CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219474Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	219474
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TTT #	2025-13357
Reviewer Name(s)	Donella Fitzgerald, PharmD, DRM
Team Leader(s)	Jacqueline Sheppard, PharmD, DRM
Division Director	Laura Zendel, PharmD, DRM
Review Completion Date	February 10, 2026
Subject	Evaluation of Need for a REMS
[Established/Proper] Name	Difamilast
Trade Name	Adquey
Name of Applicant	Acrotech Biopharma, Inc.
Therapeutic Class	phosphodiesterase-4 inhibitor
Dosage Form(s)	Ointment, 1%
Dosing Regimen	Apply a thin layer twice daily to affected areas and rub in completely

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Adquey (difamilast) is necessary to ensure the benefits outweigh its risks. Acrotech Biopharma Inc. (Acrotech) submitted a New Drug Application (NDA) 219474 for difamilast with the proposed indication for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older. This application is under review in the Division of Dermatology and Dentistry (DDD). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Difamilast, a new molecular entity (NME),[a] is a phosphodiesterase-4 (PDE-4) inhibitor proposed for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older. Difamilast's inhibition of PDE-4 (a major cyclic adenosine monophosphate [AMP]-metabolizing enzyme) increases intracellular cyclic AMP levels leading to reduced production of proinflammatory cytokines and chemokines. However, the specific mechanism(s) by which difamilast exerts its therapeutic action is not well defined (DDD, 2026). Difamilast is proposed as a 1% ointment to be applied in a thin layer twice daily to affected areas and rubbed in completely.[b] In 2021, it was approved in Japan for the topical treatment of atopic dermatitis in adults and children two years and older.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219474 relevant to this review:

- 02/13/2025: NDA 219474 submission for the treatment of mild to moderate Atopic Dermatitis in adults and pediatric patients 2 years of age and older received.
- 11/20/2025: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available safety data, there are no plans to require a Risk Evaluation and Mitigation Strategy for this application at this time.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug*

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Atopic dermatitis (AD) is a chronic skin inflammation characterized by pruritic, eczematous lesions such as erythema, papules, scales, crusts, and recurrent exacerbations (Katoh, 2018). Although the pathogenesis of AD is not completely understood, the disorder appears to result from the complex interaction between defects in skin barrier function, immune abnormalities, genetic predisposition, and environmental and infectious agents. AD can occur anywhere on the body, but is most often found on the hands, face, neck, scalp, elbows and knees. Pruritus is a key symptom of AD, significantly contributing to the disease burden and affecting the quality of life due to discomfort, appearance concerns, and treatment challenges. For some patients, reduced quality of life can lead to anxiety and depression (Peng, 2015).[c] Although it may affect all age groups, AD is most common in children with onset typically between the ages of 3 and 6 months. In the US, AD affects around 10-20% of children and 7-10% of adults totaling millions of Americans with this condition (National Eczema Association, 2026).[d]

3.2. Description of Current Treatment Options

There is no cure for AD. Treatment goals focus on the reduction of symptoms and prevention of exacerbations. A comprehensive approach to treatment includes skin hydration, barrier repair, elimination of exacerbating factors, and pharmacotherapy. See Table 1 below for a summary of the FDA approved topical treatment options for AD.

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1: Summary of Topical Treatment Options Relevant to Atopic Dermatitis **Drug Class**	**Products**	**Important Safety and Tolerability Issues**	**Risk Management Approaches in Labeling**
FDA Approved Topical Treatments for AD			
*Corticosterioids	hydrocortisone, triamcinolone, fluocinonide, mometasone	Skin atrophy, folliculitis, hypertrichosis, adrenal suppression	Warnings & Precautions
*PDE4 inhibitors	crisaborole, roflumilast	Site pain, headache, hypersensitivity reactions	Warnings & Precautions
Calcineurin inhibitors	tacrolimus, pimecrolimus	Potential for lymphoma and malignancy	Boxed Warning
Janus Kinase inhibitors	ruxolitinib	Serious infections, major cardiovascular events, thrombosis, malignancies, all-cause mortality	Boxed Warning
Aryl hydrocarbon receptor agonist (2024)	tapinarof	respiratory tract infection, folliculitis, asthma, extremity pain	Adverse Reactions
Other Topical Treatments: emollients, moisturizers, phototherapy			

*Preferred treatment option

Efficacy of the topical AD treatments varies. There is a need for additional therapeutic options because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses (DDD, 2026).

4. Benefit Assessment

The efficacy of difamilast for the treatment of AD was demonstrated in two pivotal Phase 3 studies conducted in Japan (Study 271-102-00007, National Clinical Trial [NCT] 03908970; Study 271-102-00008, NCT 03911401). The studies were similar in design: randomized, multicenter, double-blind, vehicle-controlled, parallel-group studies. Study 271-102-00007 randomized 340 subjects aged ≥ 15 years in a 1:1 ratio to receive either difamilast ointment 1% (n=170) or vehicle ointment (n=170). Study 271-102-00008 randomized 240 subjects aged 2 to 14 years in a 1:1:1 ratio to receive either difamilast ointment 0.3% (N=80), difamilast ointment 1% (N=80) or vehicle ointment (N=80). In both studies a thin layer of study drug was applied to affected areas twice daily (morning and night, approximately 12 hours apart) for 4 weeks.

