

Reimbursement Review

Roflumilast (Zoryve)

Sponsor: Arcutis Canada, Inc.

Therapeutic area: Plaque psoriasis

Summary

What Is Plaque Psoriasis?

- Plaque psoriasis is a chronic, immune-mediated inflammatory skin disease characterized by erythematous, scaly plaques that can involve the scalp, trunk, and other body areas, often accompanied by itch, discomfort, and psychosocial burden. In Canada, psoriasis affects approximately 2% to 3% of the population, with scalp involvement reported in up to 80% of patients at some point during the disease course.

What Are the Treatment Goals and Current Treatment Options for Plaque Psoriasis?

- The primary goals of treatment are to reduce disease severity, control symptoms (particularly itch), improve quality of life, and minimize treatment-related harms over the long term. Outcomes identified as most important by patient groups included itch relief, visible disease clearance (especially on the scalp), and treatments that are tolerable and practical for long-term use; clinicians additionally emphasized investigator-assessed disease severity and safety as important outcomes.
- Current treatment options for mild to moderate plaque psoriasis include topical corticosteroids, vitamin D analogues (e.g., calcipotriol), topical calcineurin inhibitors, and combination products, with phototherapy or systemic therapies reserved for more extensive or refractory disease.

What Is Zoryve and Why Did Canada's Drug Agency Conduct This Review?

- Zoryve (roflumilast 0.3% foam) is a topical PDE4 inhibitor applied once daily. Health Canada has approved Zoryve for the treatment of plaque psoriasis, including involvement of the scalp and other body areas, in adults and adolescents aged 12 years and older.
- Canada's Drug Agency (CDA-AMC) conducted this review to inform a reimbursement recommendation to participating public drug programs on whether Zoryve should be reimbursed for its Health Canada-approved indication.

How Did CDA-AMC Evaluate Zoryve?

- CDA-AMC reviewed the clinical evidence on the beneficial and harmful effects of Zoryve compared with other treatments used in Canada for plaque psoriasis, including topical corticosteroids, vitamin D analogues,

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topical calcineurin inhibitors, and vehicle or placebo. Equity and ethical considerations relevant to psoriasis management were also identified.

- The review was informed by materials submitted by the sponsor, including clinical evidence and an indirect treatment comparison (ITC), as well as by 2 patient groups and 3 clinician groups. Two clinical experts with experience in dermatology and psoriasis management were consulted as part of the review process.

What Were the Findings?

Clinical Evidence

- CDA-AMC reviewed the following clinical evidence:
 - 1 randomized, double-blind, phase III trial (the ARRECTOR study) comparing roflumilast foam 0.3% with its vehicle in patients with plaque psoriasis involving the scalp and body
 - 1 sponsor-submitted bayesian network meta-analysis comparing roflumilast foam 0.3% with selected topical and oral systemic treatments
 - evidence from the pivotal randomized trial —
 - investigator-assessed disease clearance (Scalp–Investigator’s Global Assessment and Body–Investigator’s Global Assessment): roflumilast foam 0.3% results in a clinically important improvement in scalp and body disease clearance at 8 weeks compared with the vehicle
 - itch severity (Scalp Itch Numeric Rating Scale and Worst Itch Numeric Rating Scale): roflumilast foam 0.3% may result in a clinically important reduction in patient-reported itch severity at 8 weeks compared with the vehicle
 - scalp-specific severity (75% reduction in Psoriasis Scalp Severity Index score): roflumilast foam 0.3% results in a clinically important improvement in scalp psoriasis severity at 8 weeks compared with the vehicle
 - health-related quality of life (Dermatology Life Quality Index and Children’s Dermatology Life Quality Index): roflumilast foam 0.3% may improve health-related quality of life at 8 weeks compared with the vehicle; effects on Dermatology Life Quality Index were imprecise, and results for Children’s Dermatology Life Quality Index were very uncertain due to limited adolescent representation
 - harms: roflumilast foam 0.3% is generally well tolerated; treatment-emergent adverse events were more frequent than with the

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vehicle but were mostly mild to moderate, with low rates of serious adverse events and treatment discontinuation

- indirect evidence from the network meta-analysis —
 - based on indirect evidence, roflumilast foam 0.3% may improve certain scalp-specific outcomes compared with calcipotriol
 - for other topical and oral systemic comparators, the effects of roflumilast foam 0.3% on efficacy outcomes are very uncertain due to sparse networks, reliance on indirect comparisons, substantial imprecision, and sensitivity to modelling assumptions
- evidence gaps — key gaps include the absence of direct comparative trials, limited long-term efficacy and safety data beyond 8 weeks, and uncertainty regarding comparative effectiveness versus several commonly used topical therapies.

Economic Evidence

- Zoryve is available as a topical foam (0.3% wt/wt). At the submitted price of \$290.00 per pressurized aluminum can, the per-episode cost (over 8 weeks) of Zoryve is expected to be \$828 per patient, based on the Health Canada–recommended dosage.
- Key clinical efficacy in the economic analysis (i.e., the probability of treatment response for scalp psoriasis) was derived from a sponsor-submitted ITC,¹ with the efficacy of Zoryve informed by the ARRECTOR trial.² Indirect evidence submitted by the sponsor suggests that the comparative efficacy on the treatment response of Zoryve versus comparators in patients aged 12 years or older with scalp and body psoriasis is highly uncertain. While results suggested that Zoryve may be favoured only in comparisons with calcipotriol monotherapy for the Scalp–Investigator’s Global Assessment outcome up to 8 weeks, these results were uncertain due to the identified limitations with the ITC. For all other topical and systemic comparators, effect estimates were highly imprecise and included the potential that either Zoryve or comparators could be favoured. Overall, findings from the indirect comparisons are limited by sparse networks, reliance on indirect comparisons, and sensitivity to modelling assumptions, and should therefore be interpreted with caution. Additionally, the comparative efficacy for Zoryve versus oral systemics in the economic model was sourced from naive comparison. Due to the use of naive comparison, it is not possible to determine if any differences in treatment effect are due to treatment or are instead due to bias or confounding. Therefore, the comparative efficacy for Zoryve versus oral systemics is associated with additional uncertainty.

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- The impact of Zoryve on patient health and health system costs, relative to relevant comparators, is highly uncertain due to limitations in the sponsor's assumptions regarding treatment pathway, the potential overestimation of biologic use in subsequent therapy, and uncertainty in the efficacy estimates derived from the ITC. Based on evidence reviewed for this submission, there is no robust evidence to suggest that Zoryve provides a greater health benefit than comparators. If there are no differences in health outcomes between Zoryve and comparators, then the total cost of Zoryve to the health system should not exceed that of the least costly comparator.
- CDA-AMC estimates that the budget impact of reimbursing Zoryve for the treatment of plaque psoriasis of the scalp and body in patients aged 12 years or older will be approximately \$15.2 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$99.8 million on Zoryve over this period. The actual budget impact of reimbursing Zoryve is uncertain due to uncertainty in the market uptake of Zoryve, the number of flares per year experienced by patients, and the confidential list prices of comparators. The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate.

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Abbreviations

AE	adverse event
B-IGA	Body–Investigator’s Global Assessment
BSA	body surface area
CDA-AMC	Canada’s Drug Agency
CDLQI	Children’s Dermatology Life Quality Index
CI	confidence interval
DLQI	Dermatology Life Quality Index
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	health-related quality of life
IGA	Investigator’s Global Assessment
ITC	indirect treatment comparison
MID	minimal important difference
NMA	network meta-analysis
NRI	nonresponder imputation
OR	odds ratio
PASI	Psoriasis Area and Severity Index
PSSI 75	75% reduction in Psoriasis Scalp Severity Index score
RCT	randomized controlled trial
SAE	serious adverse event
S-IGA	Scalp–Investigator’s Global Assessment
SI-NRS	Scalp Itch Numeric Rating Scale
WI-NRS	Worst Itch Numeric Rating Scale

Background

Introduction

The objectives of this report are as follows:

- Review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of Zoryve (roflumilast foam, 0.3% wt/wt) for topical use in the treatment of plaque psoriasis of the scalp and body in patients aged 12 years or older. The focus is placed on comparing Zoryve to relevant comparators in clinical practice in Canada and identifying gaps in the current evidence; this focus is outlined in [Table 1](#).
- Review and critically appraise the economic information submitted by the sponsor, including a cost-effectiveness analysis and budget impact analysis. The focus of the economic review is aligned with the scope of the clinical review, unless otherwise stated. For most reviews, a Canada's Drug Agency (CDA-AMC) base case is developed, informed by clinical expert input, the available clinical evidence, and the best interpretation of the economic evidence based on the information provided by the sponsor.

Table 1: Information on the Application Submitted for Review and on the CDA-AMC Review

Item	Description
Information on the application submitted for review	
Drug	Roflumilast (Zoryve) foam, 0.3% w/w for topical use, supplied in a 60 g pressurized aluminum can
Sponsor	Arcutis Canada, Inc. (Arcutis)
Health Canada indication^a	Zoryve (roflumilast foam, 0.3% w/w) is indicated for topical treatment of plaque psoriasis of the scalp and body in patients 12 years of age and older.
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	November 12, 2025
Mechanism of action	Roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of PDE4. Roflumilast and roflumilast N-oxide inhibition of PDE4 ([a cyclic AMP–metabolizing] enzyme) activity leads to accumulation of intracellular cyclic AMP. Roflumilast is a non-steroid, anti-inflammatory agent, which when applied topically, is thought to exert its therapeutic action via inhibition of PDE4 and subsequent inhibition of inflammatory markers associated with plaque psoriasis.
Recommended dosage	Apply roflumilast foam 0.3% to affected areas once daily. No dosage adjustments required
Submission type	Initial submission
Sponsor's reimbursement request	As per indication
Submitted price	\$290.00 per 60 g aluminum can
Information on the CDA-AMC review	
Review type	Standard

Item	Description
Clinical review focus^b	• Population: As defined in the Health Canada indication • Subgroups: None • Intervention: Per recommended dosage • Comparators: Vitamin D analogues (calcipotriol), corticosteroids, fixed-dose combinations, topical calcineurin inhibitors • Outcomes: ◦ Clinical clearance — S-IGA and B-IGA success at week 8 ◦ Itch severity — SI-NRS and WI-NRS success at week 8 ◦ Psoriasis severity — PSSI 75 (at week 8) ◦ HRQoL — DLQI and CDLQI (at week 8) ◦ Harms — AEs, SAEs, WDAEs, and AESIs

AE = adverse event; AESI = adverse event of special interest; AMP = adenosine monophosphate; B-IGA = Body–Investigator’s Global Assessment; CDA-AMC = Canada’s Drug Agency; CDLQI = Children’s Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; NOC = Notice of Compliance; PSSI 75 = 75% reduction in Psoriasis Scalp Severity Index score; SAE = serious adverse event; S-IGA = Scalp–Investigator’s Global Assessment; SI-NRS = Scalp Itch Numeric Rating Scale; w/w = weight per weight; WDAE = withdrawal due to adverse event; WI-NRS = Worst Itch Numeric Rating Scale.

^aCDA-AMC has previously issued a reimbursement recommendation for this drug for the same indication or a similar indication.

^bThe economic review aligns with the scope of the clinical review, unless otherwise stated.

Submission History for the Drug Under Review

CDA-AMC has previously reviewed roflumilast (Zoryve) for a related indication. In August 2023, CDA-AMC issued a recommendation to reimburse roflumilast cream with clinical criteria and/or conditions for the topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients aged 12 years or older. This recommendation was based on evidence from 2 phase III, randomized, double-blind, vehicle-controlled trials (the DERMIS-1 and DERMIS-2 studies), which demonstrated improvements in overall disease severity, intertriginous-area Investigator’s Global Assessment (IGA) scores, Psoriasis Area and Severity Index (PASI) scores, and itch, with no identified safety concerns. At the time of writing this report, the pan-Canadian Pharmaceutical Alliance had concluded negotiations for roflumilast cream without a letter of intent. For the current submission, CDA-AMC has not previously reviewed roflumilast foam for plaque psoriasis of the scalp and body in patients aged 12 years or older through the reimbursement review process.

Sources of Information

The contents of the Reimbursement Review report are informed by materials submitted by the sponsor, input received from interested parties (patient groups, clinician groups, and drug programs), and input from clinical experts consulted for this review.

Calls for patient group and clinician group input are issued for each reimbursement review. Two patient group submissions were received: 1 from Arthritis Consumer Experts and a joint submission from the Canadian Skin Patient Alliance and Psoriasis Canada. Three clinician group submissions were also received from the Atlantic Dermatology Group, the Dermatology Association of Ontario, and the Canadian Dermatology Association.

