NDA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	215985/S-012
Priority or Standard	Standard
Submit Date(s)	December 13, 2024
Received Date(s)	December 13, 2024
PDUFA Goal Date	October 13, 2025 (effective October 10, 2025)
Division/Office	Division of Dermatology and Dentistry / Office of Immunology and Inflammation
Review Completion Date	October 3, 2025
Established/Proper Name	ARQ-151 / roflumilast
(Proposed) Trade Name	Zoryve
Pharmacologic Class	Phosphodiesterase-4 (PDE-4) inhibitor
Code name	
Applicant	Arcutis Biotherapeutics, Inc
Dosage form	Topical cream
Applicant proposed Dosing Regimen	0.05% cream applied to affected area daily
Applicant Proposed Indication(s)/Population	Treatment of mild to moderate atopic dermatitis (AD) in patients 2 to 5 years of age
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication/Population (if applicable)	Treatment of mild to moderate atopic dermatitis (AD) in patients 2 to 5 years of age
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	Apply ZORYVE cream, 0.05% once daily to affected areas of mild to moderate atopic dermatitis

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Program
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health

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Glossary

AC	advisory committee
AD	atopic dermatitis
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IP	investigational product
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDE4	phosphodiesterase 4
PeRC	Pediatric Review Committee
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TCS	topical corticosteroids
TEAE	treatment emergent adverse event
URT	upper respiratory tract
vIGA-AD	validated Investigator Global Assessment for Atopic Dermatitis
WI-NRS	Worst Itch-Numeric Rating Scale

2 Executive Summary

2.1. Product Introduction

Zoryve (roflumilast) cream, 0.05% is a phosphodiesterase-4 (PDE-4) inhibitor developed by the Arcutis Biotherpaeutics under IND 135681 for the indication of topical treatment of atopic dermatitis (AD) in patients 2 to 5 years of age.

Roflumilast was initially approved by the FDA in 2011 (under NDA 022522) as DALIRESP oral tablets 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.

Roflumilast for topical use is approved in cream and foam formulations. The currently approved indications for the topical cream are:

- 0.3%, indicated for the topical treatment of plaque psoriasis, including intertriginous areas, in adult and pediatric patients 6 years of age and older;
- 0.15%, indicated for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older.

The currently approved indications for the topical foam 0.03% are:

- seborrheic dermatitis in adult and pediatric patients 9 years of age and older;
- plaque psoriasis of the scalp and body in adult and pediatric patients 12 years of age and older.

Arcutis has acquired right of reference to relevant clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) information from NDA 022522. Under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, the Applicant submitted Efficacy Supplement S-12 for marketing ZORYVE cream, 0.05% for the treatment of mild-to-moderate atopic dermatitis (AD) in patients 2 to 5 years of age.

2.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from one adequate and well-controlled trial ARQ-151-315 which provided evidence of the effectiveness of roflumilast cream, 0.05% QD for the topical treatment of mild to moderate AD in the target population. This trial conducted assessments using the validated Investigator's Global Assessment Atopic Dermatitis (vIGA-AD), defining success as the proportion of subjects who achieved an vIGA-AD score of clear (0) or almost clear (1) and ≥2-grade improvement after treatment with roflumilast cream 0.05% or vehicle cream for 4 weeks.

Roflumilast cream, 0.05% QD was statistically superior to vehicle on the primary efficacy endpoint in this trial. The Applicant has demonstrated that roflumilast cream, 0.05% is

effective for its intended use in the target population and has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126 (a)(b) to support approval.

2.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Atopic dermatitis (AD) is a chronic, inflammatory cutaneous disorder characterized by pruritic, xerotic skin with recurring flares and remissions. Other clinical features may include erythema, lichenification, oozing and erosions. The Applicant proposes Zoryve (roflumilast) cream, 0.05% applied once daily for the topical treatment of mild to moderate AD in patients 2 to 5 years of age via the 505(b)(1) regulatory pathway. The Applicant submitted efficacy and safety data from: one phase 2 study (ARQ-151-105) enrolling a cohort 2 to 5 years of age; one phase 3, randomized, double-blind, vehicle-controlled trial (ARQ-151-315). Additionally, the Applicant submitted safety data from one open-label, long-term safety study (ARQ-151-313); data were included for ages 2 years and older.

Efficacy

Roflumilast cream, 0.05% was statistically superior to the vehicle cream for the primary and the secondary efficacy endpoints for the intent-to-treat (ITT) population at Week 4.

The primary efficacy endpoint of the validated Investigator's Global Assessment-Atopic Dermatitis (vIGA-AD) defined success as a score=0 or 1 and at least 2-grade improvement from baseline at Week 4. The roflumilast group achieved 25.4% success compared to the vehicle group which achieved a response of 10.7% (a difference from vehicle of 14.9%, CI (9.0%, 20.8%) for a p value < 0.0001. The seven secondary efficacy endpoints were met and supportive with the p-value < 0.0001.

Safety

Analysis of the safety database for the phase 3 trial ARQ-151-315 did not identify a safety signal and was adequate to characterize the safety profile of roflumilast cream, 0.05% for the treatment of mild to moderate AD in patients 2 to 5 years of age. Adverse events reported in ≥ 1% of subjects through Week 4 treated with roflumilast, and more frequently reported compared to the vehicle group, were upper respiratory tract infection (4.1% versus 1.4%), diarrhea (2.5% versus <1%), and vomiting (2.1% versus 0). Roflumilast cream, 0.05% has an acceptable risk-benefit profile and offers an alternative treatment option for mild to moderate AD for patients 2 to 5 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Atopic dermatitis (AD) is a common, chronic, pruritic inflammatory disorder which flares and remissions. The onset of AD is often in childhood before the age of 5 years and is frequently associated with a personal or family history of asthma, allergic rhinitis, and allergies. Although not life-threatening, AD is associated with significant morbidity which affects and results in burden for the patient and family.	AD is a common, chronic dermatology condition with significant medical implications and personal and family hardship. Additional safe and effective treatment options are needed to reduce the burden of this chronic disease on patients and families.
Current Treatment Options	• FDA-approved treatment options for mild to moderate AD in patients 2 to 5 years of age include topical corticosteroids, topical calcineurin inhibitors (TCIs), a topical PDE4 inhibitor, and an aryl hydrocarbon receptor (AHCR) agonist. The safety profile for each has notable adverse reactions: topical steroids have local AEs and systemic absorption; TCIs have a boxed warning; the PDE4 inhibitor has local reactions; the (AHCR) agonist report folliculitis and skin rashes.	An additional treatment option for children 2 to 5 years would be beneficial for mild to moderate AD. As a convenient option, this drug is applied once daily while the other marketed PDE4 inhibitor cream is applied twice a day.
Benefit	• The applicant submitted efficacy data from one adequate and well-controlled Phase 3 trial (ARQ-151-315) to support the approval of ZORYVE (roflumilast) cream, 0.05% for the topical treatment of mild to moderate atopic dermatitis (AD) in patients 2 to 5 years of age. Overall, 437 subjects were exposed to roflumilast cream, 0.05% during Trial 315. Enrolled subjects also had a body surface area (BSA) involvement ≥ 3% (excluding the scalp, palms, soles) and validated Investigator's Global Assessment Atopic Dermatitis (vIGA-AD) score of Mild (2) or Moderate (3) at Baseline/Day 1. • The pre-specified primary efficacy endpoint for the trial was the proportion of subjects who achieved success on the vIGA-AD score at Day 29. Success was defined as achieving an vIGA-AD success score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from Baseline at Week 4. ZORYVE cream, 0.05% was statistically superior to vehicle cream on the primary efficacy endpoint of the study drug compared to vehicle cream	The pivotal phase 3 trial was adequate and well-controlled. The effect size was sufficient to represent clinically meaningful benefit. The evidence submitted by the applicant to support the approval of roflumilast cream, 0.05%, for the treatment of mild to moderate AD in patients 2 to 5 years has met the statutory evidentiary standard for providing substantial evidence of effectiveness under the proposed conditions of use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	25.4% vs. 10.7%, respectively, with success on all secondary endpoints; the p-value was < 0.0001 for the primary and key secondary endpoints.	
Risk and Risk Management	• There were no deaths. One subject in the controlled trial developed one serious adverse event (SAE) (cellulitis) on Day 1 that was considered unlikely related to roflumilast. During the Double-Blind period, TEAEs were reported for 130 subjects (29.7%) who received roflumilast and 47 subjects (21.9%) who received vehicle. The TEAEs reported most frequently by preferred terms and more frequently for roflumilast compared to vehicle were upper respiratory tract infection (4.1% vs 1.4%), diarrhea (2.5% vs. <1%), vomiting (2.1% vs 0%), rhinitis (1.6% vs. 0), conjunctivitis (1.4% vs. 0), influenza (1.1% vs. <1%), headache (1.1% vs. 0). There were few meaningful differences in safety between ZORYVE cream 0.05% in patients 2 to 5 years and ZORYVE cream 0.15% approved for adults and children ≥ 6 years. • An open-label extension (OLE) study (ARQ-151-313) enrolled subjects with mild to moderate AD aged ≥ 2 years from multiple trials. The rollover subjects from the phase 3 trial had been treated with roflumilast (n=256) or vehicle (n=180). • The Agency agrees with a partial waiver of assessments in the pediatric population 0 to 3 months of age because studies are impossible or highly impractical. • No serious safety concerns were identified that warranted consideration of a Risk Evaluation and Mitigation Strategy (REMS). The Prescribing Information and Patient Information adequately addresses the known risks associated with the moiety.	The safety profile of ZORYVE (roflumilast) cream, 0.05% was well characterized in the population with mild to moderate atopic dermatitis age 2 to 5 years. Generally, the adverse events observed with exposure to roflumilast cream, 0.05% were not unexpected for the pediatric age groups in which the disease commonly occurs. Some events were related to common pediatric illnesses and disorders associated with atopic dermatitis.

2.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		X	Observer reported outcome (ObsRO) WI-NRS (exploratory)	
		X	Clinician reported outcome (ClinRO) vIGA-AD and EASI	Section 8.1.1.
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

3 Therapeutic Context

3.1. Analysis of Condition

Atopic dermatitis (AD), commonly known as eczema, is a chronic, relapsing inflammatory skin condition characterized by dry, pruritic skin that occurs most frequently in children but also affects many adults. AD is associated with increases in the risk of food allergy, asthma, allergic rhinitis, other immune-mediated inflammatory diseases, and mental health disorders; and inflicts a substantial psychosocial burden on patients and their relatives (Weidinger, 2016). Clinical features of AD include skin dryness, erythema, oozing and crusting, and lichenification. Pruritis is a hallmark of the condition. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals.[3] Shaw et al. reported the prevalence of AD in the United States in individuals between 4-8 years of age to be 10.63% and in those between 9-12 years of age to be 9.96%. (Shaw, 2011)] For 10-30% of individuals with AD, it persists into the adult years. (Eichenfield, 2014)

AD is diagnosed clinically by identifying the disease pattern, history, and the medical history including personal and/or family history of AD, atopy, and asthma. AD is characterized by symmetric, lichenified plaques in flexural regions of the extremities (antecubital and popliteal fossae) that may also involve the neck and flexural aspects of the wrists. AD may be localized or generalized. While the core presentation for children with AD is comparable to adults, pediatric patients less than 2 years of age may present with more exudative lesions, perifollicular accentuation, pityriasis alba, and seborrheic dermatitis-like presentation. [Ramírez-Marín, 2022]

The pathogenesis of AD involves a complex interaction between genetic, immunological, environmental factors resulting in abnormal skin barrier function and immune dysregulation. Genetic factors focus on the fillagrin (FLG) gene loss-of-function mutations, with recent advances in genomics focusing on establishment of pathogenic mechanisms and exploration of the role of other epidermal differentiation complex gene variants. (Stefanovic, 2024) Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum which permits the penetration of environmental allergens. The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies. (Leung, 2014) Acute AD is associated with cytokines produced by T helper 2 type (Th2) cells (as well as other T-cell subsets and immune elements). These cytokines are thought to play an important role in the inflammatory response of the skin, and IL-4 and IL-13 may have functional roles in Th2 inflammation. (Boa, 2015)

3.2. Analysis of Current Treatment Options

There are multiple treatment options for AD in general, as well as for the pediatric population

with AD. Because AD is frequently a pediatric condition with onset in infancy, there are prescription drug options for use in younger age groups, some approved down to 3 months of age. Classes of drugs include topical corticosteroids, calcineurin inhibitors, PDE4 inhibitors, and biologics for moderate to severe AD.

FDA-approved corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Labeling for systemic corticosteroids do not specify any limitations on the age of indication. Although their use may result in rapid improvement, discontinuation of systemic corticosteroids commonly results in recurrence and flare of AD with an increased severity. A potential adverse event associated with prolonged or high-dose systemic corticosteroids use in children and adolescents includes the risk of decreased linear growth during therapy.

Other topical therapies indicated for AD include the topical calcineurin inhibitors, PDE-4 inhibitors and JAK inhibitors. The calcineurin inhibitors Protopic ointment and Elidel cream carry boxed warnings advising that the safety of their long-term use has not been established, and that rare cases of malignancy (e.g., skin cancer and lymphoma) have been reported in subjects treated with topical calcineurin inhibitors. For mild to moderate AD, currently available treatment options are PDE-4 inhibitors Eucrisa (age ≥ 3 months), Zoryve cream 0.15% (age ≥ 6 years) and JAK inhibitor ruxolitinib (age ≥ 12 years).

Dupilumab is an injectable IL-4 and IL-13 antagonist indicated for the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Other systemic drugs for the treatment of AD include tralokinumab, an injectable IL-13 antagonist indicated for the treatment of moderate-severe atopic dermatitis in adults; and nemolizumab, an interleukin-31 receptor antagonist indicated for the treatment of adults and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. Oral JAK inhibitors upadacitinib and abrocitinib are approved for the treatment of refractory moderate to severe AD; the indication is restricted for patients 12 years and older who failed other systemic therapies including biologics.

In general, routine skin care is critical to AD management and includes attention to bathing practices and the regular use of moisturizers, which are available in varying delivery vehicles including creams, ointments, oils, and lotions. Moisturizers are used to treat xerosis, decrease the transepidermal water loss, and provide improvement and relief of pruritus, erythema, fissuring, and lichenification.

Systemic immunomodulating agents which have been used off-label to treat AD in pediatric patients include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The safety profiles vary by product, although each product carries the potential for significant adverse effects, and labeling for all of these products include boxed warnings.

Additionally, the FDA has cleared devices for the treatment of AD. Phototherapy (UVA and UVB) is considered a safe and effective treatment option for AD patients, including pediatric patients who are candidates for systemic therapy. Narrowband UVB therapy may be considered a first-line treatment because of the safety profile relative to psoralen + UVA (PUVA). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts. However, long-term risks from phototherapy treatment of AD in children have not been evaluated. The Agency has also cleared topical emulsions functioning as protective barriers prescribed to relieve symptoms.

Table 1 below is focused on drug treatments for mild to moderate AD in the pediatric population age 2 to 5 years of age.

