# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 217242Orig1s000

# 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)**

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| **Application Type** | NDA |
| **Application Number** | 217242 |
| **PDUFA Goal Date** | December 16, 2023 |
| **OSE RCM #** | 2023-3732 |
| **Reviewer Name(s)** | May Chan-Liston, PharmD, MPH |
| **Team Leader** | Jaqueline Sheppard, PharmD |
| **Division Director** | Cynthia LaCivita, PharmD |
| **Review Completion Date** | December 15, 2023 |
| **Subject** | Evaluation of Need for a REMS |
| **Established Name** | Roflumilast |
| **Trade Name** | Zoryve |
| **Name of Applicant** | Arcutis Biotherapeutics, Inc. |
| **Therapeutic Class** | PDE-4 inhibitors |
| **Formulation(s)** | foam 0.3% |
| **Dosing Regimen** | Once daily topical treatment to affected area of seborrheic dermatitis |

## INTRODUCTION

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the Zoryve (roflumilast foam 0.3%) is necessary to ensure the benefits outweigh its risks. Arcutis Biotherapeutics, Inc. submitted a New Drug Application (NDA) 217242 roflumilast foam 0.3% for the proposed indication of topical treatment of seborrheic dermatitis (SD) in patients ≥9 years of age.[1] 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.

# 1. Background

## 1.1. Product Information

Zoryve (roflumilast foam 0.3%) is a phosphodiesterase-4 (PDE-4) inhibitor. Roflumilast oral tablets (250 mcg, 500 mcg) were approved by the FDA in 2011 (Daliresp, NDA 022522) and is indicated for the treatment to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[2] Zoryve (roflumilast topical cream 0.3%) was approved in July 2022 and is indicated for the topical treatment of plaque psoriasis.[3]

## 1.2. Regulatory History

The following is a summary of the regulatory history for NDA 217242 relevant to this review:

- 02/16/2023: NDA 217242 submission for treatment of SD in patients 9 years of age and older received.
- 07/13/2023: 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 data, there were no safety issues that require a REMS for roflumilast foam 0.3%.

# 2. Therapeutic Context and Treatment Options

## 2.1. Description of the Medical Condition

SD is a common, chronic inflammatory skin disease characterized by erythematous, scaly patches, often with a yellowish, oily, moist, and/or greasy appearance. The affected areas are distributed on areas rich in sebaceous glands, such as the scalp, the external ear, the center of the face, the upper part of the trunk, and the intertriginous areas. The prevalence of clinically significant SD is approximately 3%, peaking in the third and fourth decades. Males are affected more frequently than females. SD may be associated with certain medications and conditions such as Parkinson's disease and other neurologic conditions, Down syndrome, and human immunodeficiency virus (HIV) infection. SD is a clinical diagnosis, and its exact cause remains unknown.[1,4]

## 2.2. Description of Current Treatment Options

Current treatment options for SD include topical agents such as antifungal agents, corticosteroids, and miscellaneous agents (selenium sulfide and zinc pyrithione). Other agents, although not studied in randomized trials, have been used for severe, refractory, recalcitrant disease not adequately controlled with topical therapies or involving multiple body areas. These include oral antifungal agents (itraconazole, ketoconazole, fluconazole, and terbinafine) and ultraviolet-B phototherapy.[4]

The Applicant initiated development of roflumilast foam 0.3% as an additional medical treatment option for SD, especially for treatment in the scalp area. Relative to other topical formulations such as a cream or gel, foam formulations may be used to treat scalp psoriasis (e.g., Olux® [clobetasol] and Luxiq® [betamethasone] foams) and seborrheic dermatitis (e.g., Extina® [ketoconazole] foam) in hair-bearing areas (e.g., eyebrows, beard, scalp).[1]

# 3. Benefit Assessment

In the phase 3, double-blind, vehicle-controlled pivotal trial (ARQ-154-304), 457 subjects 9 years of age and older with moderate to severe SD were randomized 2:1 to receive roflumilast foam 0.3% (n=304) or vehicle foam (n=153) topically once a day for 8 weeks. The primary efficacy endpoint was Investigator Global Assessment (IGA) success (IGA score of Clear (0) or Almost Clear (1) and a ≥2-point improvement from baseline) at Week 8. Secondary endpoints were Worst Itch-Numerical Rating Scale (WI-NRS) success (≥4-point improvement from baseline in subjects with a baseline WI-NRS score ≥4) at Week 8, Week 4, and Week 2, IGA Success at Week 2 and 4, Overall Scaling Score of '0' at Week 8, Overall Erythema Score of '0' at Week 8 and IGA score of 'clear' at Week 8.

