

At week 56, the mean DLQI score was 3.9 (SD = 4.72) across all patients in the LTE. Patients previously treated with nemolizumab had a mean DLQI score of 4.2 (SD = 4.93), with a mean change from lead-in baseline and LTE baseline of −11.1 (SD = 7.32) and −3.6 (SD = 6.36), respectively. Patients naive to nemolizumab had a mean DLQI score of 3.7 (SD = 4.58), with a mean change from lead-in baseline and LTE baseline of −12.2 (SD = 6.92) and −6.4 (SD = 6.71), respectively.

Change From Baseline in CDLQI Total Score

At LTE baseline, the mean CDLQI score was 6.9 (SD = 6.17) across all patients in the LTE, 5.3 (SD = 5.83) for patients previously treated with nemolizumab, and 9.1 (SD = 6.00) for patients in the naive to nemolizumab group.

At week 20, the mean CDLQI score was 4.3 (SD = 4.64) across all patients in the LTE. Patients previously treated with nemolizumab had a mean CDLQI score of 4.1 (SD = 4.62), with a mean change from lead-in baseline and LTE baseline of −8.3 (SD = 6.15) and −1.9 (SD = 4.41), respectively. Patients naive to nemolizumab had a mean CDLQI score of 4.4 (SD = 4.18), with a mean change from lead-in baseline and LTE baseline of −8.3 (SD = 6.43) and −5.1 (SD = 5.65), respectively.

At week 56, the mean CDLQI score was 3.4 (SD = 4.48) across all patients in the LTE. Patients previously treated with nemolizumab had a mean CDLQI score of 2.1 (SD = 2.02), with a mean change from lead-in baseline and LTE baseline of −9.2 (SD = 6.09) and −4.5 (SD = 5.11), respectively. Patients naive to nemolizumab had a mean CDLQI score of 4.4 (SD = 5.28), with a mean change from lead-in baseline and LTE baseline of −8.2 (SD = 6.80) and −6.3 (SD = 6.77), respectively.

Harms Results

During the 52-week LTE treatment period, 63.8% of patients experienced at least 1 AE, most being mild or moderate in severity, and 16.7% experienced a study drug-related AE. A treatment-emergent SAE was experienced by 4.1% of patients. A total of 4.8% of patients experienced a severe AE, with the most common being AD (0.9%), COVID-19 (0.3%), increased blood creatine phosphokinase (0.2%), asthma (0.2%), asthenia (0.2%), impetigo (0.2%), and headache (0.2%). A treatment-emergent AESI (by investigator) was experienced by 23.7% of patients, most commonly infections (20.3%) and asthma (newly diagnosed or worsening; 4.3%). Treatment-emergent AEs leading to study drug withdrawal were experienced by 3.3% of patients; 3.1% of patients experienced an AE leading to study discontinuation.

During the LTE follow-up period, 18.4% of patients experienced at least 1 AE, most being mild or moderate in severity, and 2.7% experienced a study drug-related AE. A treatment-emergent SAE was experienced by 2.7% of patients. A total of 2.0% of patients experienced a severe AE, and the only severe AE occurring in more than 1 patient was AD (0.7%). A treatment-emergent AESI (by investigator) was experienced by 4.8% of patients, most commonly infections (3.1%) and asthma (newly diagnosed or worsening; 1.7%). No

treatment-emergent AEs led to study drug withdrawal in the follow-up period; however, 4.4% of patients experienced an AE leading to study discontinuation.

There were no deaths during the treatment or follow-up period of the LTE.

Critical Appraisal

The ARCADIA LTE was designed as a single-arm, open-label extension to assess long-term safety and efficacy of nemolizumab in the treatment of adult and adolescent patients with moderate to severe AD. This open-label design could bias the reporting for subjective efficacy outcomes and harms. The direction and magnitude of these potential bias remains unclear. In addition, the absence of statistical hypothesis testing and a control group (i.e., no active comparator or placebo arm) limits the ability to draw definitive conclusions regarding the treatment effect. The study used an every 4-week dosing regimen, which does not align with the every 8-week dosing schedule outlined in the product monograph and may not reflect real-world use.

The extension study partly consisted of patients who took part in the lead-in studies, ARCADIA 1, ARCADIA 2, and ARCADIA CYCLO trials, and therefore it is reasonable to expect that the same strengths and limitations related to generalizability apply to the extension period. Given that patients needed to complete the lead-in studies before enrolling, the treatment extension population is inherently enriched with those whose disease responded to treatment. Attrition rates were high, particularly for later time points such as week 56, which may limit generalizability and interpretability of long-term outcomes. Although the study follow-up was limited to 56 weeks, the consulted clinical experts indicated that this duration was likely sufficient to assess safety and efficacy. The study is ongoing and is expected to be completed in August 2026.

Indirect Comparisons

One NMA was submitted by the sponsor to fill gaps in the comparative evidence for nemolizumab versus relevant comparators that included abrocitinib, baricitinib, dupilumab, lebrikizumab, tralokinumab, and upadacitinib for the treatment of moderate to severe AD in patients aged 12 years who are candidates for systemic therapy. The focus of the NMA was in patients who were experienced with cyclosporine. Since baricitinib, lebrikizumab, and tralokinumab were not relevant to public payers in Canada, they were excluded from this report.