Table 1: Currently Approved products for the Topical Treatment of Mild to Moderate Atopic Dermatitis for Patients 2 to 5 years of age

Product (s) Name	Relevant Indication	Years of Approval	Dosing/ Administration	Efficacy Information/ Population	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments by Pharmacologic Class						
Topical cortico-steroids (Locoid/lipo-cream (L), Verdeso, Cutivate (C), fluocinolone acetonide (F), triamcinolone (T); ANDAs	Mild to moderate AD	First marketed in 1950s; Locoid 1997; Cutivate 2005 Verdeso 2006	For mild to moderate AD, lower potency TCS. Multiple Rx formulations available: cream, lotion, foam, ointment, gel, solution, oil. Apply to affected areas, once or twice daily per labeling.	F, L: 3 months and older; C: 1 year and older; T; 2 years and older.	TCS can cause skin atrophy, striae; hypertrich-osis. Avoid potent strengths on face, folds.	Systemic absorption has been reported
Topical calcineurin inhibitors (CI) (Protopic oint [P], Elidel cream [E])	P: short & long term Tx, signs and Sx E: second-line Tx, age ≥2 years	Protopic 2000; Elidel 2001	P: 0.1% and 0.03% strengths. E: 1%. Both: Apply to affected areas twice daily.	P: 0.03% for 2 to 15 years. 0.1% for E: for ≥ 2 years	Boxed Warning for Class: lymphoma, NMSC risk. Avoid continuous long-term use.	CI: Not for use < 2 years.

Topical PDE4 inhibitors Eucrisa (Eu) cream Zoryve cream(Z)	mild to mod AD Eu: age ≥ 3 months Z: age ≥ 6 yrs	Eucrisa (2016) Zoryve 0.15% (2024)	Eu: twice daily Z: once daily	Eu: 2 trials DB, VC, R 2:1 Eu: vehicle. Z: 2 trials R, DB, VC. ≥ 6 years	Eu: Hypersen-sitivity Rxns Z: GI Sx = nausea, diarrhea, vomiting, HA	Z: contra-indicated: mod to severe liver impairment Eu and Z: Application site pain
Aryl hydrocarbon receptor agonist VTAMA cream (tapinarof)	Topical treatment of AD Age ≥ 2 years	2022	Apply once daily	2 trials R, DB, VC, in moderate to severe AD.	ARs: Upper/ lower RTI, Folliculitis, NP, HA, asthma, ear infection, abdominal pain	

AD=atopic dermatitis; DB=double-blind; R=randomized; GI=gastrointestinal; HA=headache; NP=nasopharyngitis; Sx=symptoms; RTI=respiratory tract infection; NMSC=nonmelanoma skin cancer; TCS=topical corticosteroids; VC=vehicle-controlled.

Source: Clinical reviewer table.

4 Regulatory Background

4.1. U.S. Regulatory Actions and Marketing History

Multiple roflumilast formulations (tablet, ARQ-151 cream, ARQ-154 foam) and strengths have been approved and are marketed in the US. The actions taken are summarized as they pertain to dermatologic indications.

Oral tablet:

- In 2011, the Agency approved roflumilast (NDA 022522) oral tablets for the indication of 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. Oral roflumilast was not studied for dermatological indications.

Cream:

- July 29, 2021: Zoryve (roflumilast, ARQ-151) cream, 0.3% (NDA 215985) was approved for the topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.
- October 5, 2023: Zoryve cream, 0.3% efficacy supplement (S-2) expanded the age for topical treatment of plaque psoriasis, including intertriginous areas, in adult and pediatric patients to 6 years of age and older.
- July 9, 2024: Under efficacy supplement (S-7), the Agency approved a new strength of Zoryve cream, 0.15% for the new indication of topical treatment of mild to moderate atopic dermatitis (AD) in adult and pediatric patients 6 years of age and older.

Foam:

- December 15, 2023: Zoryve foam, 0.3% (NDA 217242) was approved for the treatment of seborrheic dermatitis in adult and pediatric patients 9 years of age and older.
- May 22, 2025: Zoryve foam, 0.3% efficacy supplement (S-5) was approved for the treatment of plaque psoriasis of the scalp and body in patients 12 years of age and older.

4.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed roflumilast cream for the topical treatment of AD under IND 135681 and submitted their marketing application (for pediatric ages between 2 to < 6 years of age) under efficacy supplement 12, and under the 505(b)(1) regulatory pathway. Milestone interactions with the Applicant included the following.

- May 4, 2020: The Sponsor submitted an iPSP for atopic dermatitis (AD) (SDN 76) to the FDA.
- August 31, 2020: The Agency agreed to the PSP.
- September 18, 2020: The Sponsor submitted an Amended iPSP (SDN 92) which proposed roflumilast cream, 0.05%. for the treatment of subjects between 2 to < 6 years of age.
- June 14, 2021: The Agency agreed to the the amended PSP.
- February 22, 2022: The Sponsor submitted an Amended Agreed PSP (SDN 154) with revisions to the timelines for the deferred pediatric studies.
- June 12, 2024: The Agency agreed to the Agreed Amended Initial Pediatric Study Plan (iPSP).
- April 15, 2025: The newly proposed strength (0.05%) of the Zoryve cream for the Indication of treatment of atopic dermatitis in pediatric patients between 2 to < 6 years of age triggered PREA requirements. The Pediatric Review Committee (PeRC) reviewed the Amended Agreed Amended iPSP on August 12, 2025, and provided the following recommendations:
    - The PeRC agrees with the Sponsor's plan for partial waiver in pediatric patients from birth to less than 3 months of age because necessary studies are impossible or highly impracticable because the diagnosis of atopic dermatitis is uncommon and often unreliably made before age 3 months.
    - The PeRC agrees with the Sponsor's plan to request a deferral of studies in pediatric patient 3 months to less than 2 years of age for atopic dermatitis until after safety and tolerability studies for roflumilast cream are complete. [Reference ID: 5582672]

5 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

5.1. Office of Scientific Investigations (OSI)

The Zoryve® cream 0.15% strength was approved on December 13, 2024, and inspection was conducted in 2018. According to OSI reviewer Stephanie Coquia, there were no concerns regarding the three study sites for trial 315. The review team for supplement 12 determined that no inspections would be necessary as the sites had been recently inspected.

5.2. Product Quality

The three strengths (approved 0.3% cream and 0.15% cream and the proposed 0.05% cream) are qualitatively identical except for (b) (4). The excipient portion of the cream is qualitatively identical among all the three strengths and, with the exception of (b) (4), quantitatively identical. The microbiology review recommendation is No Action Indicated by Jason God, dated 03/05/2025.

No changes to the drug substance sections were made in support of this supplement. Quality information for roflumilast is referred to DMA (b) (6), which remains adequate based on DMF (b) (4) chemistry review #10 by Roger N. Farr, dated 09/04/2024.

OPMA recommended approval of (b) (4) as a manufacturing, packaging, and testing site and all the testing sites for Zoryve® (roflumilast) cream, 0.05%.

The quality control specification for roflumilast cream proposed is the same for all strengths, except for any unspecified impurities (increased from NMT (b) (4)% for each individual impurity for the 0.3% cream and the 0.15% cream to NMT (b) (4)% for each individual impurity for the 0.05% cream) and total impurities (increased from NMT (b) (4)% for the 0.3% cream and the 0.15% cream to NMT (b) (4)% for the 0.05% cream). The specification for any unspecified impurities and total impurities was increased due to the amount of sample used in comparison to the 0.15% and 0.3% creams. The updates to the justification of specifications are acceptable from the CMC standpoint.

The analytical procedure for assay and impurities was revised to include sample preparation for 0.05% cream. The updated analytical procedures are acceptable from the CMC standpoint. The provided method validation reports are acceptable. All batches of roflumilast cream, 0.05% 60 g tube (lot No. SDR-1C, SES-1C, and SET-1C) and 5 g tube (lot No. SDR-C, SES-C, and SET-C) complied with the release specifications for the drug product.

Considering the similarities among the three strengths and EI assessment for the higher strength 0.3% confirming "No reportable results were observed for any elemental impurity", the current-approved EI assessment (sequence 0007) covers all three strengths. No control of elemental impurities in the proposed 0.05% strength is required.

The container closure system for commercial primary packaging of 0.05% cream is same as currently approved for 0.3% cream and 0.15% cream. The package sizes proposed for 0.05% cream are 5g and 60g.

Stability data for up to 36 months for the roflumilast cream, 0.05%, 60 g tube (lot No. SDR-1C) and for up to 24 months for the roflumilast cream, 0.05%, 60 g tube (lot No. SES-1C, and SET-1C) at the long-term condition and for 6 months at accelerated condition for the all batches of roflumilast cream, 0.05%, 60 g tube (lot No. SDR-1C, SES-1C, and SET-1C) and 5 g tube (lot No. SDR-C, SES-C, and SET-C) at horizontal position met all acceptance criteria in the stability specifications. 36 Months of long-term supportive stability data at the long-term conditions and 6 months stability data at accelerated conditions for one clinical supportive stability lot met all acceptance criteria in the stability specifications. Based on the stability results provided with this supplement, and the guidance related to data extrapolation provided in ICH Q1E, a 36-month expiry for commercially distributed roflumilast cream, 0.05% is acceptable from the CMC standpoint. The recommended storage condition planned for commercial labeling is 20°C to 25°C (68°F to 77°F); with excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Post-approval Stability Protocol and Stability Commitment for Zoryve (roflumilast) cream, 0.05% is acceptable from the CMC standpoint.

The request for Categorical Exclusion from the requirement of preparing and submitting an Environmental Assessment under 21 CFR 25.31(b) and 21 CFR 25.15(a) is acceptable from the CMC standpoint.

The DMEPA team's evaluation of the proposed Zoryve Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling did not identify areas of vulnerability that may lead to medication errors. The proposed Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling are acceptable from a medication error perspective based on the DMEPA labeling review by Amy J Bao, dated 04/25/2025. The revised Zoryve Prescribing Information, Patient Package Insert, container label and carton labeling are adequate from the standpoint of OSE-DMEPA. The container and carton labels for the 0.05% concentration submitted on July 10, 2025 are acceptable from the CMC standpoint. Minor editorial changes to Section 3, Section 11, and Section 16 of the prescribing information and Patient Package Insert (PPI) are acceptable from the CMC standpoint.

5.3. Clinical Microbiology

Not applicable.

5.4. Devices and Companion Diagnostic Issues

Not applicable.

6 Nonclinical Pharmacology/Toxicology

6.1. Executive Summary

Not Applicable. No nonclinical data were submitted for this supplement.

7 Clinical Pharmacology

7.1. Executive Summary

The Applicant (Arcutis Biotherapeutics, Inc.) submitted this efficacy supplement-12 under NDA215985 on 12/13/2024, seeking the approval of Zoryve (roflumilast) cream 0.05% to be applied once daily (QD) to affected areas for the topical treatment of mild to moderate atopic dermatitis (AD) in subjects 2 to 5 years of age. Zoryve cream 0.15% QD was approved for the treatment of mild to moderate AD in subjects 6 years of age and older. Zoryve cream 0.3% QD was also approved for the treatment of mild to moderate psoriasis in subjects 6 years of age and older. Note that roflumilast was originally approved in 2011 as oral tablet (Daliresp, NDA 022522 held by AstraZeneca) 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. This Applicant has obtained a right of reference from NDA 022522 and is following a 505(b)(1) regulatory pathway.

Table 2: List of Clinical Trials to Support the PK and Efficacy

Trial	Objective	Population	Study Design	Dosing regimen, duration, formulation[a]
ARQ-151-105 Maximal Use Trial (MUsT)	To evaluate PK, safety, and efficacy under maximal usage condition	Adolescent (12 to ≤17 years old and Pediatric Subjects (2 to ≤11 years old) with mild to moderate AD. N = 101 (enrolled)	Phase 1, Open-label 4-week study PK sampling: Cohorts 1-3: Days 1[b] (Baseline), 14[c] and 28. Cohorts 4-7: Day 1[b] (Baseline), Day-7 (except cohort 8), 14[b], and 28 (ET) Cohort 8: aged 3 m to <2y: predose at Day 14 and 28.	Cohorts 1-3 (**Non-MUsT**): BSA involved: 1.5 – 35%, once daily (QD) for 28 days C1: Cream, 0.15% → 12 to ≤17 yo [N=8] C2: Cream, 0.15% → 6 to ≤11 yo [N=11] C3: Cream, 0.15% → 2 to ≤5 yo [N=12] Cohorts 4-8 (**MUsT**): BSA involved: ≥35% in 2 to ≤11 yo, ≥25% in 12 to ≤17 yo; QD x 28 days C4: Cream, 0.15% → 12 to ≤17 yo [N=13] C5: Cream, 0.15% → 6 to ≤11 yo [N=15] C6: Cream, 0.15% → 2 to ≤5 yo [N=13] **C7: Cream, 0.05% → 2 to ≤5 yo [N=10]** C8: Cream, 0.05% → 3 months to < 2 yo [N=19]
ARQ-151-315 (Phase 3)	To evaluate efficacy and safety	Patient aged 2 to 5 years old with AD. [N = 650]	R, DB, PG, vehicle-controlled study PK samples collected at Day 29 prior to amendment 1	Roflumilast Cream, 0.05% QD or matching vehicle cream for 4 weeks [2:1]. Stratified by vIGA-AD score (Mild versus Moderate) and Site.

a. Both studies employed the to-be-marketed formulations. **b.** 2- and 4-hours post-dose. **c.** 2-, 4-, and 6-hours postdose. BSA: body surface area; C1-8: cohorts 1-8; DB: double-blind; ET: end of treatment; PG: parallel group; R: randomized; yo: years old;. Additional clinical trial was listed in section 7.1 to support safety.

To support this supplement, Clinical Pharmacology review focused on the maximal use (MUsT) cohorts 4-7 of trial ARQ-151-105. Note that MUsT cohorts 4-6 were also reviewed before (see section 6 of unireview for supplement-007 of this NDA dated July 05, 2024 [Reference ID: 5408595]).

Briefly, ARQ-151-105 was an open-label trial under maximal use conditions that evaluated PK, safety, tolerability, and efficacy of roflumilast in subjects 3 months to 17 years old. MUsT cohorts 4-6 and cohorts 7-8 applied roflumilast cream 0.15% and 0.05% once daily, respectively, on the skin surface at the rate of ~2 mg/cm^2 for 4 weeks. Each cohort includes subjects with a particular age range (C4: 12 to ≤17; C5: 6 to ≤11; C6 and C7: 2 to ≤5; C8: 3 months to <2 years of age). The treatable body surface area (BSA) with AD excluding scalp, palms, and soles was ≥25% for cohort 4 while it was ≥35% in cohorts 5-8. The PK of both roflumilast and its major metabolite, roflumilast N-oxide was characterized in this study.

In addition, the Applicant summarized PK data of Day 29 for a subset of subjects in the Phase 3 trial ARQ-151-315.