The primary efficacy endpoint for the trials was the proportion of subjects that achieved an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 4. Trial 271-102-00007 showed difamilast ointment 1% achieved IGA success in 70/182 (38.5%) subjects compared to 23/182 (12.6%) receiving vehicle, with difference from vehicle (95% CI) of 25.9 (17.5, 34.4) and p-value <0.001. Trial 271-102-00008 showed 40/85 (47.1%) subjects achieving IGA success versus 15/83 (18.1%) receiving vehicle, with difference from vehicle (95% CI) of 28.7 (15.0, 42.5) and p-value <0.001. Based on these results, the clinical team concluded that substantial evidence of effectiveness has been demonstrated through the two Phase 3 trials that showed statistically significant and clinically meaningful improvements in atopic dermatitis severity in Japanese subjects.[e]

The DDD also noted in their review that there was a terminated US Phase 3 trial (MEDI-MM36-301 [NCT05608343]) that showed no treatment effect difference between difamilast 1% and vehicle (11.7% vs 11.9%, p=0.702), though early termination of the trial for "business reasons" limits meaningful interpretation of the efficacy results in the US population (DDD, 2026).

5. Risk Assessment & Safe-Use Conditions

The review team conducted the primary safety analyses on the following pools of data:

- Pool 1: Phase 3, 4-week Japanese trials (pivotal trials)
  - 271-102-00007 (≥15 years-70 years) 2 arms: 1% and vehicle
  - 271-102-00008 (ages ≥2 to <15 years) 3 arms: 0.3 and 1% and vehicle

- Pool 2: Phase 2 and phase 3, 4-week US and Japanese trials
  - 271-102-00007 (≥15 years to 70 years) phase 3: 1% and vehicle (Japan)
  - 271-102-00008 (ages ≥2 to <15 years) phase 3: 0.3 and 1% and vehicle (Japan)
  - 271-102-00002 (ages 2 to 14 years) phase 2: 0.3 and 1% and vehicle (Japan)

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

- US-MEDI-MM36-301 (ages ≥2 years) phase 3: 1% and vehicle(aborted US trial)

Across all vehicle-controlled trials to support safety, a total of 429 subjects received difamilast 1%, including 143 subjects under 18 years of age and 286 subjects 18 years of age and older.

There were no deaths reported in the difamilast clinical development program. No serious treatment emergent adverse events (TEAEs) occurred in the pivotal trials (safety pool 1). One serious TEAE (thyroid cancer) was reported in safety pool 2. The subject was receiving difamilast 1% and did not discontinue treatment. The FDA clinical reviewer did not consider the thyroid cancer to be related to difamilast treatment (DDD, 2026).

There are no serious adverse events of significant concern for difamilast. Draft labeling does not include any contraindications or warnings and precautions.[f]

6. Expected Postmarket Use

Atopic dermatitis is typically diagnosed by primary care physicians, pediatricians and dermatologists in outpatient settings. Other likely prescribers of atopic dermatitis medications, such as difamilast, include nurse practitioners and physician assistants. If approved, difamilast will likely be dispensed from outpatient pharmacy settings and primarily be self-administered by the patient or applied by a caregiver at home. It is expected that the likely prescribers should be familiar with the management of topical atopic dermatitis treatments and patients/caregivers should be able to identify and report clinically significant adverse reactions. No concerning care gaps have been identified within the intended scope of practice. Labeling is sufficient to ensure the safe use of difamilast in the expected postmarket setting.

7. Discussion of the Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of difamilast outweigh the risks.

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for difamilast, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, expected duration of treatment, seriousness of known or potential adverse events, and the likely prescribing population.

There were no serious safety risks associated with difamilast treatment in the clinical trials. FDA expects labeling to be sufficient to communicate the common adverse reactions associated with use.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for difamilast beyond routine pharmacovigilance and labeling. The Applicant stated that the proposed labeling and routine pharmacovigilance would be sufficient to mitigate the risks and preserve the benefits in the treatment of mild to moderate AD in adults and pediatric patients 2 years of age and older.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for difamilast to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. References

Acrotech Biopharm, Inc. Adquey (difamilast ointment). NDA 219474. Draft Prescribing Information, Agency edits as of January 23, 2026.

Division of Dermatology and Dentistry (DDD). Draft Multidisciplinary Review and Evaluation for difamilast, NDA 219474, January 23, 2026.

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Peng W, Novak N. Pathogenesis of atopic dermatitis. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2015;45:566-74.

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