Patient groups gathered input primarily through online surveys. Arthritis Consumer Experts contributed feedback from 5 individuals living with plaque psoriasis, while the Canadian Skin Patient Alliance and

Psoriasis Canada drew on the input of 86 respondents from a 2023 national survey and 30 respondents from a targeted November 2025 survey focused on scalp psoriasis and experiences with roflumilast foam.

Clinician groups compiled their submissions through the review of clinical experience, clinical trial data, published literature, and consultation among their membership. The full submissions received are available on the [project landing page](#) in the consolidated input document. Drug programs also provide input for each review, identifying issues that may influence the feasibility of implementing a recommendation.

Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the clinical review and in the interpretation of the clinical and economic evidence. Relevant patient and clinician group input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

Each review team includes at least 1 clinical expert with expertise regarding the diagnosis and management of the condition for which the drug is indicated. For this review, 2 dermatologists from Ontario and British Columbia with expertise in the diagnosis and management of plaque psoriasis participated as part of the review team.

Disease Background

Psoriasis is a chronic, immune-mediated inflammatory skin disease characterized by well-demarcated erythematous plaques with overlying scale, pruritus, pain, and a relapsing-remitting course over a patient's life span. Plaque psoriasis is the most common form, accounting for roughly 80% to 90% of cases,^{3,4} and scalp involvement is very frequent, affecting an estimated 45% to 56% of people living with psoriasis; meanwhile, 21% to 30% of patients have involvement of the inverse and/or intertriginous areas.^{2,4}

Psoriasis is common in Canada. Population-based data from Ontario estimate a prevalence of approximately 2.3% to 2.5% among adults (about 1 million individuals living in Canada), similar to estimates of 1% to 3% in populations in Europe and the US.⁵ Although not typically life-shortening, psoriasis is associated with substantial morbidity, including pruritus, sleep disturbance, impaired daily functioning, and increased risks of cardiometabolic and mental health comorbidities.⁵

Diagnosis is made clinically based on lesion morphology and distribution on the scalp and body, with skin biopsy reserved for atypical or diagnostically uncertain cases, as confirmed by clinical experts consulted for this review and by clinician groups. No specific genetic mutation, biomarker, or companion diagnostic test is required for the diagnosis or treatment selection of plaque or scalp psoriasis.

Patient group input: Patient groups reported that body and scalp plaque psoriasis causes intense itching, burning, flaking, pain, and sometimes bleeding on visible areas such as the scalp, hairline, face, and ears, leading to embarrassment, social isolation, and substantial impacts on work, relationships, and self-esteem. Clinical experts consulted for this review and clinician group submissions were generally aligned with these perspectives, emphasizing that even relatively limited scalp or special-area involvement can be highly symptomatic and disabling, out of proportion to the percentage of body surface area (BSA) affected, and

highlighting the chronic, fluctuating nature of the disease and its psychosocial burden; no major contrary views were raised regarding the natural history or overall burden of plaque and scalp psoriasis.

Current Management

Treatment Goals

Patient group input: Patient groups reported that the most important goals of treatment are rapid and sustained relief of key symptoms (particularly scalp itch, burning, flaking, and pain); visible improvement or clearance of plaques on the scalp, hairline, face, and other highly visible or sensitive areas; and the ability to participate in daily activities, social interactions, work, and intimate relationships without embarrassment or constant shedding of scale. They emphasized the need for treatments that are effective, convenient, and well tolerated over the long term, with attributes such as once-daily dosing, quick absorption, minimal residue in hair, and nonsteroidal options that can be safely used across multiple body sites. Patients described being willing to accept mild local side effects or ongoing treatment burden if a therapy provides meaningful improvement in symptoms and quality of life, but they were frustrated by treatments that are messy, are slow to work, lose effect over time, or cause bothersome adverse effects.

Clinician input: Clinical experts consulted for this review and clinician group submissions indicated that treatment goals for plaque and scalp psoriasis are to achieve and maintain being clear or almost clear of signs of disease on the scalp and other involved areas, with substantial reductions in itch, scaling, and inflammation, while preserving function and quality of life. They highlighted outcomes such as Scalp–Investigator’s Global Assessment (S-IGA) and Body–Investigator’s Global Assessment (B-IGA) treatment success, PASI responses, numerical rating scales for itch, and patient-reported quality-of-life measures as being most relevant for assessing benefit, alongside sustained control of and reduction in flares over time. Clinicians also stressed the importance of steroid-sparing strategies, particularly for hair-bearing and sensitive areas (scalp, face, genitals, intertriginous regions), and the need for formulations that are cosmetically acceptable and easy to apply in real-world use to support adherence. Overall, clinician groups were largely aligned with patient and caregiver priorities around symptom relief, durability of response, convenience, and safety; they also emphasized long-term safety, the minimization of cumulative topical steroid exposure, and robust objective measures of response as key determinants of an optimal therapy.

Current Treatment Options

The management of plaque psoriasis of the scalp and body in Canada follows a stepwise approach that begins with over-the-counter emollients and medicated shampoos, and progresses to prescription topical therapies, phototherapy where available, and systemic drugs for patients with more extensive or refractory disease.^{4,6,7} Clinical experts consulted for this review noted that most patients begin with over-the-counter products marketed for psoriasis or dandruff, but prescription topicals remain the foundation of care for mild to moderate plaque psoriasis. These include topical corticosteroids in multiple formulations tailored to different body areas, vitamin D analogues, topical retinoids, fixed-dose combinations (e.g., calcipotriol–betamethasone, halobetasol propionate–tazarotene), tapinarof, and nonsteroidal options such as topical calcineurin inhibitors used off label.^{4,7,8} Clinician groups highlighted that roflumilast cream 0.3% is the only topical PDE4 inhibitor currently approved in Canada.

Phototherapy (most commonly narrowband UVB) is used when topical therapies are insufficient or impractical,⁸ but clinician groups and clinical experts noted that access is limited to select centres and that light penetration to the scalp is poor due to the presence of hair. For patients unable to achieve adequate control with topicals and/or phototherapy, systemic therapy — including methotrexate, cyclosporine, acitretin, apremilast, deucravacitinib, and biologics targeting TNF-alpha, IL-12 and IL-23, IL-23, and IL-17 — is routinely considered.^{4,7,8} Clinical experts and clinician groups highlighted that, because of limitations of current topical therapies for the scalp, some patients with relatively limited disease burden but prominent scalp involvement escalate to systemic treatments earlier than would otherwise be necessary; no contrary views on these statements were identified among experts' input.

Key characteristics of roflumilast foam are summarized with other treatments available for plaque psoriasis in the Supplemental Material document (available on the [project landing page](#)), in Table 1 in Appendix 1.

Unmet Needs and Existing Challenges

Patient group input: Patient groups described substantial unmet needs despite the availability of multiple therapies. Many respondents reported that current treatments do not adequately control key symptoms such as itching, flaking, dryness, pain, and burning, particularly on high-impact and visible areas including the scalp, face, genitals, and skin folds. These persistent symptoms were linked to sleep disruption, embarrassment, stigma, and social isolation, as well as impacts on mental health, work, school, and intimate relationships, with some patients and caregivers describing substantial strain on family life and caregiving roles.

Patients reported extensive prior treatment experience, including multiple topical and systemic therapies, but many found these either ineffective, only temporarily effective, or poorly tolerated. Surveyed patients experienced side effects with current treatments, and most had stopped at least 1 therapy because it stopped working, caused adverse effects (e.g., methotrexate was described as “awful” due to hair loss and gastrointestinal symptoms), or was unaffordable. Only a minority were satisfied with their current regimen, and a large proportion of patients expressed interest in new treatment options. Financial barriers and drug coverage gaps were highlighted as important access challenges, particularly for newcomers to Canada and for patients facing high out-of-pocket costs for systemic or newer therapies.

Across patient surveys, respondents emphasized the burden of polypharmacy (using different topicals for different body areas), messy or greasy formulations that are difficult to wash from hair or clothing, and concerns about long-term steroid use. They expressed a need for effective, well-tolerated, nonsteroidal topical options that can be used across multiple sites — including hair-bearing and sensitive areas — without compromising daily routines. Experiences with roflumilast foam during clinical trials were generally positive in terms of ease of use and symptom control, though some patients with thicker or longer hair reported residual challenges, underscoring heterogeneity in needs and the ongoing requirement for multiple acceptable options.

Clinician input: Clinical experts consulted for this review and clinician group submissions consistently identified persistent gaps in topical treatment options that closely align with patient-reported unmet needs.

They emphasized that current therapies for scalp and other hair-bearing regions are limited by formulation, effectiveness, and tolerability. Creams and ointments are often greasy and cosmetically unacceptable, difficult to apply through hair, and incompatible with routine hair care, resulting in challenges with adherence and suboptimal outcomes. Even foam or lotion formulations may cause irritation due to alcohol content, and clinicians noted the absence of a well-established, nonsteroidal, second-line topical therapy specifically suited for hair-bearing surfaces.

Despite the availability of multiple topical drugs, clinicians agreed that meaningful challenges remain in routine practice. Patients frequently require different products for different body sites (e.g., 1 drug for the scalp and another for the body), increasing regimen complexity. The long-term use of topical corticosteroids is constrained by safety concerns, while vitamin D analogues and retinoid-based combinations are often irritating, particularly on sensitive or intertriginous skin. These limitations, combined with poor cosmetic acceptability and application burden, commonly lead to reduced adherence.

Clinical experts further noted important limitations of existing topical therapies for special areas, including the face and intertriginous regions. Irritation from vitamin D analogues as well as retinoid and steroid combinations, along with long-term risks associated with topical corticosteroids (e.g., skin atrophy, telangiectasia, tachyphylaxis, potential systemic effects), restrict sustained use. As a result, many patients rely on multiple topical formulations to manage disease across different sites, increasing treatment burden and challenges with adherence. Clinician groups described this need for polypharmacy and the lack of a single, well-tolerated topical option usable across multiple body sites as a notable treatment gap.

Beyond topical therapy, clinician groups identified practical and equity-related challenges associated with phototherapy and systemic treatments. Phototherapy typically requires 2 to 3 clinic visits per week and is available in fewer than 50 centres across Canada, making it impractical for many patients, particularly those in rural or remote areas. Clinicians also noted that phototherapy is often ineffective for scalp psoriasis due to limited light penetration through hair, further exacerbating access inequities. While systemic drugs and biologics can provide effective disease control, they carry substantial monitoring requirements, safety considerations, and high costs.

Overall, clinical experts and clinician groups agreed that there is an unmet need for topical treatments that are effective, well tolerated, cosmetically acceptable, and suitable for long-term use across both scalp and body sites. Such therapies could improve adherence, reduce reliance on high-potency corticosteroids, and delay or avoid escalation to phototherapy or systemic treatments.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review and from clinician groups, as well as the reimbursement conditions proposed by the sponsor (refer to Table 2 in Appendix 1 in the Supplemental Material document). The implementation questions from the public drug programs and corresponding responses from the clinical experts consulted for this review are summarized in the Supplemental Material document, in Table 3 in Appendix 1. The following has been summarized by the review team.

Place in Therapy

Clinical experts consulted for this review indicated that roflumilast foam 0.3% would be used as a topical, symptomatic treatment for plaque psoriasis of the scalp and body, either as monotherapy or as an adjunct to existing therapies (e.g., phototherapy, conventional systemic drugs, biologics) when residual lesions persist on the scalp or other localized areas. They highlighted that, in current practice, patients often require multiple topical drugs (e.g., different formulations for scalp and non–hair-bearing skin), and viewed roflumilast foam 0.3% as a convenient, steroid-free, once-daily option that could reduce the need for topical polypharmacy in patients with limited BSA involvement but clinically meaningful disease, particularly on the scalp and in intertriginous or sensitive areas.

Experts considered roflumilast foam 0.3% appropriate for earlier use in the treatment algorithm, including as a first-line topical option in some patients, but they noted that, for financial reasons, it may be reasonable to expect many patients to have an initial trial of a topical corticosteroid (e.g., for approximately 4 weeks) before initiating roflumilast foam. They emphasized that this sequencing is driven by cost rather than by mechanistic considerations because they did not identify a biological rationale to restrict roflumilast foam 0.3% to a strictly second-line role. Overall, the experts suggested that broad availability could shift the current treatment paradigm by allowing more patients with scalp and body plaque psoriasis to remain controlled with topical therapy and potentially delaying or avoiding escalation to systemic treatment.