Key Clinical Pharmacology Findings from the MUsT

- Following application of 0.15% roflumilast cream, the systemic exposures (Cmax, $AUC_{0\text{-}24h}$) of roflumilast and N-oxide metabolite increased with decreasing age. For example, mean Cmax or $AUC_{0\text{-}24h}$ in subjects 2 to 5 years old (cohort 6) was approximately 3.2-fold higher for roflumilast and 5.2-fold higher for N-oxide metabolite than those in adolescents 12 to 16 years old (cohort 4). Furthermore, the systemic exposure in the 2 to 5 year old was approximately 0.9 – 1.4-fold (AUC) and 0.53 – 0.68-fold (Cmax) of that associated with the approved oral dose (500 µg QD) based on cross-study comparison (Bethke et al. 2007[1]).
- Due to higher exposures in 2 – 5 years old compared to adolescents and 6 – 11 years old subjects, the Applicant added an additional cohort of 2 – 5 years old (cohort 7) to evaluate lower strength of 0.05% cream.
- Exposures of roflumilast and its N-oxide metabolite were approximately 3- to 5-fold lower in 2 – 5 years old subjects receiving 0.05% cream (cohort 7) compared to that associated with 0.15% cream (cohort 6). For instances, on Day 14:
    - Mean roflumilast Cmax and AUClast in cohort 7 (3.21 ng/mL and 47.2 ng·h/mL) were 3.2- and 4.3-fold lower, respectively, compared with cohort 6 (10.2 ng/mL and 204 ng·h/mL).
    - Mean roflumilast N-oxide Cmax and AUClast in cohort 7 (14.8 ng/mL and 338 ng·h/mL) were 5.3- and 5.2-fold lower, respectively, compared with cohort 6 (78.4 ng/mL and 1760 ng·h/mL).

[1] Bethke, TD, GM Böhmer, R Hermann, B Hauns, R Fux, K Mörike, M David, D Knoerzer, W Wurst, and CH Gleiter, 2007, Dose-Proportional Intraindividual Single- and Repeated-Dose Pharmacokinetics of Roflumilast, an Oral, Once-Daily Phosphodiesterase 4 Inhibitor, J Clin Pharmacol, 47(1):26-36.

- Overall exposure in subjects 2 to 5 years old who received the lower strength of roflumilast cream, 0.05%, was similar or lower than exposure in subjects 6 to 11 years and 12 – 16 years old who received approved roflumilast cream,0.15%.

Recommendation: The Office of Clinical Pharmacology recommends the approval of this supplemental NDA for once daily application of roflumilast cream, 0.05%, for the topical treatment of subjects 2 – 5 years old with moderate to severe AD.

7.2. Summary of Clinical Pharmacology Assessment

7.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics of Roflumilast Under Maximal Use Conditions

In the maximal use PK trial (ARQ-151-105), the Applicant studied roflumilast cream, 0.15% in Cohort 4 (≥12 to ≤16 years), Cohort 5 (≥6 to ≤11 years),and Cohort 6 (≥2 to ≤5 years) who received a mean daily roflumilast dose of 16.2, 13.3 and 9.05 mg (equivalent to 10.8, 8.86, and 6.03 gram cream, 0.15%), respectively. Subsequently, Cohort 7 (≥2 to ≤5 years) and Cohort 8 (3 months to <2 years) were added to study the 0.05% strength where a mean daily dose of 2.89 and 1.67 mg (equivalent to 5.78 and 3.34 gram cream, 0.05%), respectively, was studied.

The mean predose concentrations of roflumilast at Week 4 in Cohort 4, 5, 6, 7, and 8 were 1.79, 4.43, 9.57, 2.35, and 1.47 ng/mL, respectively. The mean predose concentrations of roflumilast N-oxide (only major metabolite) at Week 4 in Cohorts 4, 5, 6, 7, and 8 were 12.9, 28.9, 99.71, 19.3, and 15.7 ng/mL, respectively. Following daily application of the 0.15% cream, overall systemic exposure to roflumilast and its N-oxide metabolite increased as age decreased. Due to this, the Applicant designed the lower strength (0.05%) of the cream for evaluation in subjects below the age of 6 years.

Following daily application of 0.05% of the cream in subjects 2 to 5 years of age, the systemic exposure of roflumilast and N-oxide was lower than the 0.15% strength of the cream and furthermore, the systemic levels following application of 0.05% cream were comparable or lower than those observed in older subjects aged 6 to 16 years old. Further, the overall systemic exposure of roflumilast and N-oxide in subjects 2 – 5 years old and 3 months to <2 years old who received 0.05% cream was similar (Table 4). It should be noted that with this supplement, the Applicant is not seeking approval of the 0.05% cream in subjects 3 months to < 2 years at this time. The steady state of roflumilast and N-oxide in all cohorts was reached by Day 14.

Pharmacokinetics of Roflumilast in Phase 3 Trial

The Phase 3 trial (ARQ-151-315) was a randomized, double-blind, placebo-controlled, parallel-group trial, roflumilast cream, 0.05% QD was evaluated in subjects 2 – 5 years of age with mild to moderate AD involving ≥3% BSA (excluding the scalp, palms, and soles). The mean affected BSA with AD was 22.5% (range: 3-82%) and 21.22% (range: 4-78.8%) in roflumilast and vehicle group, respectively. The PK (only predose on Day 29) was assessed in a subset of subjects

(N=61) with a mean AD-affected BSA of approximately 19%. The median (range) daily roflumilast cream applied topically to subjects 2 to 5 years of age was approximately 2 (0.08 – 16.3) gram. The trial demonstrated that the mean (SD [standard deviation]) predose concentration on Day 29 was 1.2 (1.61) and 14.2 (18.7) ng/mL for roflumilast and roflumilast N-oxide, respectively, while the corresponding median (range) value was 0.68 (0.0 – 7.87) and 7.69 (0.0 – 96.9) ng/mL . No meaningful differences in exposure were observed across sex, race, and ethnicity. The mean daily dose and systemic exposures in subjects 2 – 5 years of age receiving 0.05% cream under maximal use conditions were higher than that in the Phase 3 study, which supports the systemic safety of the proposed dosage regimen.

Drug Interaction of Roflumilast

No drug interaction studies were conducted with roflumilast cream. However, based on drug-drug interaction studies of oral roflumilast, the label mentions that coadministration of roflumilast with CYP3A4 and/or CYP1A2 inhibitor(s), or oral contraceptives containing gestodene and ethinyl estradiol may increase systemic exposure of roflumilast that may result in increased adverse effects. Therefore, the risk of increased adverse effects due to such coadministration should be weighed against the benefits.

7.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosing regimen is roflumilast cream, 0.05% to be applied once daily to the affected areas.

The proposed dosing regimen is supported by the overall PK, efficacy, and safety data derived from the maximal use PK and phase 3 clinical trials and therefore acceptable. Refer to sections 8.1.2 and 8.2 for efficacy and safety results.

Therapeutic Individualization

Not applicable.

Outstanding Issues

Not applicable

7.3. Comprehensive Clinical Pharmacology Review

7.3.1. General Pharmacology and Pharmacokinetic Characteristics

Roflumilast and its active metabolite, roflumilast N-oxide, are inhibitors of PDE4 (a major cyclic 3',5'-adenosine monophosphate [cyclic AMP] metabolizing enzyme) which leads to accumulation of intracllular cyclic AMP (cAMP). The anti-inflammatory effects are postulated to be produced

by the accumulation of cAMP within the cells by reducing the production of inflammatory mediators like cytokines and chemokines. The specific mechanism(s) by which roflumilast exerts its therapeutic action is not well defined.

To support this supplement, the PK of roflumilast has been characterized in subjects 2 years to 5 years old under maximal use conditions (Trial ARQ-151-105) and in the Phase 3 trial, ARQ-151-315. While the MUsT PK data of subjects 6 to 16 years of age was reviewed previously (see unireview dated July 05, 2024 [Reference ID: 5408595]), these data are included in this review to compare with that of 2 – 5 years old. The PK of Phase 3 data has also been summarized in support of the proposed dosage regimen.

Trial ARQ-151-105

Pharmacokinetics of roflumilast in subjects 2 to 5 years of age who received 0.15% cream QD has been compared with that of older subjects aged 6 – 16 years old. The data indicated that the exposure (Cmax and AUClast) on Day 14 increased with decreasing age. The mean AUClast of roflumilast was increased by approximately 100% and 220% in 2 – 5 years old receiving 0.15% cream compared to that in 6 - 11 years and 12 – 16 years old, respectively. On the other hand, the mean AUClast of roflumilast N-oxide was increased by approximately 140% and 420% in 2 – 5 years old receiving 0.15% cream compared to that in 6 -11 years and 12 – 16 years old, respectively. The mean Cmax was increased by ~100 - 130% for roflumilast and ~130 - 400% for N-oxide in 2-5 years old compared to the older pediatric subjects.

Increase in exposure of roflumilast and its N-oxide metabolite led to the evaluation of lower strength of roflumilast cream, 0.05% in 2-5 years old subjects (Cohort 7). Application of roflumilast cream, 0.05% QD in 2-5 years old decreased overall exposure of roflumilast and N-oxide by approximately 75% and 80% compared to that of roflumilast 0.15% cream in the same age group. This resulted in either comparable or lower plasma exposures of roflumilast and N-oxide in 2 – 5 years old compared to that of older pediatric subjects, thereby supporting the use of roflumilast cream, 0.05% QD in this age group (Table 3).

Table 3: Summary of Pharmacokinetic Parameters in Pediatric Subjects with Atopic Dermatitis at Day 14 of Treatment with Roflumilast Cream 0.05% or 0.15% QD Under Maximal Use Conditions (ARQ-151-105, Cohorts 4, 5, 6, and 7) (Pharmacokinetic Population)

Analyte Age Group	Roflumilast Concentration	N	Treated BSA (%) Mean (SD)	Target Dose (mg) Mean (SD)	C_{max} (ng/mL) Mean (SD)	AUC_{last} (ng·h/mL) Mean (SD)
Roflumilast						
Cohort 4, 12 to 16 y	0.15%	11	34.3 (15.3)	16.2 (7.26)	5.41 (9.01)	62.9 (53.0)
Cohort 5, 6 to 11 y	0.15%	12	43.8 (10.9)	13.3 (3.30)	5.31 (5.43)	102 (96.5)
Cohort 6, 2 to 5 y	0.15%	13	44.4 (9.96)	9.05 (2.03)	10.2 (9.10)	204 (202)
Cohort 7, 2 to 5 y	0.05%	6	41.3 (7.31)	2.81 (0.497)	3.21 (2.72)	47.2 (27.4)
Roflumilast N-oxide						
Cohort 4, 12 to 16 y	0.15%	12	33.7 (14.8)	16.0 (7.00)	15.5 (13.9)	336 (310)
Cohort 5, 6 to 11 y	0.15%	13	43.5 (10.5)	13.2 (3.17)	33.8 (31.2)	743 (710)
Cohort 6, 2 to 5 y	0.15%	13	44.4 (9.96)	9.05 (2.03)	78.4 (82.8)	1760 (1920)
Cohort 7, 2 to 5 y	0.05%	7	41.9 (6.82)	2.85 (0.464)	14.8 (11.9)	338 (280)

Source: m2.7.2-Seq0095 – Summary of Clinical Pharmacology Studies, Table 3.

Abbreviations: AUClast = area under the plasma concentration-time curve from time zero to last measurable concentration; BSA = body surface area; Cmax = maximum observed plasma concentration; QD = once daily; SD = standard deviation; y = years.
Notes: For the calculation of PK parameters, values below the limit of quantification (<0.1 ng/mL) were set equal to zero; Reviewer analysis excluded subjects who did not have at least 2 quantifiable plasma concentrations including one at predose to allow for estimation of AUC, leading to generating similar results as reported by the Applicant in this table. Further, the 24-hour post-dose concentration (last measurable concentration) was imputed from the predose concentration.

Predose plasma concentrations of roflumilast and N-oxide metabolite on Days 7, 14, and 28 of treatment in Cohorts 4 to 6 are summarized in Table 4. At Day 14 and 28, predose concentrations increased with decrease in age after application of 0.15% cream. The extrapolated AUC_{0-24} (based on predose multiplied by 24) showed similar trend. Note that the extrapolated AUC_{0-24} values remained within ±41% of the measured mean values (Tables 3 and 4). When 2 to 5 year old received 0.05% cream, the exposures (predose and extrapolated AUC_{0-24}) at Day 14 and 28 decreased to the levels that are generally lower or comparable to those of subjects 6 to 16 years of age, a consistent trend as found for Cmax and AUClast measures. The systemic concentrations were at steady state by Day 14.

Table 4: Analysis of Days 7, 14, and 28 Predose Plasma Concentrations of Roflumilast Following Daily Administration of Roflumilast Cream, 0.15% (MUsT Cohorts 4 – 6), or 0.05% (MUsT Cohorts 7 – 8), Trial ARQ-151-105

Analyte Cohort	Statistic	BSA Treated (%)	Dose (mg)	Day 7			Day 14			Day 28		
				Conc (ng/mL)	DN Conc (ng/mL/mg)	Ext AUC_{0-24} (ng.h/mL)	Conc (ng/mL)	DN Conc (ng/mL/mg)	Ext AUC_{0-24} (ng.h/mL)	Conc (ng/mL)	DN Conc (ng/mL/mg)	Ext AUC_{0-24} (ng.h/mL)
Roflumilast												
Cohort 4	N	12	12	12	12	10	12	12	11	12	12	11
≥12 to ≤16 y	Mean (SD)	33.7 (14.8)	16.0 (7.00)	2.37 (2.61)	0.13 (0.12)	68.3 (62.6)	1.91 (1.49)	0.12 (0.08)	50.0 (34.3)	1.79 (1.61)	0.11 (0.11)	46.8 (38.0)
Cohort 5	N	13	13	13	13	12	13	13	12	13	13	12
≥6 to ≤11 y	Mean (SD)	43.5 (10.5)	13.2 (3.17)	3.90 (3.59)	0.27 (0.19)	102 (85.0)	3.89 (3.58)	0.27 (0.19)	101 (84.9)	4.43 (3.96)	0.33 (0.30)	115 (93.4)
Cohort 6	N	13	13	13	13	13	13	13	13	13	13	13
≥2 to ≤5 y	Mean (SD)	44.4 (9.96)	9.05 (2.03)	3.94 (1.99)	0.44 (0.23)	94.7 (47.8)	7.94 (8.02)	0.78 (0.59)	190 (192)	9.57 (13.7)	0.88 (0.98)	230 (330)
Cohort 7	N	9	9	9	9	9	9	9	7	7	7	5
≥2 to ≤5 y	Mean (SD)	42.4 (6.21)	2.89 (0.422)	3.28 (3.16)	1.15 (1.12)	78.8 (75.9)	1.81 (2.34)	0.630 (0.793)	55.7 (58.4)	2.35 (3.13)	0.813 (0.998)	78.8 (78.9)
Cohort 8	N	17	17	-	-	-	17	17	14	17	17	15
≥3 m to <2 y	Mean (SD)	42.3 (7.62)	1.67 (0.301)	-	-	-	1.54 (1.99)	0.848 (1.09)	45.0 (49.2)	1.47 (1.79)	0.799 (0.960)	39.9 (43.7)
N-Oxide												
Cohort 4	N	12	12	12	12	12	12	12	12	12	12	12
≥12 to ≤16 y	Mean (SD)	33.7 (14.8)	16.0 (7.00)	15.8 (16.3)	0.89 (0.89)	379 (390)	14.0 (13.6)	0.77 (0.56)	336 (328)	12.9 (14.0)	0.76 (0.78)	308 (335)
Cohort 5	N	13	13	13	13	12	13	13	13	13	13	12
≥6 to ≤11 y	Mean (SD)	43.5 (10.5)	13.2 (3.17)	30.0 (29.2)	2.10 (1.60)	781 (696)	32.2 (28.4)	2.23 (1.54)	772 (681)	28.9 (22.4)	2.06 (1.43)	752 (517)
Cohort 6	N	13	13	13	13	13	13	13	13	13	13	13
≥2 to ≤5 y	Mean (SD)	44.4 (9.96)	9.05 (2.03)	62.6 (44.9)	6.59 (3.93)	1500 (1080)	75.4 (83.8)	7.31 (5.79)	1810 (2010)	99.7 (142)	9.19 (10.0)	2390 (3400)
Cohort 7	N	9	9	9	9	9	9	9	8	7	7	7
≥2 to ≤5 y	Mean (SD)	42.4 (6.21)	2.89 (0.422)	28.4 (29.4)	9.68 (9.51)	682 (704)	17.7 (19.4)	6.00 (6.33)	477 (467)	19.3 (21.4)	6.78 (6.86)	462 (514)
Cohort 8	N	17	17	-	-	-	17	17	16	17	17	17
≥3 m to <2 y	Mean (SD)	42.3 (7.62)	1.67 (0.301)	-	-	-	16.7 (15.7)	9.33 (8.12)	426 (374)	15.7 (14.0)	8.92 (7.46)	378 (335)