Description of Studies

A feasibility assessment was undertaken to ascertain the extent of clinical heterogeneity across 26 RCTs identified in the systematic literature review. Study design characteristics, baseline characteristics, treatment regimens, outcome definitions, time points, and data availability were considered potential sources of clinical heterogeneity and explored in the feasibility assessment. Of the 26 RCTs, 22 were included in at least 1 network, which included 7 trials of interest (AD Up, ARCADIA 1 and ARCADIA 2, ARCADIA CYCLO, JADE DARE, LIBERTY AD CAFÉ, LIBERTY AD CHRONOS) comparing nemolizumab, dupilumab, abrocitinib, and upadacitinib, connected via placebo. The feasibility assessment suggested that the included trials were similar in study design, patient characteristics, treatment regimens, and outcome measures. The authors noted that the main source of heterogeneity was attributed to trial data that included populations who were

both experienced and naive to cyclosporine; no other sources of heterogeneity were described. An NMA was considered feasible for patients who were experienced with cyclosporine for the following outcomes of interest at 16 weeks: EASI-75 response, PP-NRS of greater than or equal to 4-point improvement (PP-NRS response), IGA score of 0 or 1 (IGA response), DLQI change from baseline, AEs, and discontinuations due to AEs (DAEs). It was assumed that trials with outcome data reported for mixed age populations, but with a majority (≥ 75%) adult population, could be assessed in adult networks, and that outcome data could be pooled across time points to maintain network integrity. There were no data available for adolescents who were experienced with cyclosporine. Bayesian random-effect NMAs were conducted using generalized linear models to estimate odds ratios and 95% CrIs, except for DLQI change from baseline, which was assessed with mean difference and 95% CrI.

Efficacy and Harm Results

The results for EASI-75 response, PP-NRS response, and IGA response favoured upadacitinib 30 mg versus nemolizumab. The results for IGA response also favoured abrocitinib versus nemolizumab. The results for DLQI mean change from baseline did not favour any treatments. Across all outcomes, there was no difference between dupilumab versus nemolizumab. The results for AEs and DAEs did not favour any treatments.

Critical Appraisal

The protocol of the systematic review and NMA was not a priori registered. The methods used to conduct the systematic literature review used appropriate criteria to search databases, select studies, extract data, and assess risk of bias of the included studies. The NMA included relevant outcomes identified by the CDA-AMC team, which included EASI-75 response, PP-NRS response, IGA response, DLQI change from baseline, AEs, and DAEs. Analysis for all outcomes was performed at 16 weeks and did not include the maintenance treatment phase of 48 weeks for nemolizumab. This was attributed to insufficient data beyond 16 weeks for the comparators of interest, which represents a gap in the available indirect evidence.

The authors noted that the included trials were considered similar in study design, patient eligibility criteria, baseline patient characteristics, and outcome characteristics (i.e., definitions and methods of reporting outcomes). However, there were notable baseline differences with respect to mean body surface area (ranging from 42.5% to 59.5% across trials and arms), and proportion of patients with baseline IGA scores of 3 or 4 (IGA 3 score ranging from 46% to 73.9%; IGA 4 score ranging from 26.1% to 54%). The included studies enrolled a combination of patients with an inadequate response to, or intolerance to cyclosporine. Efforts were made in the NMA to reduce heterogeneity by stratifying the adult and adolescent patient populations into those with experience with cyclosporine subgroups. The results across outcomes showed low heterogeneity via the I^2 statistic, which ranged from [redacted] (indicating low heterogeneity), and the results of sensitivity analyses that removed trials with mixed patient populations (those with experience and those who were naive to cyclosporine), were consistent with the base-case analysis. There were no data available for adolescents with experience with cyclosporine, which represents a gap in the available indirect evidence.

Overall, the network was sparse (i.e., many comparisons but few studies). Since most nodes were informed by only 1 trial and had small sample sizes, comparisons were underpowered, which contributed to wide CrIs in the analyses. Most 95% CrIs included both better and worse performance, except for EASI-75, PP-NRS, and IGA response, where upadacitinib 30 mg was favoured over nemolizumab 30 mg (i.e., 95% CrIs did not cross the null). Due to the absence of closed loops in the network, it was not possible to assess for inconsistency across direct and indirect evidence in the NMA.

Economic Evidence

Economic Evaluation and Budget Impact

Nemolizumab is available as a prefilled pen for subcutaneous injection (30 mg/0.49 mL). At the submitted price of $2,995 per 30 mg prefilled pen, the annual cost of nemolizumab is expected to be $28,519 per patient in the first year of treatment and $19,534 in subsequent years, based on the Health Canada–recommended dosage.

Based on the results of the sponsor's cost comparison, nemolizumab is expected to be associated with higher drug costs compared to dupilumab, abrocitinib, and upadacitinib in the first year of treatment (incremental costs = $3,357 to $13,683 per patient). In subsequent years, costs to the health system are expected to be lower than those of dupilumab and upadacitinib 30 mg (incremental savings = $5,381 to $8,623 per patient per year), but higher than those of abrocitinib and upadacitinib 15 mg (incremental costs = $604 to $1,703 per patient per year).

CDA-AMC estimates that the budget impact of reimbursing nemolizumab for the treatment of moderate to severe AD in the requested reimbursement population will be approximately $45 million over the first 3 years of reimbursement compared to the amount currently spent on dupilumab, abrocitinib, and upadacitinib, with an estimated expenditure of $392 million on nemolizumab over this period. The actual budget impact of reimbursing nemolizumab is uncertain and will depend on the proportion of patients treated at each line of therapy, the proportion who are refractory to, or ineligible for, each line of therapy, and the proportion who will be publicly funded.

The budget impact of reimbursing nemolizumab for the full Health Canada indicated population is unknown but would be substantially higher than estimations for its reimbursement request population.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell,

Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: July 23, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
L'Agence des médicaments du Canada
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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.