Clinician group input was generally aligned with the clinical experts, describing roflumilast foam 0.3% as a versatile, steroid-free, once-daily topical monotherapy effective for both scalp and body psoriasis in adolescents and adults, with a formulation suited to hair-bearing and sensitive skin areas. Clinician groups emphasized its potential to simplify treatment by replacing multiple separate topical products, reduce burden related to greasy or hard-to-apply formulations, and improve adherence. They supported its use as a first-line topical therapy for many patients, as well as an alternative for those with an inadequate disease response, intolerance, or contraindications to topical corticosteroids or other topicals, and they agreed it could be used as adjunctive therapy in patients with an incomplete disease response to systemic or biologic treatments.

Patient Population

Clinical experts noted that plaque psoriasis of the scalp and body is common and that the population eligible for roflumilast foam 0.3% would largely reflect the trial population: adolescents and adults (aged ≥ 12 years) with scalp and body plaque psoriasis, typically with limited to moderate overall BSA involvement but with clinically meaningful disease activity, especially in visible or functionally important areas (e.g., scalp, intertriginous regions, face). The experts indicated that the sponsor's proposed eligibility criteria — alignment with key ARRECTOR trial inclusion criteria (an S-IGA score of ≥ 3 [moderate] and a B-IGA score of ≥ 2 [mild], and total scalp and nonscalp plaque involvement $\leq 25\%$ of BSA, excluding palms and soles) — were reasonable, captured those patients most likely to benefit, and should be straightforward to implement in routine practice.

Experts identified patients most in need of this intervention as those who have not responded adequately to other topical therapies, those for whom existing formulations are impractical (e.g., greasy creams or ointments in hair-bearing areas), and patients on systemic or biologic therapies who continue to have

persistent localized disease on the scalp or other difficult-to-treat sites. They did not identify specific biomarkers or clinical predictors of differential response, and they indicated that patients best suited for treatment are those with localized but bothersome lesions on the scalp, intertriginous areas, or other sensitive sites for which steroid-sparing therapy is desirable. Conversely, patients with very extensive BSA involvement were considered less suitable candidates, given the logistical challenges of applying a topical foam to large areas and the likelihood that systemic therapy would be more appropriate. Experts also considered patients with prior serious adverse reactions to roflumilast, marked challenges with adherence to topical regimens, or physical limitations that impede self-application as less suitable for treatment.

Regarding diagnosis and identification of eligible patients, the experts emphasized that psoriasis is primarily a clinical diagnosis based on history and physical examination, typically by dermatologists but also by primary care providers or pediatric specialists for adolescents, with skin biopsy reserved for atypical or uncertain cases. No companion diagnostic or specific laboratory testing is required, and misdiagnosis is more likely in nondermatology settings and in patients with darker skin tones; however, this does not pose a major barrier to identifying appropriate candidates for roflumilast foam 0.3%.

Clinician group input was consistent with the experts' views and further specified that adolescents and adults with mild to moderate plaque psoriasis affecting the scalp and/or body, particularly those with difficult-to-treat locations such as the scalp, elbows, knees, intertriginous areas, face, and palms and/or soles, would be well suited for roflumilast foam 0.3%. They highlighted patients who have experienced inadequate disease response, intolerance, or contraindications to topical corticosteroids or other topicals as key candidates and noted that roflumilast foam provides a nonsteroidal alternative for patients requiring long-term therapy or treatment on sensitive or steroid-limited areas. Clinician groups and patient input also noted that roflumilast foam is unsuitable for patients with nonplaque psoriasis phenotypes (e.g., pustular or erythrodermic disease), for patients requiring prompt systemic treatment due to severe or extensive involvement, and for those with moderate to severe hepatic impairment, in whom the product is contraindicated. They also considered use in pregnant or breastfeeding patients uncertain due to limited data.

Together, the clinical expert and clinician group input suggests that, although the full population to whom the indication applies with plaque psoriasis of the scalp and body may be eligible, the group most likely to receive roflumilast foam 0.3% in practice comprises adolescents and adults with mild to moderate disease and limited BSA involvement, but with high symptomatic or quality-of-life burden due to scalp and other visible or sensitive areas, who have either not achieved adequate disease control with other topicals or would benefit from a steroid-sparing, once-daily, versatile formulation.

Assessing the Disease Response to Treatment

Clinical experts consulted for this review indicated that assessment of disease response to roflumilast foam 0.3% in practice in Canada would rely primarily on clinical examination and patient-reported symptom improvement rather than the exclusive use of formal scoring instruments. In the ARRECTOR trial, treatment response was evaluated using the S-IGA and B-IGA tools at 8 weeks, alongside patient-reported outcomes such as itch severity. Clinical experts agreed that these end points are conceptually aligned with routine dermatology practice because they reflect visible disease severity and symptom burden; however, they noted

that formal scoring using S-IGA or B-IGA is not routinely performed at each visit outside of clinical trials, with clinicians more commonly relying on visual inspection, global clinical judgment, and patient-reported improvement.

In routine practice in Canada, dermatologists typically determine treatment benefit based on observable improvement in plaques (e.g., erythema, thickness, scaling) and meaningful symptom relief, particularly reduction in itch. Clinical experts indicated that, if required for reimbursement or documentation purposes, S-IGA and B-IGA could be applied in practice, but dermatologists will often use simpler assessments such as documentation of the patient being clear or almost clear of signs of disease, substantial improvement from baseline, or clear patient-perceived benefit. Clinician group submissions were aligned with this perspective and emphasized that these approaches are feasible to implement in both specialist and community dermatology settings.

With respect to timing, both clinical experts and clinician groups described that initial assessment is commonly performed within 4 weeks to 8 weeks of treatment initiation to identify early disease response or clear nonresponse, which is consistent with the ARRECTOR trial design and routine follow-up for topical therapies in Canada. Clinician group submissions further noted that, in practice, follow-up after treatment initiation often occurs at approximately 12 weeks, particularly when confirming whether a topical therapy has achieved sufficient benefit to justify continued use. Clinical experts consulted by CDA-AMC indicated that a more definitive assessment of disease response and durability of benefit is often made after 3 months to 4 months of treatment, reflecting real-world decision-making regarding longer-term management.

Regarding continuation of therapy, clinical experts and clinician groups indicated that a clinically meaningful response would generally include the achievement of being clear or almost clear of signs of disease on the scalp and/or body, or a degree of improvement that is judged to be meaningful by both the clinician and the patient. Improvements in itch, scaling, and overall quality of life were considered central to these determinations. While the minimum disease response required for continuation may vary somewhat across clinicians, there was broad agreement that a lack of meaningful improvement by 8 weeks to 12 weeks would prompt reconsideration of therapy, whereas a demonstration of benefit would support continued use, with reassessment over subsequent months.

The sponsor did not propose formal renewal conditions for roflumilast foam 0.3%. Clinical experts considered the favourable safety profile observed in the ARRECTOR trial and emphasized that topical therapies for psoriasis are typically continued as long as patients derive ongoing benefit and tolerate treatment, with periodic reassessment during routine follow-up rather than rigid renewal thresholds.

Overall, clinical experts and clinician groups agreed that disease response to roflumilast foam 0.3% can be assessed using existing clinical practices in Canada, without the need for specialized testing or laboratory monitoring, and that assessment at 8 weeks to 12 weeks, and longer-term evaluation at 3 months to 4 months, are all feasible and appropriate within routine care.

Discontinuing Treatment

Clinical experts consulted for this review indicated that the discontinuation of roflumilast foam 0.3% in practice in Canada would be guided primarily by a lack of clinical benefit, a loss of disease response, intolerance, or patient preference, rather than by rigid stopping rules. In the ARRECTOR trial, discontinuation was mainly related to a lack of efficacy or adverse events (AEs) during the 8-week treatment period.

Both clinical experts and clinician groups emphasized that not achieving a clinically meaningful response — such as visible improvement in plaques or meaningful relief of symptoms (e.g., itch, scaling) — would prompt discontinuation. In practice, a lack of meaningful improvement by 8 weeks to 12 weeks would generally indicate disease nonresponse and lead clinicians to stop or switch therapy. Patients whose disease initially responds but who subsequently experience a loss of benefit despite appropriate use would also be considered for discontinuation.

Experts identified pragmatic indicators supporting discontinuation, including persistent or worsening disease, an inability to achieve being clear or almost clear of signs of disease or meaningful improvement from baseline, and the need to initiate alternative topical therapy or escalate to phototherapy or systemic treatment because of inadequate disease control. Intolerance or adverse effects would also justify stopping treatment, although clinicians noted that this is expected to be uncommon given the harm profile observed in clinical studies.

Clinical experts and clinician groups further indicated that progression to more extensive disease requiring systemic therapy would generally signal that topical monotherapy is no longer sufficient.

The sponsor did not propose formal discontinuation criteria.

Prescribing Considerations

Clinical experts consulted for this review indicated that psoriasis is a clinical diagnosis that does not require specialized testing or a companion diagnostic, and that ongoing prescribing and monitoring could be appropriately managed by dermatologists and other experienced clinicians, including primary care providers with sufficient expertise, particularly for patients with established diagnoses and stable disease. Clinician groups agreed and noted that restricting prescribing solely to dermatologists could create unnecessary access barriers, particularly in regions with limited specialist availability.

Clinical experts and clinician groups did not identify a need for restrictions on dosage strength or the frequency of administration, noting that roflumilast foam 0.3% is administered once daily as per the product monograph and clinical trial evidence, and that deviation from this regimen would not be expected in routine practice. They emphasized that the simplicity of dosing supports adherence and feasibility across care settings.

With respect to combination use, clinical experts indicated that roflumilast foam 0.3% would often be used as monotherapy for localized scalp and body plaque psoriasis, but that adjunctive use with other therapies is common. This includes use alongside medicated shampoos, intermittent topical corticosteroids, phototherapy, conventional systemic drugs, or biologic therapies in patients with residual localized disease. Clinician groups were aligned with this view and emphasized that combination use reflects real-world

practice and addresses persistent site-specific disease; no safety concerns or evidence gaps were identified that would justify restricting combination use.

Both clinical experts and clinician groups agreed that treatment with roflumilast foam 0.3% is appropriate for community-based care, outpatient specialty clinics, and dermatology practices, without the need for hospital-based administration or specialized monitoring infrastructure.

The sponsor did not propose prescribing restrictions.

Clinical Review

Methods

The review team considered studies in the sponsor's systematic review (pivotal studies and randomized controlled trials [RCTs]), sponsor-submitted long-term extensions, indirect treatment comparisons (ITCs), and studies addressing gaps in the evidence for inclusion. Eligible studies for the systematic review included published and unpublished pivotal studies and phase III and phase IV RCTs, or other designs as relevant. Relevant patients and interventions were defined by the indication and the recommended dosage in the product monograph. Relevant comparators considered in this submission were drugs used in clinical practice in Canada to treat patients described in the indication under review. These included topical corticosteroids (e.g., clobetasol propionate, betamethasone, fluocinonide acetonide, fluocinolone), topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus), vitamin D and its analogues (e.g., calcipotriol, calcitriol), and fixed-dose combinations of vitamin D analogues with corticosteroids. Systemic therapies, including oral and biologic treatments, were not considered relevant comparators for this review because their place in therapy is distinct and typically reserved for patients with more extensive or refractory disease.

Long-term evidence from pivotal studies and RCTs were not included in this submission. ITCs submitted by the sponsor were included when they filled an identified gap in the systematic review evidence (e.g., missing comparator, longer follow-up time) and were used to inform the pharmacoeconomic submission.

The review team selected outcomes (and follow-up times) for review considering the sponsor's Summary of Clinical Evidence,¹ clinical expert input, and patient and clinician group input. Included outcomes are those considered relevant to expert committee deliberations, and they were selected in consultation with committee members. Evidence from the systematic review for the most important outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The outcomes were selected for assessment with GRADE because they address key treatment goals for plaque psoriasis of the scalp and body, were identified as important by patients and clinicians through patient group and clinical expert input, and, where applicable, informed key inputs in the sponsor's pharmacoeconomic model. The following outcomes were selected for inclusion in this report:

- clinical clearance —
 - S-IGA at week 8

- B-IGA success at week 8
- itch severity —
 - Scalp Itch Numeric Rating Scale (SI-NRS) success at week 8
 - Worst Itch Numeric Rating Scale (WI-NRS) success at week 8
- psoriasis severity —
 - 75% reduction in PASI score at week 8
 - 75% reduction in Psoriasis Scalp Severity Index score (PSSI 75) at week 8
- health-related quality of life (HRQoL) —
 - Dermatology Life Quality Index (DLQI) score at week 8
 - Children's Dermatology Life Quality Index (CDLQI) score at week 8
- harms — AEs, serious adverse events (SAEs), withdrawals due to AEs, AEs of special interest (depression, suicidality).