Source: m5.3.3.2-Seq0095 – Study Report of ARQ-151-105, Table 21.
AUC_{0-24} = area under the curve from time zero to 24 hours; BSA = body surface area; conc = concentration; DN = dose-normalized; Ext = extrapolated; max = maximum; min = minimum; MUSE = maximal usage systemic exposure; SD = standard deviation. Note: Ext AUC0-24 is calculated as predose concentration × 24.

Trial ARQ-151-315

In the phase 3 trial, the mean treated BSA of the PK population (N=61) was approximately 19% in the 2-5 years of age. The steady state predose concentrations of roflumilast and its N-oxide metabolite in 2 – 5 years old (Table 5) receiving roflumilast cream, 0.05% QD were generally lower compared to that of the same age group (Cohort 7, Table 4) studied under maximal usage conditions. This further supports the safety of roflumilast cream, 0.05% QD proposed for the treatment of patients 2 – 5 years of age with mild moderate AD.

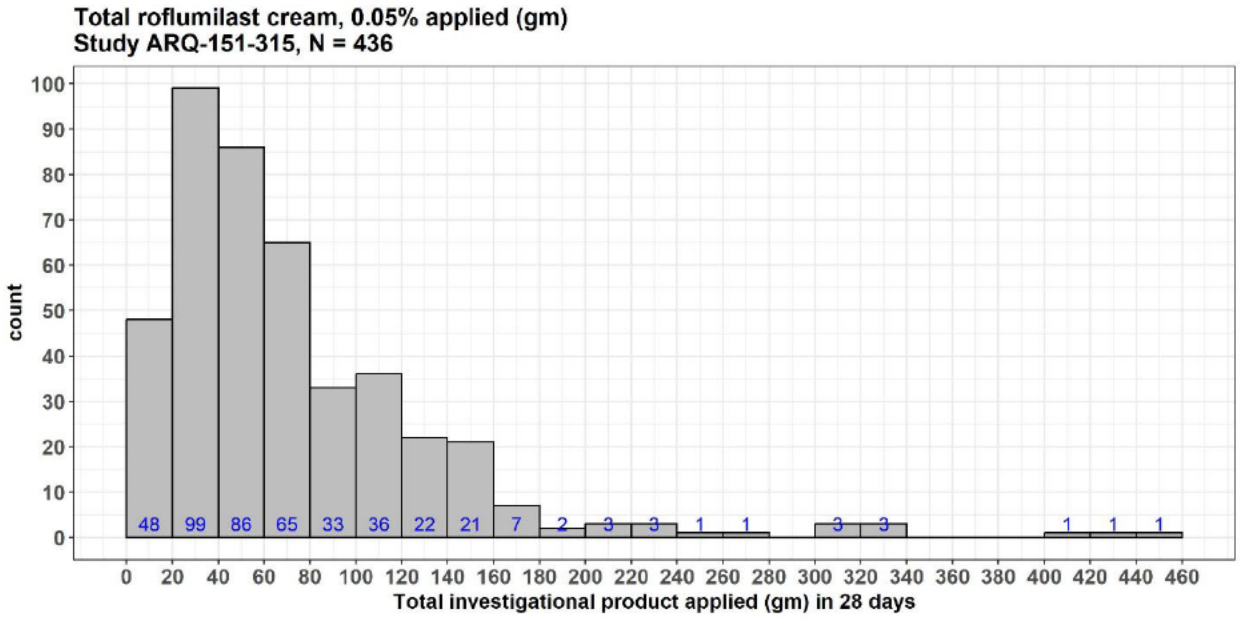
Table 5: Summary (Mean±SD) Pharmacokinetic Analysis in PK Population Following Daily Topical Administration of Roflumilast Cream 0.05%, Trial ARQ-151-315

Day	Age Group	BSA (%)	Target Dose (mg)	Roflumilast		N-Oxide	
				Conc (ng/mL)	Ext AUC0-24 (h*ng/mL)	Conc (ng/mL)	Ext AUC0-24 (h*ng/mL)
		N = 61	N = 61	N = 61	N = 52	N = 61	N = 59
29	2-5 yr	18.6 ± 17.4	1.27 ± 1.18	1.20 ± 1.61	33.9 ± 39.7	14.2 ± 18.7	353 ± 453

Values represent Mean ± SD when n>3; Ext = Extrapolated.
Source: Appendix 16.1.13.2, PK Report ADME.2022.111, Table 1.

When accounted all the patients enrolled the roflumilast cream, 0.05% QD arm of the Phase 3 trial (N = 437), the mean (SD) affected BSA by AD was 22.5 (16.4)% and median (range) was 17.3 (3.0 – 82)%. The mean (SD) total amount of roflumilast cream applied over 28 days of treatment was 73.4 (62.8) gm and the median (range) was 55.8 (2.3 – 455.2) gm. The Figure 1 below indicates that majority of patients received roflumilast cream ranged 2.3 to 120 gram.

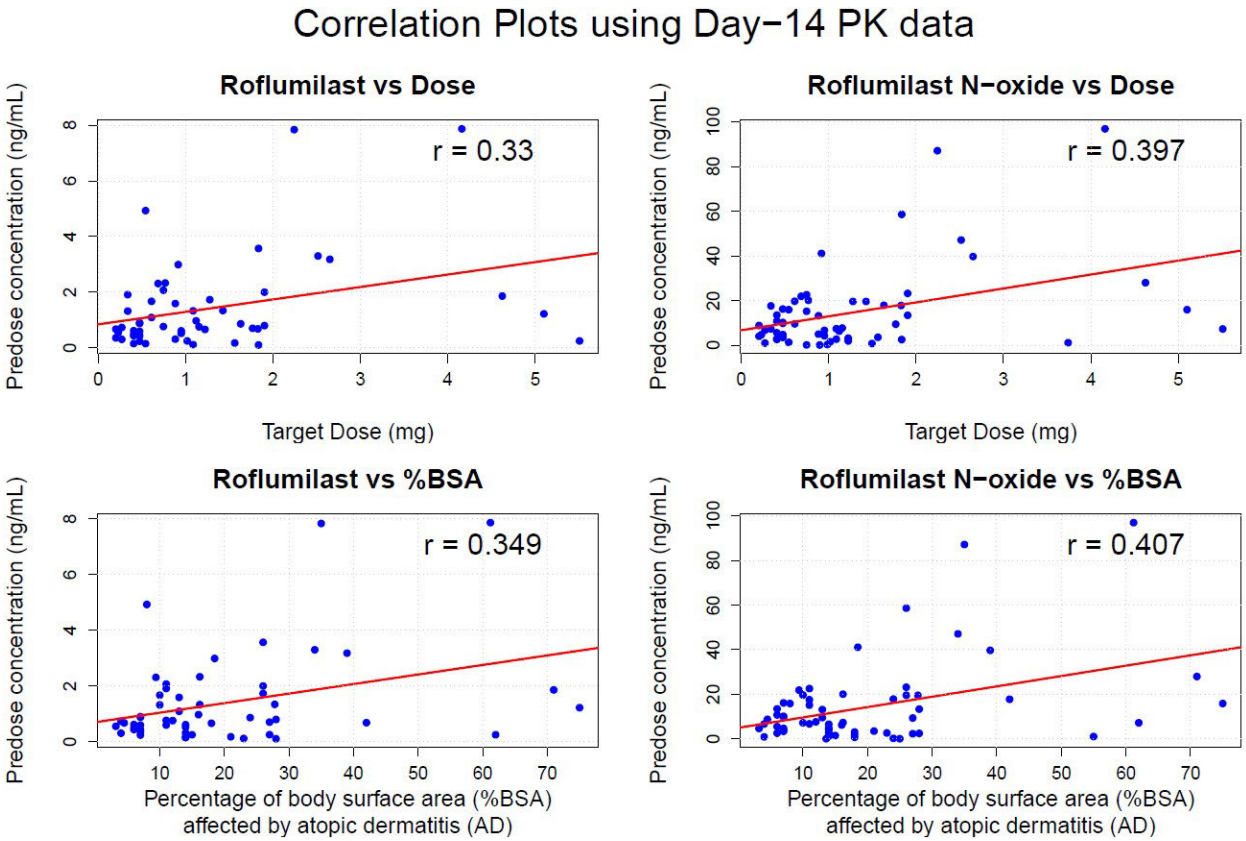
Figure 1: Distribution of Total Roflumilast Cream, 0.05% (in Gram) Applied over 28 Days in the Phase 3 Trial, ARQ-151-315



Source: Reviewer's analysis based on adsl.xpt dataset pertaining to Trial ARQ-151-315.

There is a positive weak correlation (r-value: ~0.3 - 0.4) between systemic exposure and dose or percentage of body surface area (%BSA) affected by AD, as demonstrated in Figure 2. However, the weak relationship of systemic exposure with dose or %BSA can be attributed to large PK variabilities observed in MUsT and phase 3 trials.

Figure 2: **Correlation between the Systemic Exposure and Dose or %BSA at Day-14 for Roflumilast and its metabolite, N-oxide.**



r: correlation coefficient. **Source**: Reviewer's plots based on adpc.xpt and adsl.xpt datasets pertaining to Trial ARQ-151-315.

7.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Since the product is applied to the target site (skin) and the systemic exposure is downstream, the pharmacokinetic assessment of the proposed topical product does not provide supportive evidence of effectiveness for the treatment mild to moderate AD in subjects aged 2 to 5 years old. However, the PK data derived from the maximal use PK and Phase 3 trials support for the systemic safety of roflumilast cream, 0.05%. For the evidence of efficacy, see section 8.1.2 of this multidisciplinary review.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The Applicant evaluated the once daily application of roflumilast cream 0.05% for 4 weeks in subjects 2 to 5 years of age with mild to moderate AD in the MUsT and Phase 3 trial.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No specific studies were conducted with topical roflumilast cream, 0.15% or 0.05% in subjects with hepatic or renal impairment. However, use of roflumilast cream, 0.15% and 0.05%, is contraindicated in moderate to severe liver impairment (Child-Pugh B or C), based on the increased exposure of roflumilast and N-oxide in subjects with Child-Pugh A and B following oral administration (NDA 022522). The oral administration of roflumilast 250 mg QD for 14 days increased roflumilast AUC by 51% and 92% in Child-Pugh A and B, respectively, while N-oxide AUC was increased by 24% and 41%, respectively.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interactions are not applicable for topical products. No new information on drug-drug interactions is available. There will be no changes to the DDI language which is currently in the approved labeling.

8 Sources of Clinical Data and Review Strategy

8.1. Table of Clinical Studies

For the clinical development program in the 2 to 5 years of age cohort at the 0.05% strength, one randomized, double-blind, placebo-controlled trial was conducted (Trial 315).

For additional long-term safety information, an open label extension (OLE), single arm study was conducted (Study 313). The Applicant collected data from multiple studies: subjects who had completed the trials 311 and 312 who were ≥ 6 years of age; subjects who completed trial 315 and were 2 to 5 years of age. Subjects who reported a 6th year birthday during the OLE study were transitioned from the 0.05% strength to the 0.15% strength roflumilast cream. Additionally, if a subject achieved a vIGA-AD score of 0 (clear) the regimen was changed to twice a week on noncontiguous days.

ARQ-151-105 (Study 105) was a Maximal Use Trial (MUsT) conducted in the pediatric population ≥ 3 months. Refer to Table 2 for details.

Table 6: Listing of Clinical Trials Relevant to NDA 215985, S-012

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
ARQ-151-315	NCT 04845620	Randomized, double-blind, parallel group, vehicle-controlled, multicenter	Roflumilast cream 0.05% or Vehicle cream Applied daily/ Topically	vIGA-AD score of Clear or Almost Clear plus a ≥2-grade improvement from baseline at Week 4.	4 weeks	N = 652 IP 0.05%: n=437; Vehicle n=215	Subjects 2 to ≤ 5 years of age at Baseline with ≥3% AD BSA (except scalp, palms, soles); vIGA-AD score of Mild or Moderate; EASI score ≥5	Sites: 109 Countries: 3 United States, Canada, Poland
		Studies to Support Safety						
ARQ-151-313	NCT 04804605	Long-term, single arm, multicenter, open label (OLE)	Roflumilast cream 0.15% (ARQ-151-311 or ARQ-151-312 rollovers aged ≥6 years; ARQ-151-315 rollovers who turned 6 years of age on study) or roflumilast cream 0.05% (ARQ-151-315 rollovers aged 2 to 5 years) was applied once daily (QD) for up to 52 weeks. If vIGA-AD score= 0, then use cream 2x week.	Primary: AEs and SAEs occurrences; Secondary: vIGA-AD score of 0 or 1 at each assessment (24 or 52 weeks). At week 4 if vIGA score=0, then 2xweek maintenance	2 cohorts: 24 or 52 weeks	N=562	Rollovers from studies 311, 312, and 315. IP cream 0.05% ages 2 to ≤5 yr w/ mild to moderate AD 0.15% cream if ≥ 6 yrs.	Sites: 153 Countries: 3 United States, Canada, Poland

Source: Clinical Reviewer's table.