The primary efficacy endpoint (IGA success, defined as IGA =0 or 1 and ≥2-point improvement from baseline at Week 8) results showed that in the ITT population, roflumilast foam 0.3% was statistically superior to vehicle foam. At week 8, the roflumilast group, compared to the vehicle group, achieved a response of 79.5% vs. 58.0% (p-value < 0.0001) [a treatment effect of 20.6%]. For the secondary efficacy endpoint of worst itch numeric rating scale (WI-NRS) success (≥4-points improvement from baseline) at Week 8, the roflumilast group, compared to the vehicle group, achieved a response of 62.8% vs. 40.6% (p<0.0001), [a treatment effect of 25.7%]. For the secondary efficacy endpoint of (IGA = 0) at Week 8, the roflumilast group, compared to the vehicle group, achieved a response of 50.6% vs. 27.7% (p<0.0001), [a treatment effect of 22.5%].[1,4]

# 4. Risk Assessment & Safe-Use Conditions

To determine the safety profile of roflumilast foam 0.3% once daily for the treatment of SD, the clinical review team analyzed the data from the primary safety database that consisted of 787 subjects that received at least one dose of roflumilast foam, 0.3%.

The pooled safety data were from one phase 2a (ARQ-154-203) study, one phase 3 (ARQ-154-304) study, a phase 2, open-label, long-term safety (LTS) study (ARQ-154-214), and a phase 1 open-label, maximal use/PK study (MuST: ARQ-154-116).

Data were analyzed for exposure, demographics, baseline characteristics, TEAEs [including severe TEAEs, SAEs, adverse events leading to discontinuation (AELD)], physical examinations, vital signs, weight, local tolerability assessments (LTA), pigmentation assessments, clinical laboratory parameters (hematology, chemistry, urinalysis), urine pregnancy tests for female subjects of child-bearing potential, and psychiatric assessments (PHQ-8/PHQ-A/CDI-2, C-SSRS). No adverse events of special interest (AESI) were prespecified.[4,5]

In the VC trials safety pool (ARQ-154-203 and ARQ-154-304), the most common adverse events (reported in ≥1% of subjects in the roflumilast group, and greater than in placebo group) were COVID-19 (2.6% v. 2.2%), nasopharyngitis (1.5% v. 0.4%), nausea (1.3% v. 0), contact dermatitis (1.3% v. 0.9%), and headache (1.1% v. 0). The safety results reported in the open-label, LTS study -214 were consistent with the safety results reported for the VC trials. There were no drug-related deaths or SAEs.[4]

# 5. Expected Postmarket Use

As SD is a chronic inflammatory disease, patients are intended to use roflumilast foam 0.3% as a chronic therapy in an outpatient setting. Likely prescribers include dermatologists and general practitioners who are familiar with the risks associated with roflumilast.

# 6. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for roflumilast foam 0.3% beyond routine pharmacovigilance and labeling.

# 7. Discussion of Need for a REMS

Zoryve (roflumilast foam 0.3%) is a phosphodiesterase-4 (PDE-4) inhibitor proposed for the topical treatment of SD.[1] SD is a chronic inflammatory skin disease which impacts the scalp, the external ear, the center of the face, the upper part of the trunk, and the intertriginous areas. Zoryve cream (roflumilast) has been approved for the treatment of SD however there remains a need for treatments that involve in the scalp. The foam formulation offers another treatment option for patients, including those that need to apply treatment to the scalp. The risks for Zoryve foam are similar to the risks of the approved cream formulation and include GI upset and headache.

The Clinical Reviewer recommends approval of roflumilast foam 0.3% on the basis of the efficacy and safety information. Based on the favorable safety profile of this product, this reviewer has concluded that risk mitigation measures beyond professional labeling and standard post marketing surveillance are not necessary to ensure the benefits of roflimulast foam outweigh the risks.

# 8. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for roflumilast foam 0.3% to ensure the benefits outweigh the risks. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be re-evaluated.

# 9. Appendices

## 9.1. References

[1] Arcutis Biotherapeutics, Inc. Roflumilast Foam Summary of Clinical Overview. February 16, 2023.

[2] AstraZeneca Pharmaceuticals LP. DALIRESP® (roflumilast) tablets Prescribing Information. 2018. Accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022522s009lbl.pdf on September 28, 2023.

[3] Arcutis Biotherapeutics, Inc. ZORYVE™ (roflumilast) cream Prescribing Information. 2022. Accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215985s000lbl.pdf on September 28, 2023.

[4] Food and Drug Administration. Division of Dermatology and Dentistry. Roflumilast Foam. NDA 212833. DRAFT Integrated Review. December 13, 2023.

[5] Arcutis Biotherapeutics, Inc. Roflumilast Foam Summary of Clinical Safety. February 16, 2023.

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