Methods for data extraction, risk of bias appraisal, and certainty of evidence assessment are described in the Supplemental Material document in Appendix 2.

Clinical Evidence

In this report, the following sources of evidence submitted by the sponsor were reviewed and appraised:

- 1 pivotal RCT — the ARRECTOR study, a phase III, multicentre, randomized, double-blind, vehicle-controlled study
- 1 ITC, submitted by the sponsor to contextualize the relative efficacy and safety of roflumilast foam 0.3% compared with other therapies
- studies addressing gaps in the evidence — the ARQ-154-214 study (a 52-week, open-label study in patients with seborrheic dermatitis) and Study 202 (a 52-week, open-label study of roflumilast cream 0.3% in patients with plaque psoriasis); however, in accordance with CDA-AMC requirements for standard review applications, studies submitted to address gaps in the evidence for the pivotal trial are not included in the clinical review.

Systematic Review

Description of Studies

Study Characteristics

Characteristics of the included study are summarized in [Table 2](#). Additional details on eligibility criteria, interventions and comparators, and outcome measures are provided in the Supplemental Material document (Appendix 3).

One study met the inclusion criteria for this systematic review. The ARRECTOR study was a phase III, multicentre, randomized, double-blind, vehicle-controlled trial designed to evaluate the efficacy and safety of roflumilast foam 0.3% applied once daily compared with its vehicle in patients aged 12 years or older

with plaque psoriasis involving the scalp and body. The vehicle consisted of the same foam formulation as the active product but without roflumilast. The primary objective was to assess treatment success based on S-IGA and B-IGA scores at week 8.

The study was conducted across multiple sites in North America, including 13 sites in Canada and 36 sites in the US. Patients were randomized in a 2:1 ratio to receive roflumilast foam 0.3% or the vehicle using a centralized randomization system, with stratification by baseline S-IGA score severity (3 versus 4), B-IGA score severity (3 versus 4), and study site.

The ARRECTOR study included a screening period followed by an 8-week, double-blind treatment period. Efficacy assessments were conducted at prespecified visits during the treatment period, with the primary efficacy evaluation at week 8. Safety was assessed throughout the study, including monitoring of AEs and local tolerability. The database lock and primary analyses corresponded to completion of the 8-week blinded period, after which the study closed as planned.

A treatment washout period for prior psoriasis therapies was required before randomization to establish baseline disease activity, but there was no pharmacologic run-in period involving study treatment.

No major protocol amendments that would materially affect interpretation of the results were identified. All randomized treatment groups were aligned with the Health Canada–approved dosage, and no nonapproved dosing groups were reported.

Table 2: Characteristics of the Study Included in the Systematic Review

ARRECTOR trial (study identification number ARQ-154-309)	
Designs and populations	
Study design	Phase III, randomized (2:1), parallel-group, double-blind, vehicle-controlled, multicentre trial
Locations	Total: 49 sites Canada (13) • New Brunswick (1), Quebec (1), Ontario (8), Manitoba (1), Alberta (1), and British Columbia (1) US (36) • Arizona (1), California (5), Florida (7), Illinois (2), Kentucky (1), Louisiana (1), Maryland (2), Michigan (1), Minnesota (1), Missouri (1), New Jersey (1), New York (2), North Carolina (1), Oregon (1), Pennsylvania (1), Tennessee (1), Texas (5), Utah (1), and Virginia (1)
Patient enrolment dates	Start date: August 25, 2021 End date: April 26, 2022
Randomized (N)	Screened: 574 Total randomized: 432 Roflumilast group: 281 Vehicle foam: 151
Inclusion criteria	• Aged 12 years or older (inclusive) at the time of consent or assent • Scalp psoriasis with a S-IGA score of at least moderate (3) at baseline • Extent of scalp psoriasis involving $\geq 10\%$ of the total scalp at baseline • A PSSI score of at least 6 at baseline

ARRECTOR trial (study identification number ARQ-154-309)	
	• A B-IGA (i.e., nonscalp) psoriasis score of at least mild (2) at baseline • A PASI score of at least 2 (excluding palms and soles) at baseline • Clinical diagnosis of psoriasis vulgaris of at least 6 months' duration at screening as determined by the investigator • Stable disease for the past 4 weeks • Total overall psoriasis involvement on scalp and nonscalp areas $\leq$ 25% BSA (not including palms and soles) at baseline. Total nonscalp BSA should not exceed 20%.
Exclusion criteria	• Current diagnosis of nonplaque forms of psoriasis (e.g., guttate, erythrodermic and/or exfoliative, palmoplantar only involvement, pustular) • Current diagnosis of drug-induced psoriasis • Patients with any condition on the treatment area which, in the opinion of the investigator, could confound efficacy measurements • Abnormal liver functions test results • History of severe depression, and/or suicidal ideation or behaviour • Patients with any serious medical condition or laboratory test result abnormality that would prevent study participation or place the patient at substantial risk, as determined by the investigator • Patients with a history of chronic alcohol or drug abuse within 6 months of initiation of the investigational product • Patients who had a major surgery within 4 weeks before baseline or have a major surgery planned during the study • Patients with a current cancer or a history of cancer within 5 years, with the exception of fully treated cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma, or carcinoma in situ of the cervix
Drugs	
Intervention	Roflumilast (ARQ-154) 0.3% wt/wt foam, topical, q.d. for 8 weeks
Comparator(s)	Vehicle control foam, topical, q.d. for 8 weeks. The vehicle consisted of the same foam formulation as the active product but without roflumilast.
Study duration	
• Screening phase	4 weeks
• Run-in phase	NA
• Treatment phase	8 weeks
• Follow-up phase	NA
Outcomes	
Primary end point	Coprimary end points: • S-IGA success (week 8) ◦ Defined as "clear" or "almost clear" with at least a 2-grade improvement from baseline • B-IGA success (week 8) ◦ Defined as "clear" or "almost clear" with at least a 2-grade improvement from baseline.
Secondary and exploratory end points	Secondary end points: • SI-NRS success (in patients with baseline SI-NRS pruritus score of $\geq$ 4) (week 2, week 4, and week 8) • CFB SI-NRS weekly score (week 1)

ARRECTOR trial (study identification number ARQ-154-309)	
	• CFB SI-NRS daily score (day 1, 72 hours) • WI-NRS success (in patients with baseline WI-NRS pruritus score of ≥ 4) (week 8) • PSD total score (week 8) • CFB PSD aggregate (itching and/or pain) • PSSI 75 (week 8) • S-IGA score of “clear” (week 8) • S-IGA success (week 2 and week 4) • Safety assessments: ◦ physical examinations ◦ vital signs and/or weight ◦ local tolerability assessments ◦ clinical laboratory parameters ◦ PHQ-8 depression scale ◦ PHQ-A ◦ C-SSRS ◦ AEs ◦ SAEs ◦ treatment-emergent AEs ◦ treatment-emergent SAEs
Publication status	
Publications	Gooderham MJ, Alonso-Llamazares J, Bagel J, et al. Roflumilast Foam, 0.3%, for Psoriasis of the Scalp and Body: The ARRECTOR Phase 3 Randomized Clinical Trial. <i>JAMA Dermatol</i> . Published online May 7, 2025. Clinical Trials Registry NCT05028582.

AE = adverse event; B-IGA = Body–Investigator’s Global Assessment; BSA = body surface area; C-SSRS = Columbia–Suicide Severity Rating Scale; CFB = change from baseline; NA = not applicable; PASI = Psoriasis Area and Severity Index; PHQ-8 = Patient Health Questionnaire-8; PHQ-A = modified Patient Health Questionnaire; PSD = Psoriasis Symptom Diary; PSSI = Psoriasis Scalp Severity Index; PSSI 75 = 75% reduction in Psoriasis Scalp Severity Index score; q.d. = every day; SAE = serious adverse event; S-IGA = Scalp–Investigator’s Global Assessment; SI-NRS = Scalp Itch Numeric Rating Scale; WI-NRS = Worst Itch Numeric Rating Scale; wt/wt = weight per weight.

Source: ARRECTOR trial (study identification number ARQ-154-309) Clinical Study Report.⁹

Statistical Testing and Analysis Populations

The ARRECTOR trial was powered to detect superiority of roflumilast foam 0.3% compared with vehicle for the coprimary end points of S-IGA success and B-IGA success at week 8. A planned sample size of approximately 420 patients randomized 2:1 (280 patients in the roflumilast group and 140 patients in the vehicle group) provided more than 99% power to detect an overall 35% difference in S-IGA success and an overall 25% difference in B-IGA success, using a 2-sided alpha of 0.025. Power calculations were informed by results from a prior phase II study (the ARQ-154-204 study).

Primary efficacy analyses were conducted using a stratified Cochran-Mantel-Haenszel test, with stratification by baseline S-IGA category (3 versus 4), baseline B-IGA category (3 versus 4), and study site. Continuous outcomes (e.g., change from baseline) were analyzed using analysis of covariance models with adjustment for baseline disease severity and pooled study site group. Analyses were conducted using multiple imputation, with supportive analyses based on observed data and nonresponder imputation (NRI).

The sponsor prespecified a hierarchical multiple testing strategy to control the familywise type I error rate across the coprimary and selected secondary end points. Both coprimary end points were required to demonstrate statistical significance at the 2.5% level before formal testing of secondary outcomes. Secondary end points were tested according to a prespecified fallback procedure across 3 end point families, with additional adjustment using Holm's procedure for selected end points. Outcomes not included in the testing hierarchy were analyzed descriptively, with nominal P values reported. No interim analyses or multiple data cut-offs were conducted.

Prespecified sensitivity and supplemental analyses were conducted for both coprimary end points using alternative missing-data assumptions (multiple imputation, observed data, NRI). Subgroup analyses for the coprimary and selected secondary end points were prespecified and conducted in the intention-to-treat population. The specific sensitivity analyses are presented in the Supplemental Material document (Appendix 3).

Analysis populations: The intention-to-treat population, defined as all randomized patients analyzed according to assigned treatment, was the primary population for coprimary and selected secondary efficacy analyses. The safety population included all patients who received at least 1 dose of study treatment and was analyzed according to treatment received.

Patient Disposition

Patient disposition for the included study is summarized in the Supplemental Material document (Appendix 4).

Of 574 patients screened, 432 were randomized, with 281 patients assigned to the roflumilast foam 0.3% group and 151 to the vehicle group. Completion rates through the 8-week, double-blind treatment period were high and similar between groups, with 250 of 281 patients (89.0%) in the roflumilast group and 126 of 151 patients (83.4%) in the vehicle group completing the study. The most common reasons for not advancing past screening were not meeting disease severity criteria and the use of prohibited prior treatments.

Discontinuations during the treatment period were infrequent and balanced, occurring in 31 patients (11.0%) in the roflumilast group and 25 patients (16.6%) in the vehicle group. The most common reasons for discontinuation were withdrawal of consent (3.2% versus 6.6%), loss to follow-up (3.9% versus 6.0%), AEs (1.8% versus 1.3%), and lack of efficacy (1.1% versus 0.7%) in the roflumilast group versus the vehicle group, respectively.

No notable protocol deviations were identified that were considered likely to materially affect the interpretation of the efficacy or safety results. Any deviations judged to be potentially relevant to internal or external validity are discussed further in the Critical Appraisal section.

Baseline Characteristics

Baseline demographic and disease characteristics for the included study are summarized in [Table 3](#). A full description table of baseline characteristics is described in the Supplemental Material document (Appendix 4).

In the ARRECTOR trial, baseline characteristics were generally well balanced between the roflumilast foam 0.3% and vehicle treatment groups. Patients enrolled were adolescents and adults with moderate to severe scalp psoriasis and mild to severe body plaque psoriasis, consistent with the eligibility criteria. Baseline measures of disease severity, including the S-IGA and B-IGA categories, were comparable across treatment groups.