8.2. Review Strategy

The primary source of data to support the safety of ZORYVE (roflumilast) cream, 0.05% for treatment of pediatric patients 2 to 5 years with mild to moderate atopic dermatitis was Trial ARQ-151-315. The Applicant conducted a single randomized, double-blind, vehicle-controlled, phase 3 trial (Trial 315) that enrolled subjects 2 to 5 years of age and older with mild to moderate atopic dermatitis. Subjects were randomized 2:1, exposing subjects to roflumilast cream or vehicle cream, respectively.
Enrolled subjects met the following criteria at Baseline:

- Confirmed clinical diagnosis of AD according to the criteria of Hanifin and Rajka;
- AD treatment naïve, prior non-responder to emollient use, or previously received topical corticosteroids (TCSs) or topical calcineurin inhibitor (TCIs);
- AD involvement of ≥3% treatable %BSA (excluding the scalp, palms, soles);
- vIGA-AD score of Mild (2) or Moderate (3).

Study ARQ-151-313 (Study 313) was an open-label extension (OLE) study to assess the long-term safety of roflumilast cream 0.05% and 0.15%. The OLE Study 313 enrolled subjects who completed multiple studies which used different strengths of IP cream and patient populations; trials ARQ-151-311 and ARQ-151-312 evaluated 0.15% cream in mild to moderate AD for ages ≥ 6 years of age. If during the OLE study a subject turned 6 years of age, the roflumilast cream strength was changed from 0.05% to 0.015% cream. The OLE study treatment course was 24 weeks or 52 weeks. Additionally, if a subject was assessed through vIGA-AD as '0-clear' (confirmed by the Investigator at a scheduled or unscheduled clinic visit), the subject's regimen was switched to roflumilast cream use twice a week "maintenance" treatment. This uncontrolled, OLE study was difficult to interpret due to the change of strength with age, and differing regimens according to vIGA-AD score and age, for use in a recurring, chronic condition.

In this review, Trial 315 data are evaluated for efficacy of roflumilast cream 0.05%. The clinical data collected through conducting Trial 315 and Study 313 contribute to the overall safety profile of roflumilast cream 0.05%. The design of the open-label study (i.e., no comparator arm, different strengths and application frequencies) introduced confounders and precludes making meaningful conclusions including the duration of, and maintenance of treatment effect, at a twice weekly application frequency as a"maintenance" regimen for this product.

9 Statistical and Clinical and Evaluation

9.1. Review of Relevant Individual Trials Used to Support Efficacy

9.1.1. ARQ-151-315 (Trial 315)

Trial Design

Trial ARQ-151-315 (referred to as Trial 315) was a randomized, double-blind, vehicle-controlled, parallel arm, multicenter trial intended to evaluate the efficacy and safety of roflumilast cream 0.05% (ZORVYE®) for the topical treatment of atopic dermatitis in pediatric patients 2 to 5 years of age. It was conducted in the United States (71 sites), Canada (6 Sites) and Poland (18 Sites) and enrolled a total of 651 subjects ages 2 to 5.

Eligibility and assessment of efficacy used the validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD), the Eczema Area Severity Index (EASI), and the Worst Itch-Numeric Rating Scale (WI-NRS). The vIGA-AD is an ordinal scale with 0=clear and 4=severe. The EASI is a weighted sum based on the severity and area of involvement of four signs assessed on each of four body areas, and ranges from 0 to 72 with higher score indication worse disease severity. The WI-NRS is a daily itch severity score from 0 (no itch) to 10 (worst itch imaginable) over the past 24-hour recall period. It was recorded in a daily diary by parents/caregivers. A weekly average was calculated for the 7-day period prior to each study visit as long as at least 4 days had observed data, otherwise the average was set to missing.

Eligible subjects had mild (vIGA-AD=2) or moderate (vIGA-AD=3) AD at screening and baseline, and an EASI score of at least 5. The percentage of body surface areas (BSA) with AD involvement was ≥ 3% (excluding the scalp, palms and soles). Subjects had to have least a 6-week history of AD and no significant flares for 4 weeks before screening.

Subjects with AD on the scalp were included in the study but were not permitted to treat the lesions on their scalp. Lesions on palms and soles were allowed to be treated, but those lesions were excluded from all BSA calculations and efficacy evaluations during the study. Subjects with prohibited concurrent conditions (e.g., immunocompromised, systemic or superficial infections, and dermatologic or inflammatory conditions other than AD) and those being treated with prohibited medications or procedures were excluded from participation in the trial.

After screening, subjects were randomized in a 2:1 ratio to either roflumilast cream 0.05% or Vehicle cream to be applied once daily (QD) topically to affected areas for 4 weeks. Randomization was stratified by vIGA-AD score and study site. At the baseline visit, study staff demonstrated how to apply investigational product (IP) in the appropriate dose to areas to be treated. Parents/caregivers were instructed to apply IP once daily to all treatment areas identified by the Investigator at Baseline and any new lesions at subsequent visits using a Body

Diagram. Subjects were instructed to continue all treatment of areas with study drug for the duration of the study regardless of whether treatable areas of AD clear prior to Week 4 visit. New lesions that develop during the study would also be treated (except scalp). An unscheduled visit was not required for starting treatment of new lesions.

Efficacy was assessed by the investigator at Week 1, 2, and 4. The primary timepoint for efficacy comparisons was Week 4.

All randomized subjects were included in the Intent to Treat (ITT) population for the efficacy analyses, with one exception. Subject # (b) (6) was treated with investigational product before randomization (to roflumilast arm) was completed and was excluded from the ITT population. All subjects received the correct treatment as randomized.

Study Endpoints

The primary efficacy endpoint is the proportion of subjects who achieve a vIGA-AD score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 4

The Applicant defined seven secondary endpoints to be tested in the following prespecified hierarchical order:

1. vIGA-AD Success at Week 4 in subset of subjects with a vIGA-AD score of 'Moderate' at randomization,
2. Achievement of at least 75% reduction in the Eczema Area and Severity Index (EASI-75) at Week 4
3. vIGA-AD score of 'clear' or 'almost clear' at Week 4
4. vIGA-AD Success at Week 2
5. vIGA-AD of 'clear' or 'almost clear' at Week 2
6. vIGA-AD success at Week 1
7. vIGA-AD of 'clear' or 'almost clear' at Week 1

The first included only a subset of the randomized subjects, which made up 77% of the ITT population. The assessment of EASI-75 is not clinically relevant in this patient population (baseline EASI <16). Endpoint #3, vIGA-AD score of 'clear' or 'almost clear' at Week 4, is a less stringent criteria for success than the primary endpoint. Similarly, endpoints #5 and #7 are less stringent definitions of success than endpoints #4 and #6, respectively.

The clinical reviewer did not consider the "clear or almost clear (without 2-point improvement criteria)" endpoints (#2, 4, and 6 above) as clinically relevant as they are redundant to the defined Success endpoints, but the analyses were conducted in the order as planned.

Statistical Analysis Plan

The primary and all secondary endpoints of interest were responder (binary) endpoints. For each endpoint the planned analysis used a Cochran–Mantel–Haenszel (CMH) test stratified by vIGA-AD score at Baseline (2 or 3). Randomization was also stratified by study site, but this was not included in the model because of the large number of sites.

Subjects who prematurely discontinued treatment due to an adverse event (AE) or lack of efficacy (LOE) prior to Week 4 were considered treatment non-responders (composite strategy). For events other than discontinuation due to AE or LOE, the occurrence of the intercurrent event was considered irrelevant in defining the treatment effect of interest, i.e., the value for the variable of interest is used regardless of whether the intercurrent event occurs (the treatment policy strategy). A sensitivity analysis, with all discontinuations treated as non-responders regardless of reason, yielded similar results, as did a tipping point analysis.

Missing data was handled using multiple imputation (MI), with a planned 3-stage process. The amount of non-monotone missing data across all subjects and visits was calculated. This determined the number of imputed datasets for the first stage which used the Markov-Chain Monte-Carlo (MCMC) method to impute missing data at the intermediate visits between baseline and Week 4. Due to a low rate of non-monotone missing (≤ 2%) the MCMC imputation was done once for each endpoint to produce datasets with complete data for all visits.
At the next stage, a Predictive Mean Matching (PMM) regression model was applied to the monotone dataset to generate 25 multiple-imputed datasets for the primary analysis of each endpoint. The CMH test results were combined using MI methods based on Rubin's rule.

Protocol Amendments

The protocol was amended twice (July 16, 2021; April 10, 2023). Both included notable changes to the statistical section, following Agency advice. In the first amendment, the endpoints identified as key secondary endpoints, and the order of hierarchical testing were revised. In the second, the method for handling intercurrent events of discontinuation due to adverse events or lack of efficacy to identify these subjects as non-responders was updated. These changes were made prior to completion of the study (last subject completed June 1, 2023) or unblinding of data.

9.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the trials were conducted using Good Clinical Practice according to the ethical principles founded in the Declaration of Helsinki, and guidelines and principles according to the International Council on Harmonisation Tripartite Guideline.

Financial Disclosure

The Applicant certifies that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (a list of names for the phase 3 study was included) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)). No Form 3455 was submitted.

Patient Disposition

Trial 315 enrolled and randomized a total of 651 subjects at a ratio of 2:1 to the two treatment arms. There were 71 sites in the United States, 6 sites in Canada, and 18 sites in Poland. All randomized subjects received study treatment on Day 1 and were included in the Intent to Treat (ITT) population for efficacy analyses. All subjects received the as-randomized treatment. One subject (# (b) (6)) received investigational product prior to receiving randomization assignment and is excluded from the ITT population.

As shown in Table 7, there was a higher percentage of subjects who discontinued in the vehicle arm (11%) than in the roflumilast cream arm (6%) prior to completing Week 4. The largest difference was discontinuations due to Withdrawal of Consent by Parent or Guardian.

Table 7: Subject Disposition – Trial 315

	Roflumilast Cream 0.05% (N=436)	Vehicle (N=215)	Total (N=651)
All Randomized (ITT)			
Completed 4-week DB treatment	409 (93.8)	192 (89.3)	601 (92.3)
Discontinued	27 (6.2)	23 (10.7)	50 (7.7)
Reason for Discontinuation			
ADVERSE EVENT	5 (1.1)	4 (1.9)	9 (1.4)
LACK OF EFFICACY	4 (0.9)	4 (1.9)	8 (1.2)
LOST TO FOLLOW-UP	5 (1.1)	4 (1.9)	9 (1.4)
NON-COMPLIANCE	2 (0.5)	1 (0.5)	3 (0.5)
PARENT/GUARDIAN WITHDRAWAL OF CONSENT	11 (2.5)	10 (4.7)	21 (3.2)

Source: Statistical Reviewer's Analysis; adsl.xpt
[1] ITT population: all randomized subjects
Abbreviations: DB, Double-blind treatment period through Week 4

Protocol Violations/Deviations

According to the listings, there were GCP protocol deviations considered important for the IP (n=6, %) and vehicle (n=1, %) groups. The majority of deviations for the rofluilast group were not considered major.

- Circles rather than lines placed on form
- Site did not use approved subject tolerability form
- Site recorded investigator Local Tolerability Assessment (LTA) with older version of form
- The site used photocopies of VAS forms instead of ordering color copies provided by the CRO.
- Day 29 VAS was photocopied version instead of the CRO provided original copy (site ran out of the original copies) (x3)
- **Staff not properly trained to conduct delegated tasks** (5/7)
- WINRS dates were prior to ICF signature date. (Subject's parent incorrectly dated subject diary form.)
- IP applied on site but was not recorded in subject diary
- Subject did not record time of itch severity in diary
- Study Coordinator downloaded, used the incorrect version of the VAS worksheets for all subjects; correct VAS worksheets were used for all remaining study visits (x2).
- Approved Subject LTA not used (x4)
- Missing source data: WI-NRS timepoint not recorded
- (SN) did not sign Information Notice once he was included in the site staff and no IATA certificate available (left team)(x10)

Vehicle:

- **Staff not properly trained to conduct delegated tasks** (1/2)
- Subject completed VAS using and an x instead of a line per the study reference manual.
- Site did not use approved subject tolerability form.
- Site recorded Investigator LTA with older version form.
- WI-NRS score 7 and 8 both circled on two dates
- Study Coordinator downloaded, used the incorrect version of the VAS worksheets for all subjects; correct VAS worksheets were used for all remaining study visits (2)
- WI-NRS done but timepoint not recorded (3)
- Staff not properly trained to conduct delegated tasks
- (SN) did not sign Information Notice once he was included in the site staff and no IATA certificate available (left team)(5)

Approximately 17% of the subjects in each treatment arm had protocol violations, with major deviation (use of prohibited concomitant medication; incorrect dosing of investigational product by caregiver; misclassification for randomization strata) as the most common reason overall (11%). As shown in Table 8, the incidence of protocol violation was similar across the two arms except for “No vIGA-AD assessment within Week 4 window”, which was higher in the

vehicle arm. The Applicant provided efficacy results using the Per Protocol population (PP) which excluded these 110 subjects. The results and conclusions were similar to the primary efficacy analyses for all the efficacy endpoints. There was no impact on the results or conclusions due to these protocol violations.

Table 8: Protocol Violations – Trial 315

Randomized (ITT)[1]	Roflumilast Cream 0.05% (N=436)	Vehicle (N=215)	Total (N=651)
Subjects excluded for 1 or more protocol violations	**73 (16.7)**	**37 (17.2)**	**110 (16.9)**
Reasons for Protocol Violation [2]			
<80% compliant	5 (1.1)	4 (1.9)	9 (1.4)
Major deviation	49 (11.2)	21 (9.8)	70 (10.8)
No vIGA-AD assessment within Week 4 window	24 (5.5)	22 (10.2)	46 (7.1)
Per Protocol (PP) population	**363 (83.3)**	**178 (82.8)**	**541 (83.1)**

Source: Statistical Reviewer's Analysis; adsl.xpt
[1] ITT population: all randomized subjects
[2] All protocol violations were categorized as one of three reasons. Subjects may be included in more than one category.

Table of Demographic Characteristics

As shown in Table 9, 52% of subjects were male, and most subjects (60%) were between 2 and 3 years old. Seventeen percent were Hispanic or Latino. The majority of subjects were White (69%) or Black or African American (15%). Seventy-seven percent of subjects had a baseline vIGA-AD score of Moderate, and the mean baseline percentage of body surface area was 22%. The two treatment arms were fairly well balanced across the demographic and baseline disease characteristics.
Five subjects were misclassified for the vIGA-AD strata for randomization. All were randomized as Moderate but actual baseline was Mild. Both the baseline and Randomization vIGA-AD classes are shown in Table 9. Efficacy analyses used the Randomization classification.