Table 3: Summary of Baseline Demographic and Disease Characteristics of the ARRECTOR Study (ITT Population)

Characteristic	ARRECTOR study	
	Roflumilast (n = 281)	Vehicle control (n = 151)
Age (years)		
Mean (SD)	48.6 (14.93)	45.0 (14.33)
Age group (years)		
12 to 17, n (%)		
18 to 64, n (%)		
≥ 65, n (%)		
Sex		
Female, n (%)	152 (54.1)	91 (60.3)
Male, n (%)	129 (45.9)	60 (39.7)
Ethnicity		
Race^a		
American Indian or Alaska Native, n (%)	0	3 (2.0)
Asian, n (%)	26 (9.3)	4 (2.6)
Black or African American, n (%)	12 (4.3)	6 (4.0)
Hispanic or Latino, n (%)	48 (17.1)	28 (18.5)
Not Hispanic or Latino, n (%)	224 (79.7)	121 (80.1)
Not reported, n (%)	9 (3.2)	2 (1.3)
Native Hawaiian or other Pacific Islander, n (%)	3 (1.1)	1 (0.7)
White, n (%)	225 (80.1)	129 (85.4)
Other, n (%)	11 (3.9)	7 (4.6)
More than 1 race, n (%)	4 (1.4)	1 (0.7)
Duration of scalp and body plaque psoriasis at baseline (months)		
Mean (SD)		
BSA affected		
Mean (SD), %	6.12 (4.256)	6.01 (4.325)

Characteristic	ARRECTOR study	
	Roflumilast (n = 281)	Vehicle control (n = 151)
Extent of scalp involvement		
Mean (SD), %	34.4 (25.0)	36.0 (25.8)
Baseline S-IGA category		
Moderate (3), n (%)	239 (85.1)	131 (86.8)
Severe (4), n (%)	42 (14.9)	20 (13.2)
Baseline B-IGA		
Mild (2), n (%)	76 (27.0)	43 (28.5)
Moderate (3), n (%)	191 (68.0)	99 (65.6)
Severe (4), n (%)	14 (5.0)	9 (6.0)
Baseline daily SI-NRS		
n (%)	██████	██████
Mean (SD)	5.9 (2.80)	6.1 (2.54)
Baseline daily WI-NRS		
n (%)	██████	██████
Mean (SD)	5.6 (2.79)	5.5 (2.81)
Baseline PASI		
Mean (SD)	6.70 (3.591)	6.00 (3.284)
Baseline PSSI		
Mean (SD)	21.4 (11.06)	22.2 (10.96)

AE = adverse event; B-IGA = Body–Investigator’s Global Assessment; BSA = body surface area; C-SSRS = Columbia–Suicide Severity Rating Scale; CFB = change from baseline; IQR = interquartile range; ITT = intention to treat; PASI = Psoriasis Area and Severity Index; PASI 75 = 75% reduction in Psoriasis Area and Severity Index score; PHQ = Patient Health Questionnaire; PHQ-A = modified Patient Health Questionnaire; PSD = Psoriasis Symptom Diary; PSSI = Psoriasis Scalp Severity Index; PSSI 75 = 75% reduction in Psoriasis Scalp Severity Index score; q.d. = every day; S-IGA = Scalp–Investigator’s Global Assessment; SD = standard deviation; SI-NRS = Scalp Itch Numeric Rating Scale; WI-NRS = Worst Itch Numeric Rating Scale.

*Racial categories used in the table are as reported in the source and may not align with Canada’s Drug Agency inclusive language guidelines.

Source: ARRECTOR trial (study identification number ARQ-154-309) Clinical Study Report.⁹

Treatment Exposure and Concomitant Medications

Details of patients’ treatment exposure, adherence, and use of concomitant medications in the included study are provided in the Supplemental Material document (Appendix 4).

In the ARRECTOR trial, treatment exposure was high in both treatment groups during the 8-week double-blind period. Of the 281 patients randomized to the roflumilast foam 0.3% group and 151 patients randomized to the vehicle group, the majority in each group — ██████ patients in the roflumilast group and ██████ patients in the vehicle group — met the prespecified adherence criterion and received study treatment for the full planned duration. Adherence was assessed using patient diaries and study drug canister weights and was defined by the sponsor as having received at least 80% of expected doses without missing 3 or more consecutive applications. Using this definition, adherence rates were similar between the roflumilast and vehicle groups, with detailed n (%) values reported in Appendix 4.

The use of concomitant psoriasis therapies was restricted during the randomized treatment period in accordance with the study protocol. There were no notable between-group imbalances in the use of permitted background medications.

Treatment interruptions and discontinuations related to concomitant medication use were similar between the groups, occurring in a small proportion of patients in both the roflumilast and vehicle groups (refer to Appendix 4 in the Supplemental Material document). Following completion of the 8-week randomized period, subsequent patient management occurred according to the study protocol and local clinical practice and is not considered informative for interpretation of the randomized efficacy results.

Critical Appraisal

Internal Validity

The ARRECTOR trial was a phase III, randomized, double-blind, vehicle-controlled study, and several design features support good internal validity. Randomization was conducted centrally using an interactive response system, with prespecified stratification by baseline S-IGA severity, B-IGA severity, and study site, and a 2:1 allocation ratio. Stratification factors were considered appropriate by the clinical experts consulted for this review and were intended to balance key prognostic variables between groups. Allocation concealment and blinding of patients, investigators, and study personnel were maintained using visually identical roflumilast and vehicle foam canisters. However, there remains a possibility of partial unblinding if patients or investigators inferred treatment assignment based on perceived clinical response or local tolerability, which could introduce performance or reporting bias, particularly for subjective outcomes, such as patient-reported itch measures and HRQoL. The direction of any resulting bias is uncertain, though likely to be in favour of roflumilast.

Baseline demographic and disease characteristics were generally well balanced between treatment groups. Some differences were observed (e.g., sex and racial distribution), but these were not considered clinically meaningful by the consulted clinical experts and were not expected to materially affect interpretation of the efficacy or safety results.

Completion rates through the 8-week double-blind period were high (89.0% in the roflumilast group versus 83.4% in the vehicle group). Discontinuation rates due to AEs were low and similar between groups (1.8% in the roflumilast group versus 1.3% in the vehicle group), suggesting there was a low likelihood of attrition bias affecting treatment estimates. Withdrawals due to consent withdrawal (3.2% versus 6.6%) or loss to follow-up (3.9% versus 6.0%) in the roflumilast group versus the vehicle group, respectively, were more frequent than AE-related discontinuations but were not considered differential in a manner likely to bias comparative results.

Missing data for primary efficacy outcomes were considered low overall (< 15%). Prespecified methods to address missing data included NRI and multiple imputation, with additional sensitivity analyses (per-protocol, observed data, tipping-point analyses, and analyses without site stratification) showing results consistent with the primary analysis.

The primary efficacy outcomes (S-IGA and B-IGA success at week 8) are clinically relevant, validated measures commonly used in psoriasis trials and were considered appropriate for comparative efficacy assessment by clinical experts. Patient-reported outcomes (SI-NRS, WI-NRS, DLQI, and CDLQI scores) are well established but inherently more susceptible to reporting bias. SI-NRS and WI-NRS scores were available among a subset of patients with respective scores of 4 or greater at baseline (subset representing > 70% of total patients), and it is unclear if prognostic balance was maintained between groups in these subsets of patients. The extent and direction of this potential bias were unclear. Missing data were more pronounced for HRQoL measures (■■■ in the roflumilast group versus ■■■ in the vehicle group), and CDLQI data were available only for a small subset of adolescent patients, limiting precision for these outcomes.

The statistical analysis plan was prespecified and appropriate for a superiority trial, with adequate power for the coprimary end points and a clearly defined multiplicity control strategy. The hierarchical testing procedure controlled the overall type I error across the coprimary end points (S-IGA and B-IGA success) and selected key secondary outcomes included in the testing sequence. Outcomes outside the prespecified hierarchy were considered supportive and were not adjusted for multiplicity. Subgroup analyses (including baseline S-IGA and B-IGA severity, age group, prior topical corticosteroid or vitamin D analogue use, and other prespecified subgroups) were exploratory, were not powered to detect interaction effects, and should be interpreted as descriptive.

The use of a vehicle control rather than an inert placebo may have attenuated the observed between-group differences because the vehicle itself contains emollients and other dermatologic ingredients that may confer therapeutic benefit. Because both treatment groups received the same vehicle base, the trial isolated the incremental effect of roflumilast over the vehicle; however, the magnitude of benefit of the complete commercial product (roflumilast in its foam formulation) relative to no treatment may be larger than the effect observed versus the vehicle alone.

Overall, the ARRECTOR trial was judged to be at a low risk of bias for the primary efficacy and safety outcomes, with a somewhat higher but acceptable risk of bias for patient-reported outcomes due to their subjective nature.

External Validity

The findings from the ARRECTOR trial are generally applicable in Canada to patients with plaque psoriasis involving the scalp and body who are candidates for prescription topical therapy, based on input from consulted clinical experts. The study enrolled patients aged 12 years or older with clinically meaningful disease defined by IGAs, consistent with the indicated population. However, fewer than 3% of enrolled patients were aged 17 years or younger (10 patients), limiting the available evidence in adolescents. As is typical for phase III trials, eligibility criteria and protocol restrictions excluded some patients seen in routine practice (e.g., those with certain comorbidities or recent use of prohibited therapies). Clinical experts did not consider these exclusions likely to materially affect interpretation of the results for the indicated population. Note that the clinical experts consulted for this review also highlighted that given the study enrolled fewer than 3% of patients aged 17 years or younger, the evidence and interpretation may have limited external validity to patients for this age group.

The intervention — once-daily roflumilast foam 0.3% — reflects the anticipated real-world dosing and administration in Canada, and the foam formulation supports use across multiple body sites, including hair-bearing areas. Adherence in the trial was high and supported by intensive monitoring. Adherence in routine practice may be lower, potentially attenuating effectiveness.

The outcomes assessed, including investigator-assessed clearance, itch severity, and HRQoL, are clinically relevant and aligned with patient and clinician priorities, although formal S-IGA and B-IGA scoring and HRQoL instruments are not routinely applied at every visit in practice in Canada. The randomized treatment period was limited to 8 weeks, which supports the assessment of short-term disease response but limits inference regarding long-term effectiveness and safety. For a drug that is to be taken in the long term for an incurable disease, information is limited on the stability of the effects and any delayed occurrence of harms caused by prolonged use. Differences between trial conditions and routine care, such as restrictions on concomitant therapies and limited use of rescue treatment, may also affect generalizability.

Overall, the ARRECTOR trial provides evidence that is broadly applicable to practice in Canada for the short-term use of roflumilast foam 0.3% in eligible patients, with key limitations related to limited adolescent representation, the vehicle comparator, short follow-up duration, and differences between trial and real-world care.

Results

The key efficacy and harms results and findings from the GRADE assessment are presented in this section. Reported P values were not adjusted for multiplicity. Detailed efficacy and harms results can be found in Appendix 4 in the Supplemental Material document.

Efficacy

Key results include the following.

Clinical clearance

- **S-IGA success:** At week 8, 66.4% (97.5% confidence interval [CI] [redacted]) of patients treated with roflumilast achieved S-IGA success, compared with 27.8% ([redacted]) of patients receiving the vehicle. The between-group difference was 37.1 percentage points (97.5% CI, [redacted]; $P < 0.0001$), favouring roflumilast. This corresponded to an odds ratio (OR) (97.5% CI) of [redacted].
- **B-IGA success:** At week 8, B-IGA success was achieved by 45.5% ([redacted]) of patients in the roflumilast group and 20.1% ([redacted]) in the vehicle group. This corresponded to an OR of [redacted] (97.5% CI, [redacted]) and a between-group difference of 24.8 percentage points ([redacted]; $P < 0.0001$), favouring roflumilast.

Itch severity

- **SI-NRS success:** At week 8, SI-NRS success was observed in 65.3% ([redacted]) of patients receiving roflumilast compared with 30.3% ([redacted]) of those receiving the

vehicle. The OR was [REDACTED] (97.5% CI, [REDACTED]), with a between-group difference of 35.4 percentage points ([REDACTED]; $P < 0.0001$), favouring roflumilast.

- **WI-NRS success:** For WI-NRS success, 63.1% ([REDACTED]) of patients in the roflumilast group achieved a disease response at week 8 versus 30.1% ([REDACTED]) in the vehicle group. The OR was [REDACTED] (97.5% CI, [REDACTED]), and the between-group difference was 32.8 percentage points ([REDACTED]; $P < 0.0001$), favouring roflumilast.

Psoriasis severity

- **A 75% reduction in Psoriasis Scalp Severity Index score:** At week 8, PSSI 75 was achieved by 70.9% (64.27% to 76.70%) of patients treated with roflumilast and 31.3% (23.15% to 40.72%) of those treated with the vehicle. This corresponded to an OR of [REDACTED] (97.5% CI, [REDACTED]) and a between-group difference of 37.6 percentage points (26.19 percentage points to 49.05 percentage points; $P < 0.0001$), favouring roflumilast.

Health-related quality of life

- **Dermatology Life Quality Index:** At week 8, the DLQI least squares mean change from baseline was -[REDACTED] (97.5% CI, [REDACTED]) in the roflumilast group and [REDACTED] in the vehicle group. The between-group difference was [REDACTED] (97.5% CI, [REDACTED]).
- **Children's Dermatology Life Quality Index:** For the CDLQI, results were based on a very small sample (roflumilast group, $n = [REDACTED]$; vehicle group, $n = [REDACTED]$). The mean (standard deviation) change from baseline was [REDACTED] with roflumilast and [REDACTED] with the vehicle; no P value was reported.

Harms

Key results include the following.

- **Overall AEs:** Treatment-emergent AEs occurred in 75 of 281 patients (26.7%) receiving roflumilast foam 0.3% and 25 of 151 patients (16.6%) receiving the vehicle.
- **Serious adverse events:** SAEs were rare, occurring in 2 patients (0.7%) in the roflumilast group and 1 patient (0.7%) in the vehicle group.
- **Deaths:** [REDACTED].
- **Withdrawals due to AEs:** Discontinuation due to AEs occurred in 7 patients (2.5%) in the roflumilast group and 2 patients (1.3%) in the vehicle group.
- **Most common AEs:** The most frequently reported treatment-emergent AEs ($\geq 1\%$ in either treatment group) included headache (4.6% versus 2.0% in the roflumilast versus vehicle groups, respectively) and diarrhea (3.2% versus 2.6% in the roflumilast versus vehicle groups, respectively). These events occurred at low frequencies in both groups and were generally mild to moderate in severity as considered by clinical experts consulted by CDA-AMC. The exact n (%) values for individual AEs are reported in Table 15 in the Supplemental Material document, Appendix 4).

- **Notable harms:** There were no differences between treatment groups in the occurrence of severe AEs, systemic safety concerns, or clinically meaningful laboratory abnormalities. No new or unexpected safety signals were identified during the randomized treatment period.

Summary of Findings and Certainty of the Evidence

Literature-based minimal important difference (MID) estimates were used where available. For DLQI, an MID of 2.2 points was applied, corresponding to the lower bound of reported MID values for this instrument (range, 2.2 points to 6.9 points). Additional details on outcome measures and MID considerations are provided in Appendix 3 of the Supplemental Material document.

For outcomes without published MID estimates, thresholds informed by clinical expert input were applied, including S-IGA success, B-IGA success, SI-NRS success, WI-NRS success, and PSSI 75. For these dichotomous outcomes, clinical experts suggested an overarching threshold for clinical importance of a 2% between-group absolute difference (2 patients per 100 on the absolute effects scale). For harms outcomes, where applicable, the review team considered a conservative threshold of 3 additional patients per 100 experiencing an AE. Using these thresholds, the review team assessed whether the point estimates and corresponding CI bounds reflected clinically important effects.

Overall, treatment with roflumilast foam 0.3% resulted in clinically meaningful improvements across key efficacy outcomes compared with the vehicle over 8 weeks, including scalp and body disease clearance, itch severity, and HRQoL ([Table 4](#)). High-certainty evidence supports improvements in S-IGA and B-IGA treatment success, as well as clinically important reductions in itch measured using SI-NRS and WI-NRS scores. Improvements in scalp disease severity (PSSI 75) were also observed and judged to be of high certainty with clinically important effect estimates.

For HRQoL, roflumilast improved DLQI scores compared with the vehicle; however, the CI crossed a conservative MID threshold, indicating uncertainty about the magnitude of benefit and supporting downgrading for imprecision (moderate certainty). Evidence for improvement based on CDLQI scores was derived from a very small pediatric subgroup and was judged to be very uncertain and not informative for decision-making.

With respect to harms, roflumilast was associated with a higher frequency of overall AEs compared with the vehicle, although most events were mild to moderate. The magnitude and clinical significance of this increase was uncertain because the effect estimate was rated down 1 level for imprecision due to the fact that the CI crossed a plausible conservative threshold for clinical importance. SAEs and withdrawals due to AEs were rare, and roflumilast was judged to likely result in little to no difference in either outcome compared with the vehicle.

Table 4: Summary of Findings — Roflumilast Foam 0.3% vs. Vehicle

Outcome and follow-up	Patients, N (studies)	Relative effect (97.5% CI)	Absolute effects (97.5% CI)			Certainty	What happens
			Vehicle	Roflumilast	Difference		
Efficacy (clinical clearance)							
S-IGA success Follow-up: 8 weeks ^a	432 (1 RCT)		28 per 100	66 per 100 ^b	37 more per 100 (from 26 more to 49 more)	High	Roflumilast results in an increase in the proportion of patients whose treatment achieves S-IGA success compared to vehicle.
B-IGA success Follow-up: 8 weeks ^a	432 (1 RCT)		20 per 100	46 per 100	25 more per 100 (from 14 more to 29 more)	High	Roflumilast results in an increase in the proportion of patients whose treatment achieves B-IGA success compared to vehicle.
Itch severity							
SI-NRS success Follow-up: 8 weeks ^c	326 (1 RCT)		30 per 100	65 per 100	35 more per 100 (from 22 more to 49 more)	Moderate ^d	Roflumilast may result in an increase in the proportion of patients whose treatment achieves SI-NRS success compared to vehicle.
WI-NRS success Follow-up: 8 weeks ^e	 (1 RCT)		30 per 100	63 per 100	33 more per 100 (from 19 more to 47 more)	Moderate ^d	Roflumilast may result in an increase in the proportion of patients whose treatment achieves WI-NRS success compared to vehicle.
Psoriasis severity							
PSSI 75 proportion of patients Follow-up: 8 weeks	432 (1 RCT)		31 per 100	71 per 100	38 more per 100 (from 26 more to 49 more)	High	Roflumilast results in an increase in the proportion of patients whose treatment achieves 75% reduction in PSSI score compared to vehicle.
Health-related quality of life							
DLQI ^e LSM change from baseline Follow-up: 8 weeks	 (1 RCT)	NA				Low ^g	Roflumilast may result in a decrease (improvement) in the mean change in DLQI score from baseline when compared to vehicle.
CDLQI LSM change from baseline	 (1 RCT)	At week 8, the mean change from baseline was with roflumilast and with vehicle				Very low ^h	The evidence is very uncertain about the effect of roflumilast on CDLQI

Outcome and follow-up	Patients, N (studies)	Relative effect (97.5% CI)	Absolute effects (97.5% CI)			Certainty	What happens
			Vehicle	Roflumilast	Difference		
Follow-up: 8 weeks							score compared to vehicle.
Harms							
AEs Follow-up: 8 weeks	432 (1 RCT)	NA	17 per 100	27 per 100		Moderate ⁱ	Roflumilast likely results in an increase in the proportion of patients with 1 or more AE compared to vehicle.
SAEs Follow-up: 8 weeks	432 (1 RCT)	NA	7 per 1,000	7 per 1,000		Low ^j	Roflumilast may result in little to no difference in the proportion of patients with 1 or more SAE compared to vehicle.
Withdrawal from study due to AEs Follow-up: 8 weeks	432 (1 RCT)	NA	13 per 1,000	18 per 1,000		Low ^k	Roflumilast may result in little to no difference in the proportion of patients with withdrawals due to AEs compared to vehicle.

AE = adverse event; B-IGA = Body-Investigator's Global Assessment; CDLQI = Children's Dermatology Life Quality Index; CI = confidence interval; DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; ITT = intention to treat; LSM = least squares mean; MID = minimal important difference; NA = not applicable; OR = odds ratio; PSSI = Psoriasis Scalp Severity Index; PSSI 75 = 75% reduction in Psoriasis Scalp Severity Index score; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; S-IGA = Scalp-Investigator's Global Assessment; SI-NRS = Scalp Itch Numeric Rating Scale; SPRU4-ITT = participants in the intention-to-treat population with Scalp Itch Numeric Rating Scale weekly score ≥ 4 at baseline; vs. = versus; WI-NRS = Worst Itch Numeric Rating Scale.

Note: 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.

^aProportion of patients whose treatment achieved success. Defined as a score of clear (0) or almost clear (1) plus a ≥ 2 -grade improvement from baseline.

^bPercentages are based on the ITT population with multiple imputation; numerators are derived from reported proportions.

^cProportion of patients whose treatment achieved success. Defined as at least a 4-point improvement in average weekly score among patients with a baseline SI-NRS score of ≥ 4 .

^dRated down 1 level for study limitations. The analysis is based on a subset population (SPRU4-ITT). It is uncertain if prognostic balance was maintained.

^eA ≥ 4 -point reduction from baseline among patients with baseline WI-NRS scores ≥ 4 .

^fA reduction in DLQI score means improvement (i.e., better HRQoL).

^gRated down 1 level for risk of bias (fewer patients in the vehicle group were available for analysis [i.e., of patients in the roflumilast group and of patients in the vehicle group had evaluable assessments and were included in the analyses]) and 1 level for imprecision. The MID for the DLQI in patients with psoriasis has been reported to range from 2.2 points to 6.9 points. Using a lower bound of 2.2 points, the CI for the between-group difference (-2.7 points to -1.15 points) includes values both lower and higher than this threshold, indicating that the true effect may range from trivial to clinically important. This uncertainty supports concerns about imprecision in the estimate.

^hSmall pediatric subgroup ($n = \text{img alt="Forest plot point estimate for small pediatric subgroup: 10% difference"}$). The measure of dispersion (SD) around the estimated between-group difference was very wide and included both clinically important benefit and harm. Due to extreme imprecision and the exploratory nature of this analysis, the certainty of evidence was deemed very low.

ⁱThe CI crosses a plausible conservative threshold for clinical importance of 3 per 100; hence, CDA-AMC rated the certainty down 1 level for imprecision in the magnitude of the effects on AEs.

^jThe CI does not cross a plausible threshold for clinical importance of 30 per 1,000. Due to the small number of events, the certainty was rated down 2 levels for imprecision.

^kSmall number of events and the CI touches a plausible conservative threshold for clinical importance of 30 per 1,000. Due to the uncertainty in the threshold and the small number of events, the certainty was rated down 2 levels for imprecision.

Sources: Details included in the table are from the sponsor's Summary of Clinical Evidence and ARRECTOR trial (study identification number ARQ-154-309) Clinical Study Report.⁹

Long-Term Extension Studies

No long-term extension studies were included.

Indirect Evidence

The objective of the indirect evidence submitted by the sponsor was to estimate the comparative efficacy and safety of roflumilast 0.3% foam relative to alternative topical treatments used in clinical practice for adolescents and adults (≥ 12 years) with plaque psoriasis involving the scalp and body. Because no direct head-to-head randomized trials comparing roflumilast foam with relevant active topical comparators were available, the sponsor conducted a network meta-analysis (NMA) to inform comparative effectiveness.

Description of ITC(s)

The sponsor submitted 1 NMA, which aimed to compare roflumilast 0.3% foam with commonly used topical therapies for plaque psoriasis. The primary objective of the NMA was to estimate relative treatment effects for outcomes related to investigator-assessed disease clearance and itch severity, using vehicle- or placebo-controlled trials as the basis for indirect comparisons.

Study Selection and Review Methods

The NMA was informed by a sponsor-conducted systematic literature review of RCTs evaluating topical treatments for plaque psoriasis. Eligible studies enrolled adolescents and/or adults with scalp and/or body psoriasis and evaluated topical interventions at doses consistent with product labelling or common clinical use. Outcomes of interest aligned broadly with those assessed in the ARRECTOR trial, including IGA-based response measures and patient-reported itch outcomes, typically assessed at short-term follow-up (approximately 6 weeks to 8 weeks).

Both published and unpublished randomized trials were eligible for inclusion. Searches were conducted in major biomedical databases, with the most recent search performed close to the time of submission. Study selection and data extraction were conducted by the sponsor; limited information was provided regarding duplicate independent screening. Authors used a standardized critical appraisal tool (Cochrane Risk of Bias version 2). The exclusion of studies was based on limited comparability with the ARRECTOR trial, with detailed justification for exclusions reported in the technical report.

ITC Analysis Methods

The sponsor conducted a bayesian NMA to estimate the comparative short-term efficacy of roflumilast foam 0.3% versus alternative topical treatments. Where feasible, anchored indirect comparisons using the vehicle or placebo as a common comparator were performed. However, due to limited network connectivity, several comparisons relied on adjusted indirect comparisons, and unanchored comparisons were conducted when no shared comparator was available. Individual topical drugs were analyzed as separate nodes rather than pooled by class. No prespecified subgroup analyses were reported.