Table 9: Demographic and Baseline Characteristics - Trial 315 (ITT population)

Subgroup	Roflumilast Cream (N=436)	Vehicle Cream (N=215)	Total (N=651)
Sex, n (%)			
Female	211 (48.4)	99 (46.0)	310 (47.6)
Male	225 (51.6)	116 (54.0)	341 (52.4)
Age (yrs)			
Mean (SD)	3.3 (1.09)	3.2 (1.10)	3.3 (1.09)
Median	3	3	3
Min, Max	2, 5	2, 5	2, 5
Age Group n (%)			
2 years	130 (29.8)	81 (37.7)	211 (32.4)
3 years	127 (29.1)	54 (25.1)	181 (27.8)
4 years	97 (22.3)	46 (21.4)	143 (22.0)
5 years	82 (18.8)	34 (15.8)	116 (17.8)
Race, n (%)			
Amer. Indian or Alaskan Native	1 (0.2)	2 (0.9)	3 (0.5)
Asian	37 (8.5)	17 (7.9)	54 (8.3)
Black or African American	68 (15.6)	32 (14.9)	100 (15.4)
Native Hawaiian or Pac. Islander	0	0	0
White	294 (67.4)	156 (72.6)	450 (69.1)
Multiple Races Checked	28 (6.4)	4 (1.9)	32 (4.9)
Other	8 (1.8)	4 (1.9)	12 (1.8)
Ethnicity n (%)			
Hispanic or Latino	82 (18.8)	31 (14.4)	113 (17.4)
Not Hispanic or Latino	351 (80.5)	184 (85.6)	535 (82.2)
Not Reported	3 (0.7)	0	3 (0.5)
Fitzpatrick Skin Type n (%)			
Type I	33 (7.6)	14 (6.5)	47 (7.2)
Type II	144 (33.0)	87 (40.5)	231 (35.5)
Type III	102 (23.4)	47 (21.9)	149 (22.9)
Type IV	77 (17.7)	33 (15.3)	110 (16.9)
Type V	53 (12.2)	22 (10.2)	75 (11.5)
Type VI	27 (6.2)	11 (5.1)	38 (5.8)
Baseline vIGA-AD n (%)			
Mild (2)	103 (23.6)	44 (20.5)	147 (22.6)
Moderate (3)	333 (76.4)	171 (79.5)	504 (77.4)
Randomized vIGA-AD strata n (%)			
vIGA-AD Mild (2)	99 (22.7)	43 (20.0)	142 (21.8)
vIGA-AD Moderate (3)	337 (77.3)	172 (80.0)	509 (78.2)

Subgroup	Roflumilast Cream (N=436)	Vehicle Cream (N=215)	Total (N=651)
% Baseline BSA			
Mean (SD)	22.5 (16.40)	21.2 (15.65)	22.1 (16.15)
Median	17.2	16.5	17.0
Min, Max	(3, 82)	(4, 78.8)	(3, 82)
Baseline EASI (range 0-72)			
Mean (SD)	12.2 (6.94)	11.6 (6.23)	12.0 (6.71)
Median	10.2	9.5	9.9
Min, Max	(4.6, 42.0)	(5.0, 32.9)	(4.6, 42.0)
Baseline WI-NRS (range 0-10)			
Mean (SD)	6.1 (2.31)	5.9 (2.20)	6.1 (2.27)
Median	6.6	6.3	6.4
Min, Max	(0, 10)	(0, 10)	(0, 10)

Source: Source: Statistical Reviewer's Analysis; adsl.xpt
Abbreviations: EASI, Eczema Area Severity Index; min, minimum; max, maximum; N, number of subjects in each treatment arm; n, number of subjects in each subgroup; SD, standard deviation;; vIGA-AD, validated Investigator Global Assessment scale for Atopic Dermatitis; WI-NRS, Worst Itch–Numeric Rating Scale; yrs, years

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Regarding compliance, less than 1% of subjects in each arm was considered noncompliant. Additionally, a smaller percentage of subjects in the roflumilast arm compared to the vehicle control arm were considered < 80% compliant at 1.1% and 1.9%, respectively.

Efficacy Results – Primary Endpoint

The primary endpoint is the proportion of subjects who achieved a vIGA-AD score of Clear (0) or Almost Clear (1) and at least a 2-grade reduction from baseline at Week 4. Roflumilast cream was tested for superiority to vehicle cream using a Cochran Mantel Haenszel (CMH) test stratified by Randomization vIGA-AD score (mild (2), moderate (3)).

Subjects who discontinued due to adverse event or lack of efficacy were considered treatment failures (composite estimand strategy). Rescue medications for AD were not allowed during the

double-blind period through Week 4. This included topical antibiotics, topical antihistamines, or any other topical agents being applied to the treated areas.

The vIGA-AD was assessed at each study visit. If the assessment after baseline was missing, the subject was considered a non-responder for the vIGA-AD success endpoints.

As shown in Table 10, roflumilast cream demonstrated superiority to vehicle cream ($p<0.0001$) with 25% of subjects in the roflumilast cream arm achieving a vIGA-AD score of Clear (0) or Almost Clear (1) and at least a 2-grade reduction from baseline at Week 4 versus 11% of subjects in the vehicle cream arm.

Table 10: Results for Primary Efficacy Endpoint - Trial 315 (ITT)

Primary Endpoint [1]	Roflumilast Cream (N=436)	Vehicle Cream (N=215)
Proportion of subjects who achieved a vIGA-AD score of Clear (0) or Almost Clear (1) and at least a 2-grade reduction from baseline at Week 4		
Mean % Success [2]	25.4%	10.7%
95% CI	(21.5%, 29.7%)	(7.2%, 15.6%)
Difference in means % success	14.9%	
95% CI on Difference	(9.0%, 20.8%)	
p-value	<0.0001	

Abbreviations: CI, Confidence Interval; ITT, intent-to-treat; MI, multiple imputation; N, number of subjects in each treatment arm; n, number of subjects classified as responder; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis
Source: Source: CSR Table 14.2.1.2
[1] Statistics based on 25 imputed datasets.
[3] Cochran Mantel Haenszel model stratified by randomized baseline vIGA-AD score.

Efficacy Results – Key Secondary Endpoints

The Applicant defined seven secondary endpoints to be tested in the following prespecified hierarchical order:

- Proportion of subjects with vIGA-AD Success at Week 4 for subjects with baseline score of moderate
- Achieve EASI-75 at Week 4
- Proportion of subjects with vIGA-AD clear (0) or almost clear (1) at Week 4
- Proportion of subjects with vIGA-AD Success at Week 2
- Proportion of subjects with vIGA-AD clear (0) or almost clear (1) at Week 2
- Proportion of subjects with vIGA-AD Success at Week 1
- Proportion of subjects with vIGA-AD clear (0) or almost clear (1) at Week 1

All are dichotomized responder endpoints were analyzed using the same approach and model as the primary endpoint. The same multiple imputation approach for missing data and handling of intercurrent events were applied as well.

As shown in Table 11, Roflumilast cream demonstrated superiority to vehicle cream (all p<0.0001) on all seven key secondary endpoints. These results are consistent with and provide supportive evidence for the primary efficacy outcome. While all seven are presented, and were tested in this hierarchical order, only the Proportion of subjects with vIGA-AD Success at Week 2 and Week 1 are considered appropriate for inclusion in the label for this patient population.

Table 11: Results for Secondary Efficacy Endpoints - Trial 315

Secondary Endpoints	Roflumilast Cream (N=436)	Vehicle Cream (N=215)
Proportion of subjects with vIGA-AD Success at Week 4 for subjects with baseline score of moderate		
N (subset of ITT)	333	171
Mean % Success [2]	27.7%	11.0%
95% CI	(23.2%, 32.9%)	(7.1%, 16.8%)
Difference in means % success	16.7%	
95% CI on Difference	(9.9%, 23.5%)	
p-value	<0.0001	
Proportion of subjects who achieved EASI-75 at Week 4 (75% reduction from baseline)		
Mean % Success [2]	39.4%	20.6%
95% CI	(34.8%, 44.1%)	(15.7%, 26.6%)
Difference in means % success	18.3%	
95% CI on Difference	(11.1%, 25.5%)	
p-value	<0.0001	
Proportion of subjects with vIGA-AD clear (0) or almost clear (1) at Week 4		
Mean % Success [2]	35.4%	14.6%
95% CI	(31.0%, 40.0%)	(10.4%, 20.0%)
Difference in means % success	19.7%	
95% CI on Difference	(13.5%, 26.3%)	
p-value	<0.0001	
Proportion of subjects who achieved a vIGA-AD score of Clear (0) or Almost Clear (1) and at least a 2-grade reduction from baseline at Week 2		
Mean % Success [2]	21.2%	6.8%
95% CI	(17.6%, 25.4%)	(4.1%, 11.1%)
Difference in means % success	14.6%	
95% CI on Difference	(9.4%, 19.7%)	

Secondary Endpoints	Roflumilast Cream (N=436)	Vehicle Cream (N=215)
p-value	<0.0001	
Proportion of subjects with vIGA-AD clear (0) or almost clear (1) at Week 2		
Mean % Success [2]	30.4%	10.6%
95% CI	(26.2%, 34.9%)	(7.1%, 15.6%)
Difference in means % success	18.9%	
95% CI on Difference	(13.0%, 24.8%)	
p-value	<0.0001	
Proportion of subjects who achieved a vIGA-AD score of Clear (0) or Almost Clear (1) and at least a 2-grade reduction from baseline at Week 1		
Mean % Success [2]	9.4%	0.9%
95% CI	(6.7%, 13.0%)	(0.3%, 3.3%)
Difference in means % success	8.6%	
95% CI on Difference	(5.6%, 11.6%)	
p-value	<0.0001	
Proportion of subjects with vIGA-AD clear (0) or almost clear (1) at Week 1		
Mean % Success [2]	17.0%	3.7%
95% CI	(13.7%, 20.8%)	(1.9%, 7.2%)
Difference in means % success	12.5%	
95% CI on Difference	(8.4%, 16.7%)	
p-value	<0.0001	

Abbreviations: CI, Confidence Interval; ITT, intent-to-treat; MI, multiple imputation; N, number of subjects in each treatment arm; n, number of subjects classified as responder; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis
Source: Source: CSR Tables 14.2.2.1, 14.2.3.1, 14.2.1.1
[1] Statistics based on 25 imputed datasets.
[3] Cochran Mantel Haenszel model stratified by randomized baseline vIGA-AD score.

Data Quality and Integrity

There were no data quality or integrity issues for the statistical analysis of efficacy. Explanations and clarifications, sent as information requests, were provided by the Applicant.

There was an inconsistency in the description of the stratification factors in the CMH model for

the primary analyses. Randomization was stratified by baseline vIGA score and site. The footnotes of the CSR tables in Section 14 included baseline vIGA score and pooled site as factors in the model. The statistical analysis plan clarified that due to the large number of sites, analyses would not be stratified by site. Using the SAS programs submitted with the application the statistical reviewer was able to verify site was not a factor in the primary efficacy analyses.

Additional Analyses Conducted on the Individual Trial

The statistical analysis plan included two sensitivity analyses to assess the impact of missing data. In the non-responder imputation (NRI) analysis all missing vIGA values, regardless of reason, were classified as non-responders. The planned tipping point analysis used shift parameters ranging from 0 to 2 by increments of 0.3 for the roflumilast arm and -2 to 0 by units of 0.2 for the vehicle arm (i.e. shifting each closer to the null hypothesis).

The results and conclusions for on the NRI analysis for the primary and key secondary endpoints were consistent with the primary results in favor of Roflumilast cream. In addition, for the primary endpoint, the tipping point analysis indicated that none of the scenarios under the range of shift parameters would result in rejecting the null hypothesis.

Descriptive statistics for the efficacy results across demographic and baseline strata subgroups are shown in Table 12. The proportion of responders in the Roflumilast cream arm was better than the proportion of responders in the vehicle cream arm across all subgroups except the Black or African American subgroup. These results are not intended to support conclusions or between-group comparisons.

Table 12: Results for Primary Efficacy Endpoint by Subgroups – Trial 315 (ITT)

	Roflumilast Cream (N=436)		Vehicle Cream (N=215)	
Subgroups	**n**	**Incidence % [1]**	**n**	**Incidence % [1]**
Age (years)				
2	23	18%	9	11%
3	39	31%	4	7%
4	26	27%	7	15%
5	19	23%	2	6%
Sex				
Female	51	24%	12	12%
Male	56	25%	10	9%
Race				
White	82	28%	16	10%
Asian	11	30%	1	6%
Black or African American	7	10%	4	13%
People of Color [2]	7	19%	1	10%
Ethnicity				
Hispanic or Latino	27	33%	4	13%
Not Hispanic or Latino	80	23%	18	10%
Country				
United States	69	23%	14	10%
Canada	7	20%	2	11%
Poland	31	31%	6	12%
Baseline vIGA-AD				
Mild (2)	16	16%	4	9%
Moderate (3)	91	27%	18	10%
Baseline %BSA				
< 10%	22	25%	7	16%
≥ 10%	85	24%	15	9%

Source: Statistical Reviewer adsl.xpt, adeff.xpt
[1] Statistics based observed data.
[2] American Indian or Alaskan Native, or Multiple Races
Abbreviations: ITT, Intent to Treat (all randomized subjects); N, number of subjects in each treatment arm; n, number of subjects in each subgroup

9.1.3. Integrated Assessment of Effectiveness

Trial 315 was the only efficacy study in support of this supplement. No integrated assessment of effectiveness was needed.

9.2. Review of Safety

9.2.1. Safety Review Approach

The primary source of data to support the safety of ZORYVE (roflumilast) cream, 0.05% for treatment of pediatric patients 2 to 5 years with mild to moderate atopic dermatitis was Trial ARQ-151-315 (Trial 315). The Applicant conducted a single randomized, double-blind, vehicle-controlled, phase 3 trial (Trial 315) that enrolled subjects 2 to 5 years of age and older with mild to moderate atopic dermatitis. Subjects were randomized 2:1, exposing subjects to roflumilast cream or vehicle cream, respectively.
Enrolled subjects met the following criteria at Baseline:

- Confirmed clinical diagnosis of AD according to the criteria of Hanifin and Rajka;
- AD treatment naïve, prior non-responder to emollient use, or previously received topical corticosteroids (TCSs) or topical calcineurin inhibitor (TCIs);
- AD involvement of ≥3% treatable %BSA (excluding the scalp, palms, soles);
- vIGA-AD score of Mild (2) or Moderate (3).

On February 2, 2025, the Agency sent an information request (IR) to the Applicant for additional Trial 315 datasets and tabular analyses to include enrollment and adverse events by age in years. The Applicant responded to the request on March 31, 2025.

Study ARQ-151-313 (Study 313) was an open-label extension (OLE) study to evaluate long-term use of roflumilast cream (0.05%). The OLE Study 313 enrolled subjects which rolled over from multiple studies which used different strengths of IP cream and patient populations; trials ARQ-151-311 and ARQ-151-312 evaluated 0.15% cream in mild to moderate AD for ages ≥ 6 years of age were enrolled in the OLE. If during the OLE study a subject turned 6 years of age, the roflumilast cream strength was changed to 0.015% cream. The OLE study treatment course was 24 weeks or 52 weeks. Additionally, if a subject was assessed through vIGA-AD of '0-clear' as confirmed by the Investigator at a scheduled or unscheduled clinic visit, the subject was switched to twice a week "maintenance" treatment. This study was difficult to interpret due to the change of strength with age, and differing regimens due to vIGA-AD score for a recurring, chronic condition.