Relative treatment effects were estimated using hierarchical models that synthesize direct and indirect evidence while accounting for correlations arising from multiarm trials. Analyses were implemented using Markov chain Monte Carlo methods, with convergence assessed using Brooks-Gelman-Rubin statistics and visual inspection of trace plots. Results were summarized using 95% credible intervals. Random-effects

models were specified as the primary analytical approach, with fixed-effects models explored in sensitivity analyses; the justification for model selection was not consistently reported.

Between-study heterogeneity and inconsistency were assessed where feasible using standard bayesian approaches, including estimation of heterogeneity parameters and node-splitting methods. Model fit was evaluated using bayesian goodness-of-fit statistics (e.g., deviance information criterion). The ability to formally assess heterogeneity and inconsistency was limited by sparse evidence networks and small numbers of contributing studies.

Further methodological details are provided in Appendix 6 of the Supplemental Material document.

Summary of Included Studies

The systematic literature review identified 82 unique RCTs, of which 13 were included in the quantitative synthesis informing the NMA. The included trials enrolled adolescents and adults with plaque psoriasis and primarily evaluated topical therapies over follow-up periods broadly aligned with the 6-week to 8-week time frame of the ARRECTOR trial. Selected oral systemic therapies were also included in the networks to improve connectivity; however, these comparators are outside the primary scope of this review. Sample sizes varied across trials, and the number of patients contributing to individual treatment comparisons was limited, with few studies informing each comparison within the networks.

A risk of bias assessment was conducted by the sponsor using the Cochrane Risk of Bias tool for randomized trials. Most included studies were assessed as having a low to moderate risk of bias, reflecting their randomized, double-blind design; however, variability was noted across domains, particularly related to measuring outcomes, the handling of missing data, and the reporting of prior or concomitant therapies.

Across the included studies, patient populations differed with respect to baseline disease severity, including variation in scalp and body involvement. To improve comparability, the sponsor undertook prespecified scenario analyses restricting evidence to more comparable populations (e.g., moderate to severe disease) and harmonized outcome definitions by treating related IGA scales as conceptually equivalent. Additional sources of heterogeneity included differences in topical formulations and vehicles, dosing regimens consistent with approved labelling, variability in outcome definitions, and differences in follow-up duration.

Safety outcomes beyond the short-term randomized period were summarized descriptively rather than modelled. The resulting evidence networks were small and sparsely connected, with few studies contributing to most treatment nodes and limited direct head-to-head evidence. Consequently, most comparative estimates relied on indirect evidence and in some cases, on comparisons without a shared common comparator.

Full key methodological details and scenario analyses are reported in Appendix 6 of the Supplemental Material document.

Critical Appraisal of the ITC

The sponsor submitted an indirect evidence package consisting of a bayesian NMA supported by a systematic literature review. The analysis was based on a prespecified analytical framework broadly

consistent with National Institute for Health and Care Excellence Decision Support Unit guidance. Risk of bias was assessed for included trials using established tools aligned with Cochrane methods; however, assessments were conducted at the trial level rather than by outcome, which may not fully capture outcome-specific sources of bias, particularly for subjective efficacy and safety end points. Contributing studies were randomized, double-blind trials, supporting internal validity at the individual study level. Nevertheless, the overall credibility of the NMA is limited by small, sparsely connected networks, a reliance on indirect evidence for most comparisons, and extensive population and outcome harmonization.

A key limitation of the NMA was limited network connectivity, with few studies contributing to most comparisons. This constrained the assessment of key assumptions underlying indirect comparisons, including heterogeneity, inconsistency, and transitivity. Although heterogeneity was explored using I^2 statistics and inconsistency assessed using node-splitting methods where feasible, these diagnostics were inherently limited by sparse networks with few closed loops and small numbers of studies. As a result, uncertainty in between-study variability could not be reliably quantified.

Random-effects models were specified as the primary analytical approach, with fixed-effects models explored in sensitivity analyses. However, the estimation of between-study heterogeneity was often unstable or infeasible due to sparse data. In such cases, fixed-effects results were presented because they were more readily estimable, but these assume no between-study heterogeneity and may overestimate precision given known clinical and methodological differences across trials. Conversely, random-effects models applied to very sparse networks may overfit the data. Differences observed between fixed- and random-effects estimates indicate sensitivity of results to modelling assumptions and suggest that key similarity assumptions may not have been adequately met.

Additional concerns relate to residual clinical and methodological heterogeneity across included studies, such as differences in baseline disease severity, topical formulations, outcome definitions, vehicle formulations that are not equivalent to inert placebo, and short follow-up durations. Several potential effect modifiers identified in the ITC and by clinical experts — such as baseline B-IGA and S-IGA severity — were incompletely reported or missing for some studies, limiting assessment of their impact. No subgroup analyses or meta-regression analyses were conducted to explore or adjust for these factors, and no analyses were performed to formally evaluate whether differences in vehicle formulations may have biased comparative estimates.

The ITC did not include comparative analyses of harms or safety outcomes, further limiting its ability to inform benefit-risk assessments. In addition, the evidence base may not fully reflect real-world treatment strategies relevant to practice in Canada, and the potential for publication or selective reporting bias cannot be excluded.

Overall, while the ITC provides supportive contextual evidence in the absence of head-to-head trials, substantial uncertainty remains due to network sparsity, heterogeneity, imprecision, and sensitivity to modelling assumptions. These limitations substantially reduce confidence in the magnitude and precision of the comparative efficacy estimates.

Efficacy Results of the ITC

Key results of the ITC are presented in [Table 5](#) and [Table 6](#).

Table 5: S-IGA Response at Week 8 (RE and FE Models, Topical Treatments), Roflumilast 0.3% vs. Comparators [Redacted]

Comparator	Random effects (95% CrI)	Fixed effects (95% CrI)
Betamethasone dipropionate	[Redacted]	[Redacted]
Calcipotriol	[Redacted]	[Redacted]
Calcipotriol plus betamethasone dipropionate	[Redacted]	[Redacted]
Tacrolimus	[Redacted]	[Redacted]
Vehicle or placebo	[Redacted]	[Redacted]

CrI = credible interval; FE = fixed effects; RE = random effects; S-IGA = Scalp–Investigator's Global Assessment; vs. = versus.

Note: Although this network included both topical and oral treatments, oral therapies were not considered relevant comparators for this reimbursement review and were included solely to inform the estimation of relative treatment effects. All treatment effects are reported as odds ratios with 95% CrIs.

Sources: Arcutis indirect treatment comparison report (2025).¹⁰ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 6: B-IGA Response at Week 8 (RE and FE Models, Topical and Oral Systemic Treatments), Roflumilast 0.3% vs. Comparators [Redacted]

Comparator	Random effects (95% CrI)	Fixed effects (95% CrI)
Calcipotriol	[Redacted]	[Redacted]
Vehicle or placebo	[Redacted]	[Redacted]

B-IGA = Body–Investigator's Global Assessment; CrI = credible interval; FE = fixed effects; RE = random effects; vs. = versus.

Note: Although this network included both topical and oral treatments, oral therapies were not considered relevant comparators for this reimbursement review and were included solely to inform the estimation of relative treatment effects. All treatment effects are reported as odds ratios with 95% CrIs.

Sources: Arcutis indirect treatment comparison report (2025).¹⁰ Details included in the table are from the sponsor's Summary of Clinical Evidence.

Across networks, results suggested that patients receiving roflumilast foam 0.3% may have higher odds of achieving S-IGA response at week 8 compared with the vehicle or placebo and with calcipotriol, with credible intervals excluding the null. For B-IGA response at week 8, results were directionally favourable for roflumilast compared with the vehicle or placebo and with calcipotriol; however, estimates from the random-effects models were highly imprecise, reflecting sparse data and limited network connectivity.

Studies Addressing Gaps in the Systematic Review Evidence

No studies addressing gaps were included in this review report.

Discussion

Efficacy

The evidence indicates that roflumilast foam 0.3% provides clinically meaningful short-term benefits for patients with plaque psoriasis involving the scalp and body. Patient group input identified itch, visible disease (particularly scalp involvement), and the burden of managing disease in hair-bearing and sensitive

areas as the most important outcomes. The pivotal trial directly assessed these priorities, with consistent improvements observed in investigator-assessed clearance and patient-reported itch compared with the vehicle. Benefits were demonstrated across multiple, conceptually related end points (S-IGA, B-IGA, SI-NRS, WI-NRS, and PSSI 75 scores), supporting internal consistency and reinforcing the clinical relevance of the findings. The certainty of evidence for these core short-term efficacy outcomes was generally high, suggesting that the observed benefits are unlikely to be explained by bias or chance within the 8-week randomized period.

From a clinical perspective, the pattern of benefit reflects improvements in both visible disease severity and symptom burden, particularly itch — an outcome emphasized by both patients and clinicians as a major driver of impaired quality of life and treatment dissatisfaction. Improvements in scalp-specific outcomes (e.g., S-IGA and PSSI 75 scores) were viewed by clinical experts and clinician groups as especially meaningful, given the practical limitations of existing topical therapies in hair-bearing areas. While HRQoL outcomes favoured roflumilast, uncertainty in the magnitude of effect limits confidence in the degree of patient-reported benefit. This uncertainty is more pronounced in adolescents, who comprised fewer than 3% of the trial population, resulting in very limited evidence for HRQoL effects in this subgroup.

Limitations of the efficacy evidence relate primarily to scope and duration because randomized data are limited to short-term follow-up and do not establish long-term durability of response or safety. This is particularly important for a product that is indicated for the prolonged treatment of a chronic disease. Some patient subgroups commonly encountered in practice in Canada were under-represented; however, clinical experts and clinician groups did not identify a strong biological or clinical rationale to expect materially different short-term efficacy in these populations.

In the absence of head-to-head trials, the sponsor submitted indirect evidence to contextualize efficacy relative to topical and selected oral systemic therapies. The bayesian NMA suggests that roflumilast may be favoured over calcipotriol monotherapy for S-IGA and B-IGA outcomes; however, estimates were highly uncertain, with wide credible intervals, sensitivity to modelling assumptions, and heterogeneity across contributing studies. Clinical experts identified fixed-dose calcipotriol-corticosteroid combination products as more relevant comparators in practice in Canada. Indirect comparisons versus these combination therapies were limited and highly uncertain, with no clear evidence that roflumilast provides superior or equivalent efficacy. For other topical comparators, the direction and magnitude of comparative effects remain unclear, and it is uncertain whether observed differences, where present, represent clinically meaningful benefits. Clinical experts considered these indirect findings exploratory and supportive only.

Overall, the totality of evidence supports the conclusion that roflumilast foam 0.3% addresses an important unmet need for an effective, nonsteroidal topical therapy — particularly for scalp and other difficult-to-treat areas — while acknowledging uncertainty related to durability of response, HRQoL effects (especially in adolescents), and comparative effectiveness versus active treatments.

Harms

Overall, the short-term safety profile of roflumilast foam 0.3% appears acceptable and manageable within the context of an 8-week randomized trial. Treatment-emergent AEs were more frequent with roflumilast

than with the vehicle, but most events were mild to moderate, localized, and consistent with expectations for topical therapy. SAEs were rare and balanced across treatment groups, [REDACTED]. Clinical experts indicated that the observed AE profile aligns with what is typically seen in topical psoriasis treatments and does not raise concerns that would preclude use in routine practice, particularly given the nonsteroidal mechanism of action.

Similar to efficacy, important limitations of the harms evidence relate primarily to duration and scope. Safety data are limited to short-term exposure, and the trials were not designed or powered to detect rare or delayed AEs. While the absolute increase in overall AEs with roflumilast introduces some uncertainty in the magnitude of harm, the clinical importance of this difference is unclear, and thresholds for clinically meaningful increases in minor AEs are inherently uncertain. Patient group input emphasized a willingness to tolerate mild, local adverse effects (such as application-site discomfort) if treatment provides meaningful relief of itch and visible disease, suggesting that the observed harms would generally be considered acceptable considering the benefits.

Comparative harms were not assessed in the NMA submitted by the sponsor.

Key evidence gaps remain, including the lack of robust, long-term safety data, limited information in specific subgroups (e.g., prolonged use in sensitive areas or pediatric populations), and uncertainty regarding comparative harms versus commonly used topical drugs in real-world practice. Overall, the available evidence supports a conclusion that roflumilast foam 0.3% has an acceptable short-term safety profile, with harms that are generally aligned with patient and clinician expectations for topical psoriasis therapy and considered acceptable in relation to the observed benefits.

Ethics and Equity Considerations

Plaque psoriasis, particularly when involving the scalp and other visible or difficult-to-treat areas, can substantially affect quality of life, social functioning, and mental well-being. Patient group input highlighted the psychosocial burden associated with visible disease, persistent itch, and stigma related to scalp involvement, which may be more pronounced for adolescents, working-age adults, and individuals whose employment or social roles place greater emphasis on appearance. Race and ethnicity were evaluated in prespecified subgroup analyses; however, subgroup sample sizes were small, and analyses were not powered to detect interaction effects. Although numerical differences in treatment response were observed across some racial or ethnic subgroups, estimates were imprecise with wide CIs, and no definitive conclusions regarding differential efficacy can be drawn. Overall, under-representation and limited subgroup power reduce the certainty about whether trial results fully reflect the experiences of all populations affected by psoriasis in Canada.

Access and treatment burden are central equity considerations for this indication. Clinician and patient input consistently identified limitations of existing topical therapies for scalp and hair-bearing areas, including poor cosmetic acceptability, difficulty of application, and irritation, which contribute to poor adherence and suboptimal outcomes. These challenges may disproportionately affect patients with limited access to specialist care, those managing multiple responsibilities, or those unable to accommodate complex or time-consuming treatment regimens.

Roflumilast foam is administered topically and does not require clinic visits, specialized equipment, or laboratory monitoring, potentially reducing barriers associated with travel, time off work, or caregiver involvement when compared with phototherapy or systemic therapies. This may be particularly relevant for patients in rural or remote communities, where access to specialists, dermatology services, and phototherapy centres are limited.

From an ethical perspective, the availability of an effective, nonsteroidal topical option suitable for long-term use across scalp and body may support patient autonomy and dignity by expanding choice and reducing reliance on treatments associated with safety concerns (e.g., prolonged high-potency topical corticosteroids) or escalation to systemic therapy in patients with limited BSA involvement but clinically meaningful disease affecting visible or socially impactful areas (e.g., scalp). Patient groups emphasized the importance of safe, tolerable options that can be used chronically without fear of cumulative harm, which aligns with the observed short-term safety profile of roflumilast in the randomized trial. As the first topical PDE4 inhibitor approved in Canada for plaque psoriasis, the absence of long-term comparative safety data introduces residual uncertainty, particularly for patients requiring ongoing treatment.

Overall, the evidence suggests that roflumilast foam 0.3% has the potential to address equity-relevant gaps related to treatment burden and access for patients with scalp and body psoriasis, while acknowledging remaining uncertainties related to long-term use and representation of diverse patient populations in the evidence base.

Conclusion

Based on the totality of the clinical evidence, roflumilast foam 0.3% provides a clinically relevant treatment option for patients aged 12 years or older with plaque psoriasis involving the scalp and body. High-certainty evidence from the pivotal randomized trial, the ARRECTOR study, indicates that roflumilast improves investigator-assessed disease clearance and patient-reported itch outcomes compared with the vehicle over 8 weeks, outcomes that were consistently identified by patients and clinicians as priorities for symptom control and daily functioning. These effects are internally consistent across multiple related end points and align with the intended use of a topical, nonsteroidal therapy for difficult-to-treat and visible areas.

The short-term (8-week) safety profile of roflumilast foam 0.3% appears acceptable, with treatment-emergent AEs generally mild to moderate and few SAEs or discontinuations due to AEs. While harms were more frequent than with the vehicle, the magnitude and clinical importance of this difference are uncertain, and there was no sign of serious or systemic safety concerns during the randomized period. Evidence for longer-term safety and durability of benefit is lacking, representing an important gap in the current evidence base.

In the absence of head-to-head comparative trials, indirect evidence from an NMA provides limited contextual information on comparative efficacy. Among topical comparators, the NMA provided uncertain evidence suggesting a favourable short-term (8-week) effect for roflumilast-only treatment versus calcipotriol and limited to the S-IGA outcome. For other topical and systemic comparators, effect estimates were highly imprecise and included the potential that either roflumilast or comparators could be favoured. Overall,

these findings are limited by sparse networks, reliance on indirect comparisons, and sensitivity to modelling assumptions, and should therefore be interpreted cautiously.

Overall, the evidence supports the conclusion that roflumilast foam 0.3% addresses an unmet need for an effective, well-tolerated, nonsteroidal topical option, particularly for scalp and other hair-bearing areas where existing therapies are often limited by tolerability or adherence. Remaining evidence gaps include the absence of long-term comparative efficacy and safety data, limited evidence in certain patient subgroups, and uncertainty regarding comparative effectiveness versus commonly used topical strategies in real-world practice.

Economic Review

Methods

The review team appraised the pharmacoeconomic evidence submitted by the sponsor on the cost-effectiveness and budget impact of roflumilast compared to other relevant therapies for the treatment of plaque psoriasis of the scalp and body in patients aged 12 years or older.

Summary of the Submitted Economic Evaluation

The sponsor submitted a cost-utility analysis to estimate the cost-effectiveness of roflumilast from the perspective of a public health care payer in Canada over a 5-year horizon.¹¹ The modelled population comprised patients aged 12 years or older with scalp and body psoriasis, which is aligned with the Health Canada indication and was based on the participants in the ARRECTOR trial.² The sponsor's base-case analysis included costs related to drug acquisition costs and direct medical costs associated with dermatologist visits.

In the sponsor's base case, roflumilast was associated with lower total costs (i.e., cost savings of \$3,735 versus corticosteroids, \$2,938 versus vitamin D analogues, \$3,616 versus fixed-dose combination therapy, \$15,913 versus apremilast, and \$6,928 versus conventional systemics) and similar quality-adjusted life-years gained compared to comparators. Of the incremental benefit compared to all topical treatment comparators, more than 90% of the benefit was predicted to be accrued after the observation period of the ARRECTOR trial (observation period = 8 weeks). Additional information about the sponsor's submission is summarized in the Supplemental Material document, Appendix 10.

CDA-AMC identified several key issues with the sponsor's analysis (refer to [Table 7](#); full details are provided in the Supplemental Material document, Appendix 11).

Table 7: Key Issues With the Sponsor's Economic Submission

Issue	What evidence is there to inform this issue?	How was this issue addressed by CDA-AMC?	Did CDA-AMC explore uncertainty in a scenario analysis?
The modelling approach may not adequately reflect the clinical pathway associated with psoriasis.	The sponsor developed a scalp psoriasis treatment-driven model, where body psoriasis response did not influence patient movement between health states; this does not meet face validity according to clinical experts consulted by CDA-AMC. Additional assumptions regarding treatment pathway, including the proportion of patients initiating oral systemics after initial topical therapy (20%), the proportion of patients initiating biologic therapy after discontinuing oral systemics (100%), and the proportion of patients who remain on biologics over time (100%), did not meet face validity and appeared likely overestimated according to clinical expert feedback. Overestimation of these inputs likely resulted in overestimated cost savings associated with roflumilast.	CDA-AMC could not address the assumption that body psoriasis response did not influence patient movement between health states in the base case due to a lack of flexibility in the economic model. CDA-AMC could not address the assumptions surrounding treatment pathway inputs in the base case due to a lack of clinical data.	No scenario analysis was conducted.
The comparative clinical efficacy of roflumilast vs. topical treatment and oral systemic comparators is highly uncertain.	The CDA-AMC review team concluded that treatment response with roflumilast vs. topical and systemic comparators is highly uncertain due to a lack of head-to-head evidence and several limitations identified with the ITC. Treatment response vs. oral systemic therapies is impacted by additional uncertainty due to the naive comparison used. Relapse rates in the model were informed by naive comparison. Overall, there is an absence of evidence to support additional benefit with roflumilast vs. all comparators, except for the comparison vs. calcipotriol monotherapy, which may favour roflumilast.	CDA-AMC could not address this issue in the base case due to the lack of head-to-head evidence to inform treatment response and relapse.	No scenario analysis was conducted.

CDA-AMC = Canada's Drug Agency; ITC = indirect treatment comparison; vs. = versus.

Note: Full details of the issues identified by CDA-AMC are provided in the Supplemental Material document, Appendix 10.

CDA-AMC Assessment of Cost-Effectiveness

The CDA-AMC clinical review concluded that roflumilast foam 0.3% improves investigator-assessed disease clearance and patient-reported itch outcomes compared with the vehicle over 8 weeks. There have been

no head-to-head trials of roflumilast against any comparators. The ITC submitted by the sponsor provided evidence suggesting that roflumilast may be favoured only in comparisons with calcipotriol monotherapy for the S-IGA outcome up to 8 weeks, although these results were uncertain due to the identified limitations with the ITC. For all other topical comparators and systemic comparators, effect estimates were highly imprecise and included the potential that either roflumilast or comparators could be favoured. Overall, findings from the indirect comparisons are limited by sparse networks, reliance on indirect comparisons, and sensitivity to modelling assumptions, and should therefore be interpreted with caution.

The indirect evidence for roflumilast versus comparators is therefore highly uncertain and there is insufficient evidence to determine whether roflumilast provides a greater health benefit than topical treatments or oral systemics, although the sponsor's submission estimated similar quality-adjusted life-years gained relative to all comparators. Additional limitations in the economic analysis were identified, including a modelling approach that did not reflect clinical practice, uncertainty in assumptions regarding the treatment pathway, and uncertainty in the publicly listed drug prices, which resulted in cost savings predicted with roflumilast that were highly uncertain. As such, no reanalyses were performed because there is insufficient evidence to support an incremental benefit with roflumilast versus relevant comparators and predicted cost savings with roflumilast were highly uncertain. Roflumilast was associated with higher per-episode drug acquisition costs compared to all other comparators (refer to the Supplemental Material document, Appendix 8).

Summary of the Budget Impact

The sponsor submitted a budget impact analysis to estimate the 3-year (2027–2029) budget impact of roflumilast for use in the treatment of plaque psoriasis of the scalp and body in patients aged 12 years or older.¹² The sponsor assumed that the payer would be public drug plans that participate in the CDA-AMC reimbursement review process and derived the size of the eligible population using an epidemiologic approach. The price of roflumilast was aligned with the price included in the sponsor's economic evaluation, while the prices of comparators were based on the publicly available list prices. Additional information pertaining to the sponsor's submission is provided in the Supplemental Material document, Appendix 12. CDA-AMC identified a number of issues with the sponsor's estimated budget impact and made changes to model parameters and assumptions in consultation with clinical experts to derive the CDA-AMC base case (Supplemental Material document, Appendix 12). CDA-AMC estimated that by year 3 of reimbursement, 456,184 patients would be eligible for roflumilast; of them, 114,735 patients would be expected to receive roflumilast. The estimated incremental budget impact of reimbursing roflumilast is predicted to be approximately \$15.2 million over the first 3 years, with an expected expenditure of \$99.8 million on roflumilast. The actual impact of reimbursing roflumilast will depend on the market share of roflumilast, the number of flares per year experienced by patients, and the confidential list prices of comparators.

Conclusion

Based on the CDA-AMC clinical review of the sponsor-submitted ITC, roflumilast may be favoured only in comparisons with calcipotriol monotherapy for the S-IGA outcome at 8 weeks, although these results were associated with uncertainty. For all other topical comparators and systemic comparators, effect estimates were highly imprecise and included the potential that either roflumilast or comparators could be favoured.

Additionally, no conclusion can be drawn regarding the safety of roflumilast relative to comparators given that safety outcomes were not assessed in the sponsor-submitted ITC. Overall, findings from the indirect comparisons are limited by sparse networks, reliance on indirect comparisons, and sensitivity to modelling assumptions, and should therefore be interpreted with caution. There have been no head-to-head trials of roflumilast against any comparators.

The indirect evidence for roflumilast versus comparators used in the economic model is therefore highly uncertain and there is insufficient evidence to determine whether roflumilast provides a greater health benefit than topical treatments or oral systemics. If there are no differences in health outcomes between roflumilast and comparators, then the costs of roflumilast to the health system should not exceed those of the least costly comparator for the treatment of plaque psoriasis of the scalp and body in patients aged 12 years or older.

The budget impact of reimbursing roflumilast to the public drug plans in the first 3 years is estimated to be approximately \$15.2 million. The 3-year expenditure on roflumilast (i.e., not accounting for current expenditure on comparators) is estimated to be \$99.8 million. The actual impact of reimbursing roflumilast will depend on the market share of roflumilast, the number of flares per year experienced by patients, and the confidential list prices of comparators. The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate.

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