The clinical data collected through conducting Trial 315 and Study 313 contribute to the safety profile of roflumilast cream 0.05%. The design of the open-label Study 313 (i.e., no comparator arm, different strengths and application frequencies) introduced multiple variables such that no clinically meaningful conclusions could be made regarding the efficacy trends of twice a week application as maintenance therapy. The AE profile reported in trial 313 were consistent with that reported for trial 315, and did not identify any new safety concerns.

To determine the safety profile of roflumilast cream, 0.05% for the treatment of mild to moderate AD in subjects between 2 to less than 6 years of age, the review team analyzed the data for exposure, demographics, baseline characteristics, TEAEs including severe TEAEs, SAEs, adverse events leading to discontinuation, local tolerability assessments by investigator (Berger

and Bowman Scoring Scale) and directed physical examinations, clinical laboratory measurements (chemistry, hematology), vital signs (blood pressure, heart rate, temperature, including weight and baseline height).

No adverse events of special interest were prespecified in the protocol.

9.2.2. Review of the Safety Database

Overall Exposure

Overall, the randomized, vehicle-controlled phase 3 trial 315 provided data from 437 subjects exposed to study drug. The ITT population consisted of 436 subjects because one subject received study drug before randomization; however, the safety database includes 437 subjects because this patient was exposed and continued in the study.

The number of subjects exposed to roflumilast in uncontrolled studies equals 190. A MUsT clinical pharmacology study enrolled 10 subjects in the 2 to 5 years of age cohort. The open-label Study 313 enrolled 180 subjects from the vehicle group who completed Trial 315; these subjects were unexposed to roflumilast cream prior to enrollment in Study 313.

Table 13: Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N=627 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=627)	Active Control (n=0)	Placebo (n=215)
Controlled trials conducted for this indication[2]	437	0	215
All other than controlled trials conducted for this indication (MUsT)	190	0	0
Controlled trials conducted for other indications[4]	0	0	0

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
Clinical reviewer's table.

The numbers of subjects exposed to roflumilast cream 0.05%, exclusively during Trial 315 and OLE Study 313 for at least 52 weeks was 212 and 82, respectively, for a total of 294 subjects.

Adequacy of the safety database:

The safety database presented by the Applicant is adequate to characterize the safety profile of roflumilast cream, 0.05% QD for the treatment of subjects between 2 to < 6 years of age with mild to moderate AD. The safety assessments were reasonable and consistent with the known adverse events for roflumilast cream in the AD target population:

- The size of safety database and subject exposure are adequate:
  - 437 subjects were exposed to at least one dose of the study drug during the pivotal phase 3 Trial 315
  - 294 subjects were treated for at least one year during the development program.
- The demographics of the study population are sufficiently representative of the target population.

9.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The OCS Clinical Services and the statistical and clinical teams evaluated the data fitness. The data submitted by the Applicant to support the safety and efficacy of roflumilast cream, 0.05% for the proposed indication was adequate.

Categorization of Adverse Events

Phase 3 protocol ARQ-151-315 defined an adverse event (AE) as:
An adverse event (AE) was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not it was considered related to the IP.

A serious AE (SAE) was any AE that, in the view of either the investigator or the sponsor, resulted in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that might not have resulted in death, been life-threatening, or required hospitalization could have been considered serious when, based upon appropriate medical judgment, they might have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed in the above definition.

At each clinic visit after Screening, the study staff questioned subjects in an open-ended manner and reviewed subject diaries regarding AEs. If a potential AE was recorded determined if an AE occurred.

AEs (serious or nonserious) and clinically significant abnormal laboratory test value(s) were evaluated by the principal investigator and treated and/or followed for up to 30 days after end of treatment or until the symptoms or value(s) returned to normal or acceptable levels, as judged by the principal investigator. If the subject enrolled in the ARQ-151-313 OLE study, AEs from the ARQ-151-315 pivotal study were followed through the subject's exit from this study.

SAEs were collected following informed consent of the subject through subject study completion. A treatment-emergent adverse event (TEAE) was defined as an AE that started post application of investigational product (IP) through study completion. The investigator reviewed each event and assessed its relatedness to the IP. Each sign or symptom reported was to be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 5-point severity scale. For each event, the date and time of onset, relationship to IP dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) were to be reported.

Routine Clinical Tests

Clinical laboratory samples (complete blood count and serum chemistry) were obtained at Screening and on Week 4/Day 29 according to the initial Schedule of Visits and Assessments in the original version of protocol for trial 315. There were no restrictions regarding food and the timing of unscheduled collection of specimens deemed necessary by the investigator. With implementation of Amendment 1 dated July 16, 2021, safety laboratory sampling was eliminated at Week 4/Day 29 from the study assessments to reduce pediatric subject burden and address enrollment challenges.

Laboratory test results were summarized descriptively by treatment and time point as both observed values and changes from baseline.

9.2.4. Safety Results

Deaths

No deaths were reported during the clinical trial and the OLE study.

Serious Adverse Events

For pivotal study ARG-151-315, one serious adverse event (SAE) was reported in the roflumilast cream 0.05% group. No SAE was reported in the vehicle group.

Subject (b) (6) was a 2-year-old Asian female, who after treatment with IP cream on Day 1 reported temperature elevation to 39.7˚. She was diagnosed with AE streptococcal pharyngitis

and prescribed amoxicillin BID, She was given oral ibubrofen and acetaminophen as needed. On Day 2, the subject was noted to have right calf swelling on an area unaffected by eczema. She was taken to urgent care and hospitalized for right leg cellulitus. Her laboratory tests showed leukocytosis (24,000), and elevated C-reactive protein (0.8) and procalcitonin (0.74) levels (normal ranges were not provided). Also on Day 2, abdominal distension was noted and resolved without treatment after one day. She was treated with IV clindamycin and discharged from the hospital on Day 4 with treatment through Day 11. She was afebrile with mild erythema in the affected area at the Day 8 clinic follow-up visit. The SAE cellulitis and nonserious streptococcal pharyngitis were considered resolved on Day 11. The subject resumed IP treatment on Day 18, and completed the study on Day 32.

The investigator and Sponsor considered the SAE as unlikely related to IP treatment.

> *Reviewer comments: There was one application of IP drug (Day 1) after which the subject went to the emergency department for evaluation and was admitted. While it is possible though unlikely that the SAE of cellulitis was caused by study drug, it is difficult to assess whether or not the cellulitis was exacerbated by IP exposure. Though not considered serious, the subject also reported abdominal distension on Day 2 which resolved in one day. It is possible that the AE of abdominal distension was related to IP exposure, the event did not recur when the IP was restarted.*

Dropouts and/or Discontinuations Due to Adverse Effects

The frequency of Drop outs during Trial 315 was 6.2% in the roflumilast arm, compared to a higher frequency in the vehicle control arm at 10.7%. Discontinuations due to adverse effects were reported at a frequency of less than 2% for each arm, and also at a higher frequency for the vehicle control group. The discontinuations due to AEs in the roflumilast group (n=7, 1.5%) were slightly lower than that in the vehicle group (n=4, 1.9%).

Seven subjects treated with roflumilast cream discontinued the study due to TEAE. Each TEAE was reported once, and included varicella; worsening of eczema; burning with IP application; application site irritation; impetigo; prurigo nodularis; and abdominal pain. All involved the application site (except abdominal pain) and were mild or moderate in severity, none was severe. Regarding relatedness, the AEs of abdominal pain and prurigo nodularis were considered possibly related, and the AE of burning with IP application and application site irritation were considered likely related to IP use; the other AEs were considered as unlikely related.

Five subjects in the vehicle cream group reported TEAEs leading to IP discontinuation. The TEAEs reported once were worsening of AD pruritus of skin, burning at application site, atopic dermatitis flare, and hives (suspected, not present during clinic exam), and upper respiratory tract (URT) infection. All were moderate in severity. Regarding relatedness, the AEs of burning at the application site and hive (by history) were considered likely related, the worsening of atopic dermatitis possibly related, and the AD flare and URT infection as unrelated.

Treatment Emergent Adverse Events and Adverse Reactions

The number of of subjects reported with at least one TEAE for the roflumilast group and the vehicle group were 29.7% and 21.9%, respectively. The proportion of subjects reporting more than one TEAEs considered related to the study drug were comparable for the roflumilast group (3.4%) and the vehicle (2.8%) group. There was only one serious TEAE reported in the roflumilast group. More subjects in the vehicle group, compared to the roflumilast group, discontinued due to TEAEs. Refer to Table 14.

Table 14: Overall Summary of TEAEs for Trial ARQ-151-315

	Roflumilast Cream 0.05% (N=437)	**Vehicle (N=215)**
Number of Subjects with at least 1 TEAE	130 (29.7)	47 (21.9)
Subjects with ≥1 TEAE, Treatment Related	15 (3.4)	6 (2.8)
Subjects with at least 1 Serious TEAE	1 (0.2)	0
Subjects with ≥ 1 TEAE leading to IP discontinuation	5 (1.1)	5 (2.3)
Subjects with ≥ 1TEAE leading to study discontinuation	5 (1.1)	4 (1.9)
Subjects with at least one TEAE Grade ≥ 3	1 (<1)	1 (<1)
Grade 3 (Severe)	1 (<1)	1 (<1)
Subjects with ≥ 1 TEAE, application site	23 (5.3)	13 (6.0)

Source: Agency OCS Analysis Studio, Custom Table Tool

The TEAEs reported most frequently during trial 315 were among the clinical signs and symptoms commonly reported in the pediatric population. The TEAEs reported more frequently in the roflumilast group compared to the vehicle group were upper respiratory tract infection (4.1% vs. 1.4%), diarrhea (2.5% vs. <1%), and vomiting (2.1% vs. 0%). Refer to Table 15.

Table 15: Trial ARQ-151-315: Summary of Subjects with TEAEs ≥ 1% by SOC and PT

System Organ Class Preferred Term	Roflumilast cream 0.05% N=437 n(%)	Vehicle N=215 n(%)
Any AE	**130 (29.7)**	**47 (21.9)**
Infections and Infestations	**74 (16.9)**	**24 (11.2)**
URT infection	18 (4.1)	3 (1.4)
Rhinitis	7 (1.6)	-
Conjunctivitis	6 (1.4)	-
Influenza	5 (1.1)	2 (0.9)
Gastrointestinal Disorders	**23 (5.3)**	**2 (0.9)**
Diarrhea	11 (2.5)	1 (<1)
Vomiting	9 (2.1)	-
Resp, Thoracic, Mediastinal Disorders	**11 (2.5)**	**4 (1.9)**
Injury, Poisoning, Procedural Compl.	**6 (1.4)**	**1 (<1)**
Nervous System Dis.	**6 (1.4)**	**-**
Headache	5 (1.1)	-

Source: Clinical reviewer's table.

Laboratory Findings

One subject treated with the vehicle cream during Trial 315 was reported with an increased value for alkaline phosphatase. No TEAEs related to abnormal laboratory values were reported for subjects treated with the roflumilast cream.

Vital Signs

Vital signs (blood pressure, heart rate, and temperature) were collected at all visits, in a seated position, after 5 minutes of rest. The Case Study Report (CSR) provided the results in a listing format. An information request (IR) was sent to the Applicant requesting the results be tabulated by age groups. No safety signals were identified by the review team.

Height was collected at Screening and Week4/Day 29 visits. Weight was collected at each visit on the same scale, measured in triplicate and the average was reported. Weight loss of ≥ 5% from baseline was reported by the investigators to the medical monitor.

QT and Electrocardiograms (ECGs)

The Agency waived the requirement for a thorough QT study for roflumilast cream, 0.3% in an Advice letter dated February 3, 2020, based on the TQT study previously conducted with oral roflumilast, existing nonclinical and clinical cardiovascular safety

data for the oral formulation, and the pharmacokinetics and safety profile to date of ARQ-151 cream. Due to the known safety profile of roflumilast cream for the 0.3% and 0.15% strengths, and the 3- to 6-fold lower concentration of roflumilast cream in this development program (0.05%), electrocardiograms (ECGs) were not conducted during Trial 315.

Immunogenicity

Not Applicable.

9.2.5. Analysis of Submission-Specific Safety Issues

Safety issues specific to the roflumilast cream, 0.05%, drug development program are local skin reactions, gastrointestinal disorders, and infections.

9.2.5.1. Local Skin Reactions

During trial 315, the percentage of subjects reported with local skin reactions were comparable for the roflumilast group (3.0%) and the vehicle group (3.3%). Application site pain was the most frequently reported administration site reaction, at a frequency of < 2% for both groups, and at a lower frequency in the roflumilast group compared to the vehicle group.

Table 16: Application Site Adverse Events, Trial ARQ-151-315

Administration Site Reaction	Roflumilast N=437 n(%)	Vehicle N=215 n(%)	RD (95% CI)
Application Site Total	**13 (3.0)**	**7 (3.3)**	**-0.04 (-2.49, 2.42)**
Pain	7 (1.6)	4 (1.9)	-0.26 (-2.41, 1.90)
Reaction	2 (0.5)	-	0.46 (-0.18, 1.09)
Pruritus	1 (0.2)	1 (0.2)	-0.24 (-1.25, 0.78)
Rash	1 (0.2)	-	0.23 (-0.22, 0.68)
Abscess	1 (0.2)	-	0.23 (-0.22, 0.68)
Pustules	1 (0.2)	-	0.23 (-0.22, 0.68)
Urticaria	-	1 (0.5)	-0.47 (-1.37, 0.44)
Infection	-	1 (0.5)	-0.47 (-1.37, 0.44)

RD=risk difference; CI=confidence interval
Sources: Reviewer Table, adapted from OCS Analysis Studio, Safety Explorer output.

The Applicant utilized their Local Tolerability Assessment (LTA) scales and reported scores for trial 315. The scales were different for investigators and subjects: investigators assessed appearance (i.e., erythema, papules and glazing, peeling) at Weeks 1, 2, and 4; subjects assessed the "sensation" (i.e., warming, tingling) of the skin

site 10 to 15 minutes after IP application in the clinic. Overall, the Applicant considered the IP and vehicle as well tolerated by subjects and the majority of subjects did not show signs of irritation.

Reviewer comment: The scales were not considered validated by the Division of Dermatology and Dentistry and Division of Clinical Outcomes Assessments; therefore, no further analyses were conducted.

9.2.5.2. Gastrointestinal Disorders

The adverse event profile of roflumilast, a PDE-4 inhibitor, includes gastrointestinal disorders. Diarrhea and vomiting were reported at a frequency of > 2%, and more frequently in the roflumilast group compared to the vehicle group. Refer to Table 17.

Table 17: AESI of Gastrointestinal disorders reported in trial ARQ-151-315

Preferred Term	Roflumilast Cream 0.05% (N=437)	Vehicle (N=215)
Diarrhea	11 (2.5)	1 (<1)
Vomiting	9 (2.1)	0
Abdominal pain	2 (<1)	0
Nausea	1 (<1)	1 (<1)

Source: OCS Analysis Studio, Safety Explorer.

9.2.5.3. Infections

The most frequent TEAEs for infection in the roflumilast group, and reported at a greater frequency than the vehicle group, were upper respiratory tract infection (4.1%), followed by rhinitis (1.6%), conjunctivitis (1.4%), and influenza (1.1%). Refer to Table 15.

9.2.6. **Safety Analyses by Demographic Subgroups**

In response to an IR sent to the Applicant by the Agency, the Applicant submitted safety analyses for each age in years (ages 2 years to five years). The AEs reported for each age were few in number and similar across the years. Adverse events occurring more than once were reported for the more common AEs of URT infections and diarrhea. TEAEs reported by maximum severity included one Grade 3 (severe) TEAE reported in a 2-year-old subject who was hospitalized for cellulitis (Refer to Serious Adverse Events section of this review). No TEAEs were assessed as Grade 4 or 5 during trial 315.

Table 18: Summary of Trial ARQ-151-315 Treatment Emergent Adverse Events by Age, Safety Population

	2 years		3 years		4 years		5 years	
	Roflumilast N=130 n(%)	**Vehicle N=81 n(%)**	**Roflumilast N=127 n(%)**	**Vehicle N=54 n(%)**	**Roflumilast N=97 n(%)**	**Vehicle N=46 Nn%)**	**Roflumilast N=83 n(%)**	**Vehicle N=34 n(%)**
Subjects with ≥1 TEAE	39 (30.0)	15 (18.5)	44 (34.6)	12 (22.2)	24 (24.7)	13 (28.3)	23 (27.7)	7 (20.6)
TEAE Tx-related	6 (4.6)	1(1.2)	3 (2.4)	3 (5.6)	4 (4.1)	1 (2.2)	2 (2.4)	1 (2.9)
Severe TEAE	1 (0.8)	-	-	-	-	-	-	-
TEAE lead to IP d/c	3 (2.3)	1(1.2)	1 (0.8)	2(3.7)	1 (1.0)	2 (4.3)	-	-
TEAE lead to study d/c	3 (2.3)	1(1.2)	2 (1.6)	2 (3.7)	-	1 (2.2)	-	-
≥TEAE on appl site	5 (3.8)	2 (2.5)	9 (7.1)	4 (7.4)	4 (4.1)	5 (10.9)	5 (6.0)	2 (5.9)

d/c=discontinuation; appl=application; TEAE=treatment emergent adverse event; Tx=treatment; IP=investigational product.
Source: Clinical Reviewer Table.

According to the System organ class (SOC) classification, the most frequently reported TEAEs were in the SOCs of Infections and infestations and Gastrointestinal disorders; reported at a greater frequency in the roflumilast group compared to the vehicle group, for the 2-, 3-, and 5-year-old subjects. Regarding preferred terms, upper respiratory tract infections and diarrhea were reported at a higher percentage in the roflumilast group compared to vehicle group in the 2- and 3-year-old cohorts. The reported TEAEs are those commonly known to occur in the pediatric population 2 to 5 years of age.

Table 19: Treatment Emergent Adverse Events by System Organ Class and Preferred Term reported at a frequency of ≥ 2% for roflumilast, by Age, Safety Population for Trial ARQ-151-315

	2 years		3 years		4 years		5 years	
System Organ Class (SOC) Preferred Term (PT)	**Roflumilast N=130 n(%)**	**Vehicle N=81 n(%)**	**Roflumilast N=127 n(%)**	**Vehicle N=54 n(%)**	**Roflumilast N=97 n(%)**	**Vehicle N=46 N(%)**	**Roflumilast N=83 n(%)**	**Vehicle N=34 n(%)**
GI Disorder	**9 (6.9)**	**2 (2.5)**	**6 (4.7)**	**0%**	**24 (24.7)**	**13(28.3)**	**2 (2.4)**	**0%**
Diarrhea	5 (3.8)	1 (1.2)	5 (3.9)	-	1 (<1)	-	-	-
Vomiting	3 (2.3)	-	1 (<1)	-	3 (3.1)	-	2 (2.4)	-
Abd. Pain	1 (<1)	-	-	-	1 (<1)	-	-	-
General Disorders	**7 (5.4)**	**3 (3.7)**	**11 (8.7)**	**4 (7.4)**	**4 (4.2)**	**3 (6.5)**	**3 (3.6)**	**3 (8.8)**
Pyrexia	5 (3.8)	2 (2.5)	3 (2.4)	2 (3.7)	3 (3.1)	1 (2.2)	1 (1.2)	1 (2.9)
Appl site pain	2 (2.4)						2 (2.4)	2 (5.9)
Infections / Infestations	**25 (19.2)**	**6 (7.4)**	**27 (21.3)**	**6 (11.1)**	**9 (9.3)**	**10 (21.7)**	**13 (15.7)**	**2 (5.9)**
NP	4 (3.1)	3 (3.7)	-	-	-	-	1 (1.2)	-
URT infection	4 (3.1)	-	9 (7.1)	1 (1.9)	3 (3.1)	2 (4.3)	2 (2.4)	-
GE /viral	3 (2.3)	-	1 (<1)	-	2 (2.1)	1 (2.2)	1 (1.2)	1 (2.9)
Rhinitis	3 (2.3)	-	1 (<1)	-	2 (2.1)	-	1 (1.2)	-
Conjunctivitis	1 (<1)		5 (3.9)	-	-	-	-	-
Ear/otitis med.	3 (2.3)	-	3 (2.4)	-	1 (1.0)	1 (2.2)	-	-
Influenza	1 (<1)	-	2 (1.6)	-	-	2 (4.3)	2 (2.4)	-

For TEAE PTs reported ≥ 2% in one age group treated with roflumilast, all other ages were listed for comparison.
Appl=application; GE=gastroenteritis; abd.=abdominal; med=media;
Source: Clinical reviewer's table; Applicants Table 2.2, IR submission.

No clinically meaningful safety trends could be identified for subgroups by sex or by ethnicity.

9.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies or tumors were reported during the clinical trial.

Human Reproduction and Pregnancy

No pregnancies were reported.

Pediatrics and Assessment of Effects on Growth

As a part of vital signs, height and weight were recorded at Baseline. Height was reported at Screening and Week 4. Weight was monitored during the pivotal study at Screening, Weeks 2 and 4. No clinically significant changes in height were seen during the phase 3 trial 315, which lasted for 4 weeks. For weight loss ≥ 5%, the Applicant reported a higher frequency for roflumilast cream of 2.7% (11 subjects) compared to the vehicle cream at 1.6% (3 subjects).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

For trial 315, no overdose was reported. There is no known potential for abuse, withdrawal or rebound.

9.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant submitted post-marketing reports and Development Safety Update Reports through November 27, 2024. For the Zoryve cream strengths 0.3% and 0.15%, Zoryve foam and completed and ongoing clinical trial reports, the specific trial and cumulative reports did not identify new safety signals or concerns.

Expectations on Safety in the Postmarket Setting

The roflumilast cream, 0.05% for AD for the population of patients 2 to 5 years of age is of a lower strength (one-third) compared to the approved Zoryve cream, 0.15% for patients ≥ 6 years of age. The safety profile is expected to be comparable to that of the approved 0.15% strength.

9.3. Statistical Issues

There were no notable statistical issues with the review of Trial 315 in this application.

9.4. Conclusions and Recommendations

The applicant provided a single randomized, double-blind, vehicle-control, parallel-arm trial (Trial 315) to support the efficacy and safety of roflumilast cream, 0.05% for the treatment of atopic dermatitis in pediatric patients 2 to 5 years of age with mild to moderate AD. The single primary endpoint was the proportion of responders, defined as a vIGA-AD score of clear (0) or almost clear (1) at Week 4 with at least a 2-grade improvement from baseline. Key secondary endpoints of clinical interest, tested in hierarchical order, were the proportion of responders at Week 2 and Week 1. Roflumilast cream, 0.05% demonstrated statistical significance versus

vehicle cream (all p-values < 0.0001) on all three of these endpoints.

From a statistical perspective, Trial 315 supports the indication of treatment of mild to moderate atopic dermatitis in pediatric patients 2 to 5 years of age.

To define the safety profile of roflumilast cream, 0.05%, the Applicant conducted assessments of safety of the drug product in the target population. There were no deaths and one serious adverse event (cellulitis) deemed as unlikely to be related to study drug. The size of the safety database, subject exposure, and safety assessments were adequate to characterize the safety profile of roflumilast cream, 0.05% for the target population.

In the safety data pool of 734 subjects, the most frequently reported adverse events were diarrhea, upper respiratory tract infection, pyrexia, and conditions commonly seen in the 2 to 5 year-old pediatric population.

The Applicant provided adequate efficacy and safety data to support the conclusion that the benefit-risk analysis is favorable for the approval of this sNDA. This reviewer recommends approval of roflumilast cream, 0.05%, applied topically once a day, for the treatment of mild to moderate atopic dermatitis in patients 2 to 5 years of age.

10 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was held. Zoryve cream, 0.15% was approved by the FDA for pediatric patients (6 years of age and older) with mild to moderate AD in December 2024; a higher strength than the drug product considered in this review. There were no issues that required committee discussion.

The Division of Pediatrics and Maternal Health (DPMH) was consulted regarding labeling. Refer to Section 10.

11 Pediatrics

Zoryve cream is approved for the pediatric population at the following strengths and for the following ages:

- 0.3%, is indicated for the topical treatment of plaque psoriasis, including intertriginous areas, in pediatric patients 6 years of age and older;
- 0.15%, is indicated for the topical treatment of mild to moderate atopic dermatitis in pediatric patients 6 years of age and older

This supplemental NDA submission proposes Zoryve cream, 0.05% for the treatment of atopic dermatitis in the pediatric population aged 2 to 5 years. Regarding the pediatric study plan, the Applicant requested a waiver for ages 0 to < 3 months, and a deferral for ages 3 month to 23 months, both of which were granted.

The Division of Pediatrics and Maternal Health was consulted on this application regarding labeling and Dr. Ndidi Nwokorie provided recommendations.

Refer to Section 13 regarding the PREA Postmarketing Requirement (PMR).

12 Labeling Recommendations

12.1. Prescription Drug Labeling

Prescribing information

Refer to the Associate Director for Labeling Review of the Prescribing Information in DARRTS for the differences between the Applicant's proposed PI and the agreed upon PI. This review includes a high-level summary of the rationale for major changes to the PI as compared with the Applicant's draft PI.

Other Prescription Drug Labeling

DDD consulted the Division of Medication Error Prevention and Analysis 1 (DMEPA 1), in the Office of Medication Error Prevention and Risk Management (OMEPRM) to evaluate updated Zoryve carton labeling. Reviewer Amy Bao reviewed the proposed labeling updates made by Arcutis Biotherapeutics, Inc., including changes to the carton color panels and positioning of the carton end flaps. DMEPA did not identify areas of vulnerability that may lead to medication errors and there were no recommendations.

The final labeling will be appended to the Action Letter.

13 Risk Evaluation and Mitigation Strategies (REMS)

The Agency does not recommend a REMS program or other safety interventions at this time.

14 Postmarketing Requirements and Commitment

On August 12, 2025, the Division of Dermatology and Dentistry met with the Pediatric Review Committee (PeRC). After discussion with DDD, the PeRC agreed with the Division and issued the following recommendations:

- The PeRC agreed with granting a partial waiver in pediatric patients of age birth to less than 3 months with atopic dermatitis on the basis that necessary studies are impossible or highly impracticable because atopic dermatitis in this age group is difficult to diagnose.
- The PeRC agreed with issuing a PREA PMR for a 4-week open-label safety trial evaluating 0.05% Zoryve cream in 100 evaluable pediatric patients 3 to less than 24 months with atopic dermatitis and at least 3% BSA involvement enrolling at least 100 subjects.

PREA PMR:
For Study ARQ-151-218: Conduct a 4-week, open-label safety trial with Zoryve cream, 0.05% with 100 evaluable pediatric subjects 3 months to <2 years of age with mild to moderate atopic dermatitis and at least 3% BSA involvement.

Timeline:

a. Study Completion: July 2026
b. Final Report Submission: February 2027

15 Division Director (DHOT) Comments

APPEARS THIS WAY IN ORIGINAL

16 Division Director (OCP) Comments

17 Division Director (OB) Comments

18 Division Director (Clinical) Comments

19 Office Director (or designated signatory authority) Comments

I agree with the team conclusion to approve ZORYVE (roflumilast) cream, 0.05% for the treatment of mild to moderate atopic dermatitis in children 2 to 5 years of age.

20 Appendices

20.1. References

Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. J Allergy Clin Immunol. 2014;134:769-79.

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Shaw TE et al. Eczema prevalence in the United States: Data from the 2003 National Survey of Children's Health. J Invest Dermatol. (2011) 131, 67-73.

Stefanovic N, Irvine AD. Filaggrin and beyond: New insights into the skin barrier in atopic dermatitis and allergic diseases, from genetics to therapeutic perspectives. Ann Allergy Asthma Immunol. 2024 Feb;132(2):187-195. doi: 10.1016/j.anai.2023.09.009. Epub 2023 Sep 25. PMID: 37758055.

Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016 Mar;387(10023):1109-22

20.2. Financial Disclosure

For this NDA supplement (S-012) for Zoryve cream, the applicant attested that none of the clinical investigators reported financial disclosures, proprietary interest, or equity relationship with the sponsor. The Applicant submitted a completed Form FDA 3454, attesting to the absence of financial interests and arrangements described in 21 CFR 54.4(a)(3).

The Applicant included lists of clinical investigators for phase 2 Study ARQ-151-105 and phase 3 Trial ARQ-151-315.

Covered Clinical Studies : ARQ-151-105 and ARQ-151-315

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified (in parentheses): **ARQ-151-105 - (10); ARQ-151-315 – (106)**		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

20.3. OCP Appendices (Technical documents supporting OCP recommendations)

20.3.1. Bioanalytical Method Validation and In-Study Method Performance

The bioanalytical method (171410VEMB_ARCMC_R1) used to measure roflumilast and roflumilast N-oxide concentrations in human plasma samples of the Study ARQ-151-105 and ARQ-151-315 was previously validated and submitted. The method validation was reviewed and found acceptable. Refer to page 130 of original unireview (Reference ID: 5020282) and page 144 of unireview for supplement-7 (Reference ID: 5408595) of this NDA. The validated is a liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method with an assay range of 0.1 to 100 ng/mL.

Reproducibility and reliability of the analytical method was demonstrated by repeating the analysis in a separate run on a separate day of a subset of subject samples (incurred sample reanalysis [ISR]) from Study ARQ-151-105 and ARQ-151-315. The respective bioanalytical reports indicate that at least two-thirds of the repeated sample results were within 20% of the original results for both roflumilast and roflumilast N-oxide, confirming reproducibility of the methods. Overall, the method performance for assay of study samples is reliable and reproducible, hence acceptable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID N TABATABAI
10/04/2025 08:46:52 AM

TATIANA OUSSOVA
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